

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SHANGHAI HONGENE BIOTECH CORPORATION,
Petitioner

v.

CHEMGENES CORPORATION,
Patent Owner

Case IPR2023-00490
U.S. Patent No. 9,884,885

PETITIONER'S REPLY TO PATENT OWNER RESPONSE

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PETITIONER’S CURRENT EXHIBIT LIST

CURRENT EXHIBIT LIST

Exhibit No.	Title	Abbreviation
1001	U.S. Patent No. 9,884,885	the '885 Patent
1002	File History of U.S. Patent Appl. No. 13/261,029 (which issued as the '885 Patent)	the '885 File History
1003	Declaration of Phil S. Baran, Ph.D. in support of Petition for <i>Inter Partes</i> Review of the '885 Patent	Baran Decl.
1004	S.L. Beaucage & M.H. Caruthers, <u>Deoxynucleoside Phosphoramidites</u> – A New Class of Key Intermediates for <u>Deoxypolynucleotide Synthesis</u> , Tetrahedron Letters (1981) Vol. 22, No. 20, 1859-1862	Beaucage (1981)
1005	M.D. Matteuci & M.H. Caruthers, <u>Synthesis of Deoxyoligonucleotides on a Polymer Support</u> , J. Am. Chem. Soc. (1981) 103, 3185-3191	Matteuci (1981)
1006	L.J. McBride & M.H. Caruthers, <u>An Investigation of Several Deoxynucleoside Phosphoramidites Useful for Synthesizing Deoxyoligonucleotides</u> , Tetrahedron Letters (1983) Vol. 24, No. 3, 245-248	McBride (1983)
1007	S.L. Beaucage & R.P. Iyer, <u>Advances in the Synthesis of Oligonucleotides by the Phosphoramidite Approach</u> , Tetrahedron (1992) Vol. 48, No. 12, 2223-2311	Beaucage (1992)
1008	A Simple Guide to Phosphoramidite Chemistry and How It Fits in Twist Bioscience’s Commercial Engine (9/13/2018) ¹	Twist (2018)

¹ <https://www.twistbioscience.com/blog/science/simple-guide-phosphoramidite-chemistry-and-how-it-fits-twist-biosciences-commercial>

Exhibit No.	Title	Abbreviation
1009	C.B. Reese, <u>Oligo- and poly-nucleotides: 50 years of chemical synthesis</u> , Org. Biomol. Chem. (2005) Vol. 3, 3851-68	Reese (2005)
1010	J.G. Lackey & M.J. Damha, <u>The Acetal Levulinyl Ester (ALE) Group for the 2'-Hydroxyl Protection of Ribonucleosides and the Synthesis of Oligoribonucleotides</u> , Nucleic Acids Symposium Series No. 52 (2008), 35-36	Lackey (2008)
1011	G.W. Ashley, <u>Modeling, Synthesis, and Hybridization Properties of (L)-Ribonucleic Acid</u> , J. Am. Chem. Soc. (1992) Vol. 114, No. 25, 9731-9736	Ashley (1992)
1012	A. Ohkubo et al., <u>'Protected DNA Probes' Capable of Strong Hybridization Without Removal of Base Protecting Groups</u> , Nucleic Acids Research (2008) Vol. 36, No. 6, 1952-1964	Ohkubo (2008)
1013	M. Scherr et al., <u>Synthesis and Properties of Hammerhead Ribozymes Stabilized Against Nucleases by Different 2'-Modifications: methoxyethoxy-, fluoro- and amino groups</u> , Biorganic & Medicinal Chemistry Letters (1997) Vol. 7, No. 13, 1791-1796	Scherr (1997)
1014	T. Brown et al., <u>A New Base-Stable Linker for Solid-Phase Oligonucleotide Synthesis</u> , J. Chem. Soc., Chem. Commun. (1989) 891-893	Brown (1989)
1015	N. Usman et al., U.S. Patent Appl. Pub. No. US 2006/0142557 A1	Usman (2006)
1016	U.S. Patent No. 5,808,039	the '039 Patent
1017	U.S. Patent No. 5,898,031	the ' 031 Patent

1018	S. Pitsch et al., <u>Reliable Chemical Synthesis of Oligoribonucleotides (RNA) with 2'-O-[(Triisopropylsilyl)oxy]methyl(2'-O-tom)-Protected Phosphoramidites</u> , Helvetica Chimica Acta – Vol. 84 (2001), 3773-3795	Pitsch (2001)
1019	Y. Fan et al., <u>Transient Silylation of the Guanosine O6 and Amino Groups Facilitates N-Acylation</u> , Organic Letters (2004) Vol. 6, No. 15, 2555-2557	Fan (2004)
1020	U.S. Patent No. 7,879,991	the ' 991 Patent
1021	S. Pitsch & P. Weiss, <u>Preparation of 2'-O-[(Triisopropylsilyl)oxy]methyl-protected Ribonucleosides</u> , Current Protocols in Nucleic Acid Chem. (2001) 2.9.1-2.9.14	Pitsch #2 (2001)
1022	S.A. Scaringe et al., <u>Chemical synthesis of biologically active oligoribonucleotides using β-cyanoethyl protected ribonucleoside phosphoramidites</u> , Nucleic Acids Research (1990) Vol. 18, No. 18, 5433-5441	Scaringe (1990)
1023	C. Scheuer-Larsen et al., <u>Introduction of a Universal Solid Support for Oligonucleotide Synthesis</u> , Nucleosides, Nucleotides & Nucleic Acids (1997) 16:1-2, 67-80	Scheuer-Larsen (1997)
1024	R.K. Gaur et al., <u>Novel Solid Phase Synthesis of 2'-O-Methylribonucleoside 5'-Triphosphates and Their α-Thio Analogues</u> , Tetrahedron Letters (1992) Vol. 33, No. 23, 3301-3304	Gaur (1992)
1025	B.S. Sproat et al., <u>2'-O-alkyloligoribonucleotides Synthesis and Applications in Studying RNA Splicing</u> , Nucleosides and Nucleotides (1991) 10:1-3, 25-36	Sproat (1991)

1026	H. Inoue et al., <u>Synthesis and hybridization studies on two complementary nona(2'-O-methyl)ribonucleotides</u> , Nucleic Acids Research (1987) Vol. 15, No. 15, 6131-6148	Inoue (1987)
1027	H.A. White, <u>Manual Oligonucleotide Synthesis Using the Phosphoramidite Method</u> , Methods in Molecular Biology Vol. 4 (1988), Ch. 14, 193-213	White (1988)
1028	G.G. Sivets et al., <u>Synthesis and Conformational Analysis of 1'- and 3'-Substituted 2-Deoxy-2-fluoro-D-ribofuranosyl Nucleosides</u> , Helvetica Chimica Acta – Vol. 90 (2007), 1818-1836	Sivets (2007)
1029	R.A. Donga et al., <u>Ion-tagged synthesis of an oligoribonucleotide pentamer — The continuing versatility of TBDMS chemistry</u> , Can. J. Chem. (2007) Vol. 85, 274-282	Donga (2007)
1030	N. Usman et al., U.S. Patent 6,528,639 B2	Usman (2003)
1031	Jeremy J. Edwards Declaration in Support of Motion to Stay	
1032	Reissue Preliminary Amendment in Reissue Application No. 18/130,902	
1033	Baran Declaration in Support of Hongene's Reply Brief	
1034	Curriculum Vitae of Phil S. Baran	
1035	Deposition Transcript of Patrick J. Hrdlicka, Ph.D. (December 20, 2023)	
1036	DNA Synthesis Without Base Protection, <i>Current Protocols in Nucleic Acid Chemistry</i> (2004), 3.10-3.10.15	
1037	Paul Gaytán, <i>BioTechniques</i> 47:701-702 (August 2009)	Gaytán 2009

1038	Xue-Feng Zhu, et al., An Improved Transient Method for the Synthesis of <i>N</i> -Benzoylated Nucleosides, <i>Synthetic Communications</i> , 33:7, 1233-1243 (2003)	Zhu 2003
1039	Todd D. Nelson, et al., Selective Deprotection of Silyl Ethers, February 26, 1996	
1040	M. P. Reddy, et al., Ultrafast Cleavage and Deprotection of Oligonucleotides Synthesis and Use of C ^{Ac} Derivatives, <i>Nucleosides, Nucleotides & Nucleic Acids</i> , 16:7-9, 1589-1598, 1997	Reddy 1997
1041	Dimitrios Stefanidis, et al., General Base Catalysis of Ester Hydrolysis, <i>J. Am. Chem. Soc.</i> 1993, 115, 6045-6050	Stefanidis 1993
1042	Advanced Organic Chemistry, Reactions, Mechanisms, and Structure, 1992, Chapter 4, Stereochemistry, 94-164	
1043	U.S. Patent No. 5,525,719	
1044	Phil S. Baran, Ph.D. Declaration in Support of Motion...	
1045	U.S. Patent No. 5,606,049	
1046	New Universal and Degenerate Bases, <i>The Glen Report</i> , Volume 8, Number 1, June 1995	
1047	U.S. Patent No. 5,214,135	

I. SUMMARY

All claims of the '885 Patent are invalid. Chemgenes' arguments to the contrary are meritless.

II. CHEMGENES' POSA DEFINITION IS FLAWED, BUT ALL CLAIMS ARE INVALID REGARDLESS.

Chemgenes' proposed POSA definition is flawed because it excludes highly skilled practitioners in the field of oligonucleotide chemistry, such as people with strong backgrounds in synthetic organic chemistry. (Ex. 1033¶5.) Chemgenes has not explained how this difference leads to any different results concerning invalidity. Dr. Hrdlicka's and Dr. Baran's opinions are the same under either definition. (Ex. 1033¶6.)

III. DR. BARAN IS IMMENSELY QUALIFIED.

Chemgenes incorrectly asserts that Dr. Baran "does not appear to have a deep background" in the relevant field. (POR17.) Dr. Hrdlicka did not state this. The Board should reject this unsupported attorney argument. As amply demonstrated in his first declaration, resume, and testimony, Dr. Baran is one of the world's preeminent synthetic organic chemists and has an extensive background in the field and his groundbreaking work on P(V) chemistry for oligonucleotide chemistry, which earned him prestigious awards, built on, and required a deep understanding of, P(III) chemistry. (Ex. 1033¶¶7-8.)

Chemgenes' other baseless tack is to paint Dr. Baran as a late entrant to the field. (POR17.) But Dr. Baran was exposed to nucleoside chemistry as an undergraduate in 1996, and in the 2003-2009 period, he both taught classes, and consulted with companies concerning, nucleotide synthesis. (Ex. 1033¶8.) Chemgenes' characterization of him as a late entrant, based solely on his publication history, improperly ignores his experience. (*Id.*)

IV. CHEMGENES MISREPRESENTS THE HIGHLY ADVANCED STATE OF THE ART.

Chemgenes incorrectly argues that Hongene has "oversimplified" the science of SPOS "and the challenges that a POSA would have faced" in 2009. (POR6-8.) Although SPOS was complex and involved some degree of unpredictability, POSAs in 2009 would have been well-equipped to manage that, and Hongene has not downplayed any aspect of it. (Ex. 1033¶9.)

First, under either definition, the level of skill in the art was very high. (Ex. 1033¶10.) Second, the art was highly advanced by 2009. (Ex. 1033¶11.) Chemgenes relies on Beaucage (1991) as purportedly showing "adversity in developing SPOS," but it actually describes how each of the issues addressed were *overcome*, and does not mention ongoing "adversity." Rather, Beaucage conveys that as even in 1991, this field was heavily studied, highly advanced, and replete with *successful* efforts. (*Id.*)

Indeed, in 1999, *Chemgenes itself* stated that “[c]hemical synthesis of RNA has been *perfected* to the extent that long sequences...and multi-milligram quantities can be produced efficiently...” (Ex. 1033¶12 (emphasis added).) Dr. Hrdlicka testified that he had not considered this in rendering his opinions in this proceeding. (Ex. 1035 at 39:2-40:20.)

Further, in 2001, Pitsch noted:

[M]any groups have *successfully* contributed to the development of a *reliable* chemical synthesis of nucleic acids [and] the synthesis of DNA oligonucleotides is probably *the most evolved chemical process known so far and has almost reached perfection in terms of efficiency and automation*.

(Ex. 1033¶13 (emphases added).) Pitsch explained that phosphoramidite chemistry “can, in principle, also be applied to the synthesis of the structurally very similar RNA oligonucleotides.” (*Id.*) And, as detailed below, Pitsch reported successful synthesis of acetyl-protected phosphoramidite and its successful use in RNA oligonucleotide synthesis. (*Infra* at VII.B.1. & 2.)

V. GROUND I AND VI

Chemgenes concedes that Claims 1 and 5 are anticipated, seeking entry of Substitute Claims 6 and 7. (POR20-21, 76-77.) Hongene opposes that motion separately.

VI. THE “LEAD COMPOUND” FRAMEWORK IS INAPPOSITE, BUT CLAIMS 2-4 ARE OBVIOUS UNDER ANY OBVIOUSNESS FRAMEWORK.

Chemgenes criticizes Hongene for not satisfying the “lead compound” framework for obviousness as to Claims 2-4. (POR21-24, 64, 69, 73-74.) But “lead compound” is not the only test for obviousness, even for chemical compounds. *UCB, Inc. v. Accord Healthcare, Inc.*, 890 F.3d 1313, 1329 (Fed. Cir. 2018); *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1291 (Fed. Cir. 2012).

The PTAB has declined to apply the lead compound analysis in at least one case involving claims to *chemical reagents*. *NOF Corp. v. Nektar Therapeutics*, IPR2019-01397, 2021 WL 3438554, at *5 (PTAB Aug. 5, 2021). As in *NOF*, the claims here are directed to *reagents* used in the production of oligonucleotides, not therapeutic compounds, so the lead compound approach is inapposite. (Ex. 1033¶¶17-21.) Unlike with therapeutic compounds, the selection and development of these reagents focuses on the optimization of chemical processes and purity to ensure the reliable and consistent production of high-quality reagents. (Ex. 1033¶17.)

Even the oligonucleotides made using such reagents often were not themselves used as therapeutics. Oligonucleotides had diverse applications, like DNA sequencing, genetic research, and molecular diagnostics. (Ex. 1033¶18.) The properties of the oligonucleotide are often driven by the targeted sequence and

not necessarily by the properties of the individual building blocks used to synthesize them. (*Id.*) Accordingly, there were myriad motivations at play for POSAs in developing and improving upon oligonucleotide building blocks, and which set of motivations might be at play would have depended on the use case and could shift depending on the stage of development and scale of production. (*Id.*) For instance, relatively small amounts of oligonucleotide are needed for biological research, as compared to clinical trials. (*Id.*)

And it was known that introducing various chemical modifications to nucleoside building blocks could enhance the properties of the resulting oligonucleotide. (Ex. 1033¶19.) Common modifications included 2'-O-methyl, 2'-O-methoxyethyl, 2'-fluoro, or phosphorothioate groups to improve stability, nuclease resistance, and cellular uptake. (*Id.*) Indeed, Dr. Hrdlicka agreed that the selection of such substituents depends on the “planned applications” and “context.” (*Id.*)

Further, desired base pairing characteristics of oligonucleotides varied depending on the application. For some applications, such as diagnostics, it was important to have a high degree of binding specificity and strength, but when trying to modulate gene expression, such as with antisense oligonucleotides, some mismatch was desirable. (Ex. 1033¶20.)

Importantly, the selection of protecting groups for the exocyclic amine of a nucleobase (“PGs”) was not a zero-sum game; rather, PG selection was “dictated by many considerations” and consequently, there were an array of motivations in 2009 to select from “an assortment” of PGs, depending on the use case. (Ex. 1033¶21.) This is illustrated by the Chemgenes catalogues, showing various SPOS reagents, including their use as basic research tools. (*Id.*)

Nevertheless, as explained in the Petition and below, Claims 2-4 of the ’885 Patent are obvious under any obviousness framework, including “lead compound.”

VII. GROUND II

A. There was ample reason to select Compound x.

Chemgenes argues that Hongene has not shown why POSAs “would have selected Compound x...as the most promising to modify in order to improve upon its activity.” (POR22-23.) First, even under the inapposite lead compound test, requiring a *single* lead compound is erroneous. *Altana Pharm. AG v. Teva Pharms. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009).

Second, as Hongene explained, POSAs would have recognized the utility of Compound x in SPOS, and the ’031 Patent contemplates such use. (Ex. 1033¶¶25-27.) Because nucleosides were building blocks for a wide variety of compounds that themselves had a wide variety of uses, this utility of Compound x *alone* was a reason for POSAs to select it. (Ex. 1033¶25.) Also, as Hongene explained,

Compound x was the *end product* of Example 4, which the '031 Patent said illustrated how to prepare building blocks used in making the compounds of the '031 invention. (Ex. 1033¶26.) Hongene also noted that the '031 Patent discloses several nucleoside amidites that “had useful properties,” “clearly describes how monomeric phosphoramidites” such as Compound x “can be prepared,” “and the ways these compounds can be used to synthesize oligonucleotides with therapeutic potential.” (Ex. 1033¶27.) Indeed, one of the “useful properties” of nucleoside amidites identified throughout the '031 Patent is that 2'-fluoro substituted nucleosides were preferred and used to make preferred oligomers with enhanced binding affinity. (*Id.*)

Third, Chemgenes incorrectly argues that the '031 Patent does not provide “data” showing Compound x “being used to incorporate 2'-fluoro-2'-deoxyguanosine monomers into any oligonucleotides[.]” (POR23.) There are *four* examples (12.iii, 13.iii., 13.v, and 14.i) necessarily contemplating precisely that. (Ex. 1033¶¶29-31.) All four refer to preparing compounds having 2'-fluoro-nucleosides in their wing segments, and to preparing them “in the manner of Example 8,” which discloses a general synthetic process for oligonucleotide synthesis. (Ex. 1033¶¶29-30.) Contrary to Dr. Hrdlicka's deposition testimony, POSAs would have known to deploy the appropriate 2'-fluoro phosphoramidite

reagents in that process to make the oligonucleotides of those four examples. (Ex. 1033¶30.)

All four of those examples *necessarily* describe using Compound x, because (a) Example 8 describes using phosphoramidites to introduce 2'-fluoro monomers, including guanine monomers, in the wing segments of the oligonucleotides and (b) Compound x is the *only* 2'-fluoro guanosine phosphoramidite disclosed in the '031 Patent, which Dr. Hrdlicka confirmed. (Ex. 1033¶¶28-31.)

Fourth, Chemgenes incorrectly argues that because the figures of the '031 Patent do not present data on any oligoribonucleotides containing 2'-fluoro monomers, POSAs would not have selected the Compound x. (POR23.) POSAs would not rely on the presence of such *illustrative* data to disregard the known advantages of using 2'-fluoro monomers, especially when such advantages are emphasized in the '031 Patent. (Ex. 1033¶32.)

Fifth, Chemgenes incorrectly asserts that POSAs would not select Compound x because the '031 Patent does not disclose deprotection rates. (POR23.) But as explained above, there were other reasons to select Compound x. And the '031 Patent's use of a 24-hour deprotection period would have prompted POSAs to explore shortening that period, especially in view of the iterative nature of SPOS. (Ex. 1033¶33.)

Sixth, Chemgenes itself in 2009 offered 2'-fluoro phosphoramidites for sale in its own catalogue, characterizing them as being “for modified RNA synthesis,” and—citing publications from the 1990's—touting their “significant biological activity,” use as “versatile probes” and that incorporating them into oligonucleotides “imparts many interesting biological properties”. (Ex. 1033¶35.)

Finally, Dr. Hrdlicka himself agreed at deposition that likely POSAs “would have known that 2 prime fluoros can be incorporated into oligonucleotides and increase affinity towards...certain target strands.” (Ex. 1033¶36.)

B. Chemgenes' scattershot motivation arguments are meritless.

1. Chemgenes' “instability” argument is meritless.

Chemgenes incorrectly argues that POSAs would have eschewed acetyl PGs as unstable under basic conditions. (POR24-27.) First, Pitsch alone refutes this argument. (Ex. 1033¶38.) Pitsch teaches a robust, successful synthesis using acetyl PG under basic conditions. (*Id.*) Indeed, Pitsch touts the use of acetyl PG under basic conditions, reporting an extensive workup and concluding that acetyl “***is indeed suited for a labile universal nucleobase protection.***” (*Id.* (emphases added).)

Pitsch reported that (a) their successful syntheses using the acetyl PG showed “very good coupling yields and indicated a very clean and reliable deprotection process,” (b) they “optimized all feasible reaction and

deprotection parameters,” and (c) under their “robust deprotection conditions” which they “optimized,” they “never observed indications of incomplete deprotection and/or concomitant strand scission.” (*Id.*)

Pitsch further reported that the RNA sequences they prepared had “the correct sequence composition,” and “the complete absence of any unnatural connections” and “the full integrity of the nucleosides during the phosphoramidite synthesis, the sequence assembly, and the two deprotection reactions.” (*Id.*)

Second, Chemgenes incorrectly asserts that Khorana (1972), taught away from using acetyl PG. (POR24-25.) Khorana’s decision to depart from acetyl PG was made in 1972 while conducting *phosphodiester* coupling chemistry,² many years before the advent of the very different *phosphoramidite* coupling chemistry, and decades before Pitsch. (Ex. 1033¶¶39-43.) Unlike the phosphoramidite methods used in 2009, phosphodiester coupling used prolonged and harsh deprotection conditions. (Ex. 1033¶¶39-40.)

Thus, POSAs would have known in 2009 that Khorana’s preference for isobutyryl over acetyl did not apply to phosphoramidite-based synthesis,

² Dr. Hrdlicka confirmed this. (Ex. 1035 at 113:12-15.)

and could actually hinder it. (Ex. 1033¶¶39-41.) For example, Schulhof explained in 1987 that:

(a) Khorana's PG preference "dates back to...phosphodiester methodology";

(b) "[w]ith respect to the progress achieved in the field of phosphotriester and phosphoramidite synthesis, the [PGs that Khorana used] present now a few shortcomings," like requiring "a long and drastic deprotection step" that is "time-consuming," and "forbids the synthesis of modified oligonucleotides containing alkali-sensitive bases";

(c) "[i]n the methods presently available," the "conditions of condensation are much milder than in the phosphodiester approach"; and

(d) the "high stability" of Khorana's preferred PGs "is no more necessary."

(Ex. 1033¶40.)

Also, phosphodiester conditions were problematic for RNA oligonucleotide synthesis, which, unlike Khorana's DNA oligonucleotide synthesis, required protection of the 2'-O position and milder conditions. (Ex. 1033¶41.)

Third, Chemgenes incorrectly argues that acetyl was not used after Khorana. (POR25-26.) This ignores that Pitsch not only used acetyl, but heavily touted such use in a leading journal. (Ex. 1033¶43.) It also ignores Compound 5 of the '991 Patent. (Ex. 1033¶44.) It also ignores Chemgenes' own patent from 1996, which identified and claimed acetyl-protected guanosine phosphoramidites. (Ex. 1033¶43.)

Fourth, none of the remaining literature cursorily cited by Chemgenes (POR25-27) would have dissuaded POSAs from using acetyl. (Ex. 1033¶43.)

None criticizes acetyl, nor states or suggests that acetyl was never used, and most of it predates the advent of phosphoramidite synthesis, Pitsch, and/or the '991 Patent. (*Id.*) The mere disclosure of other PGs does not teach away from acetyl. *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 964 (Fed. Cir. 2014).

2. Chemgenes' "insolubility" argument is meritless.

Chemgenes incorrectly asserts that POSAs lacked motivation to use acetyl because it would reduce the solubility of the resulting guanosine in organic solvents. (POR27-29.)

First, this ignores Pitsch, which, as detailed above, reported a robust workup of reaction conditions, emphatic success in using acetyl-protected phosphoramidites to synthesize RNA oligonucleotides, and did not report any solubility problems. (Ex. 1033¶46.) This alone refutes Chemgenes' argument.

Second, even assuming acetyl would reduce solubility, this would not dissuade POSAs, who would have understood that (a) solubility is a question of degree, (b) in *solid phase* synthesis (SPOS), a high degree of solubility is not needed, and (c) solubility could be improved using routine adjustments, like using solvent admixtures. (Ex. 1033¶47.)

Third, Chemgenes' two cited publications (POR28-29) do not suggest a solubility problem with acetyl. Sinha (1993) refers to DNA synthesis, and does not suggest any problem using base-labile PGs in oligonucleotide synthesis involving

2'-fluoro-substituted monomers (like Compound x) or RNA synthesis (as in Pitsch). (Ex. 1033¶48.) Further, Sinha (1993) is vague; does not specify what the problems were, their context, or which PGs were implicated, nor does it suggest that the solution is to avoid any PG, let alone acetyl. (*Id.*)

Schaller (1963) fares no better. (Ex. 1033¶¶49, 80.) Published long before the advent of the phosphoramidite-based synthesis, it did not address SPOS. (*Id.*) Regardless, Schaller *successfully* acetylated deoxyguanosine. (*Id.*) Even if Schaller raised a relevant solubility issue (it did not), Schaller also resolved it.

Fourth, Donga used acetylated guanosine-phosphoramidite to build an RNA oligonucleotide using *solution-phase synthesis*, illustrating the *lack* of solubility concerns with using acetylated guanosine. (Ex. 1033¶50.)

3. Chemgenes' arguments about Pitsch and Fan are meritless.

Citing no literature support, Chemgenes incorrectly asserts that Pitsch and Fan were “not relevant” to “2'-fluoro-2'-deoxyribonucleotide phosphoramidites for modified oligonucleotide synthesis” because the Pitsch and Fan monomers would have been used to make “unmodified RNAs” and not oligonucleotides having 2'-fluoro-2'-deoxynucleotides. (POR33-36.)

Chemgenes is wrong and is restricting and compartmentalizing the teachings of Pitsch and Fan contrary to both the state of the art and Pitsch itself. (Ex.

1033¶¶52-54.) Taking an overly cramped view of prior art is erroneous. *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 964 (Fed. Cir. 2014).

First, RNA and 2'-fluoro-2'-deoxynucleosides were intimately related and used together to create “antisense” oligonucleotides, known for having better target affinity and significant utility in “fundamental research, chemotherapy, and agriculture.” (Ex. 1033¶56.) Indeed, 2'-fluoro-2'-deoxynucleosides were considered “RNA-like.” (*Id.*) Thus, POSAs would have applied the teachings of Pitsch and Fan to improve Compound x. (*Id.*)

Second, Pitsch does not suggest that acetyl could be used *only* to protect unmodified RNA nucleosides. Rather, Pitsch describes acetyl as suited for “universal nucleobase protection.” (Ex. 1033¶53.)

Third, POSAs would have been motivated to apply Pitsch *irrespective* of what resided at the 2' position of the given monomer. (Ex. 1033¶¶54-55.) The 2' substitution is considered independently from the nucleobase PG, because those sites are chemically distant and not expected to affect each other's reactivities. (*Id.*) Zhu illustrates this, reporting little or no variation in reaction times, regardless of the 2' group. (Ex. 1033¶55.)

4. Chemgenes' “degradation” argument is meritless.

Chemgenes incorrectly asserts that oligonucleotides containing 2'-fluoro-2'-deoxyribonucleotides had a “persistent problem” of degradation. (POR32-33.)

Both of Chemgenes' cited references show the opposite. Sinha (2013) does not cite any instance of degradation *actually* being a problem. Instead, it notes a *potential* for degradation under certain conditions and provides a "postulated" mechanism. (Ex. 1033¶58.) Notably, it explains that this *potential* can be *minimized* using ethanolic ammonia.³ (*Id.*) Similarly, Kawasaki noted only the *potential* for degradation, then reported *successfully* using "methanolic ammonia at room temperature," reporting analytical data and clean removal of PGs, including from guanosine. (Ex. 1033¶59.) Moreover, the '031 Patent adopts this same approach, using "methanolic ammonia for 24 hrs at room temperature" to deprotect during its syntheses involving 2'-fluoro-2'-deoxyribonucleosides. (Ex. 1033¶60.)

5. Chemgenes' deprotection rate argument are meritless.

Chemgenes asserts that Pitsch and Fan would not motivate POSAs to modify Compound x because they do not facilitate direct comparison of deprotection rates of acetyl versus isobutyryl. (POR36-40; Ex. 1033¶62.)

This is not how POSAs would have approached and used the information at hand. First, regardless of Pitsch and Fan, there was motivation to increase deprotection speeds to save time. Ex. 1033¶63.) Pitsch touts these very benefits of acetyl PGs; this *alone* would have motivated switching to acetyl, especially in light

³ Sinha (2013) is not prior art. If it demonstrates a degradation problem (it does not), then it also reflects a known workaround. (Ex. 1033¶58.)

of the known downsides of using isobutyryl. (Ex. 1033¶64.) POSAs would not have demanded comparative deprotection speed data before acting on that information. (*Id.*)

Second, the Fan data suggested to POSAs that acetyl would deprotect faster than isobutyryl. (Ex. 1033¶65.) Indeed, Dr. Hrdlicka admitted that “acetyl likely would deprotect faster than isobutyryl.” (Ex. 1035 at 137:1-4.)

Chemgenes argues that deprotection rates for nucleoside derivatives could “not have reliably transposed to a different nucleoside” or to corresponding oligonucleotides. (POR39.) But *relative* nucleoside deprotection speed was helpful information known and used to predict *relative* deprotection rates for phosphoramidites and oligonucleotides. (Ex. 1033¶66.) Schulhof exemplifies such comparison and prediction. Schulhof tested the deprotection speeds of various protecting groups on various nucleosides, concluding that the faster-deprotecting groups “should allow a gain of time in the preparation of DNA fragments...” and “exhibit correct values to expect a final removal from oligonucleotides within a few hours...”, contrasting that with the “long and drastic deprotection step” for the slower-deprotecting groups. (*Id.*)

Third, Chemgenes’ critique of the deprotection conditions used in Fan misses the mark. (Ex. 1033¶67.) Fan chose those deprotection conditions to facilitate the comparison of isobutyryl and acetyl deprotection rates. (*Id.*) POSAs

would not view those conditions as a reason to disregard the data reported in Fan.
(*Id.*)

C. POSAs would have reasonably expected success in making the claimed compound.

The expectation of success need only be reasonable, not absolute. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Chemgenes attempts to rebut Hongene’s showing of reasonable expectation of success through several assertions. All are meritless. (Ex. 1033¶69.)

1. Chemgenes’ arguments regarding Example 4 are meritless.

Chemgenes incorrectly asserts that POSAs would not have had a reasonable expectation of making the compound of Claim 2 following Example 4 because acetylation of guanosine derivatives was known not to work well. (POR44-45.)

First, Chemgenes argues that Fan reported obtaining dark reaction mixtures and unsatisfactory *yields* when trying to acetylate a guanosine derivative. (POR44-45.) But *yield* is irrelevant. Hongene need only show a reasonable expectation of success in arriving at *the claimed invention*, nothing more. *NOF Corp.*, 2021 WL 3438554 at *12 (PTAB Aug. 5, 2021). Claim 2 claims the compound, not any particular *yield*.

Nevertheless, *Fan reports successfully acetylating guanosine*, “smoothly” and “without generation of dark mixtures” using TMSCl to treat an intermediate similar to the ’031 intermediate “Compound i” (both have a silyl group

simultaneously protecting the 3' and 5' positions). (Ex. 1033¶71.) Donga also used acetylated guanosine and did not report any difficulties obtaining it. (Ex. 1003¶72.)

Second, Chemgenes incorrectly asserts that removing the 5'-O,3'-O-silyl in step iii of Example 4.d with TBAF “seriously risked” removing the acetyls. (POR45-47.) Chemgenes has not shown that TBAF would not work. Chemgenes relies only on Ober, which reported “difficulty” (not failure) deprotecting a *different* intermediate that had 5' and 3' TBDMS, which, as demonstrated in Nelson (1999), is harder to remove than siloxane. (Ex. 1003¶73.) Even so, *Ober successfully overcame its difficulty* by using a different deprotection complex. (*Id.*) Logically, Ober’s *actual success* cannot undermine an expectation of success. (*Id.*)

Third, citing no literature support,⁴ Chemgenes speculates that the lower solubility of acetylated intermediate (versus isobutyrylated intermediate) “could have negatively affected purification and caused the synthesis to fail,” and implies that acetylated guanosine derivatives are “not functionally soluble.” (POR47-48.) There is no reason to expect that removing two carbon atoms from a large nucleoside monomer (going from isobutyryl to acetyl) would have a solubility effect profound enough to prevent the molecule from reacting in subsequent

⁴ The Baran testimony Chemgenes cites merely notes that acetyl is more polar than isobutyryl, not that acetylated guanosine is “not functionally soluble.” (Ex. 2009 at 176:4-6.)

chemistry. (Ex. 1033¶74.) And indeed, Chemgenes' speculation is refuted by literature reporting using acetyl protected nucleosides, including Pitsch, Donga, and Reddy, *none* of which mention solubility-induced reactivity challenges. (*Id.*) Finally, the subsequent steps in Example 4 use highly polar reagents (THF, Dioxane, MeOH/H₂O, pyridine) that POSAs would not expect to present solubility issues. (*Id.*)

Fourth, Chemgenes incorrectly argues that using sodium hydroxide (NaOH) in Example 4-d, step v., would cleave the 2'-acetyl and/or the N2-acetyl, causing the synthesis to fail. (POR49-50.) But Pitsch used NaOH at the analogous step in its synthesis, obtaining a 77% yield, and did not report any problems. (Ex. 1033¶75.) This alone refutes Chemgenes' argument.

The Buchi data cited by Chemgenes (POR50) shows only *partial* de-acetylation of deoxyguanosine-5'-phosphates in NaOH. (Ex. 1033¶76.) After two hours in NaOH (the same duration used in Example 4), only 18% had been de-acetylated. (*Id.*) This is not failure, but rather confirmation of a good 82% yield. (*Id.*) POSAs would simply account for yield and proceed with the synthesis, not abandon it. (*Id.*)

2. Chemgenes' arguments regarding Sivets are meritless.

First, there is no support for Chemgenes' incorrect argument that standard methods used to convert 2'-deoxyguanosine to phosphoramidite would not work to

convert Sivets Compound 15 (a 2'-F-guanosine) to phosphoramidite, because the presence of 2'-F supposedly would lead to different "reactivities." (POR52-54.) The only literature Chemgenes cites (Guschlbauer) does not compare reactivities of 2'-fluoro-2'-deoxyguanosine and 2'-deoxyguanosine, let alone do so using reagents involved in converting nucleosides to phosphoramidites. (Ex. 1033¶82.)

As Dr. Baran explained in his deposition, 2'-fluoro-guanosine and 2'-deoxyguanosine would react similarly, because like hydrogen, fluorine is a small atom, does not require any PG chemistry, and is minimally disruptive to the other parts of the molecule. (Ex. 1003¶78.) This is corroborated by Zhu, which shows that the 2'-substituent had little or no effect on reactivities. (Ex. 1033¶¶81-83.)

Second, Chemgenes repeats its solubility arguments regarding acetylation here. (POR52-53.) As explained above, these are meritless. (*Supra*, Section VII.B.2.)

Third, Chemgenes incorrectly argues that the protocols of Pitsch, Pitsch #2, and Example 4-d from the '031 Patent do "not make sense to cite" because they do not teach installation of PGs on 2'-deoxyguanosine or 2'-fluoro-2'-deoxyguanosine. (POR53-54.) But POSAs would have expected the installation of PGs on 2'-deoxy- and 2'-F-monomers to be *easier* than on the more complicated monomers protected in Pitsch, Pitsch #2, and the '031 Patent, because the former do not have a reactive oxygen-bound substituent at the 2' position. (Ex. 1033¶84.)

Fourth, Chemgenes incorrectly argues that Pitsch has a “flawed protocol” that uses an amount of NaOH insufficient to remove all the O-acetyl groups. (POR54.) But Pitsch *succeeded* in making the acetylated guanosine. This alone refutes Chemgenes’ argument. (Ex. 1033¶85.)

Indeed, NaOH can work *catalytically* (without the need for molar equivalence), because O-acetyl groups are esters and the use of catalytic hydroxide in ester hydrolysis was well-known. (*Id.*) Even so, simply using more NaOH would have been a trivial adjustment necessarily suggested by the supposed “flaw,” and even absent such adjustment, the reaction would yield *some* intermediate, which could be converted to the phosphoramidite. (*Id.*)

D. Chemgenes’ secondary considerations arguments are meritless.

First, Chemgenes’ secondary considerations arguments are entitled to little or no weight, because they rely on the ’885 applicants’ self-serving characterizations, not independent commentary. *NOF Corp.*, 2021 WL 3438554 at *15-16. Although the ’885 Patent refers to work by others, none of it identifies the purported “need” or “failures” advanced by Chemgenes. (Ex. 1033¶87.) The ’885 Patent characterizes two presentations, but does not provide the reaction details, and Chemgenes did not provide copies of the presentations. (*Id.*)

Second, contrary to Chemgenes’ argument, Sinha (2013) does not “corroborate” the existence of the supposed “need” or “unexpected result.”

(POR57, 59-60; Ex. 1033¶88.) It was published in 2013, years after the '885 priority date. If it corroborates the existence of the “need,” it also proves that the '885 inventors did not fulfill it. (Ex. 1033¶88.) Regardless, as noted above, Sinha (2013) and Kawaski each show how to *avoid* degradation of oligonucleotides containing 2'-fluoro-2'-deoxyribonucleotides by using milder deprotection conditions. (*Id.*; *supra* section VII.B.4.)

Third, Chemgenes argues that their results were unexpected because they solved a supposed purity/degradation “challenge” associated with incorporation of 2'-F-2'-deoxy-monomers into oligonucleotides. (POR58-60.) As discussed above, there was no such “challenge.” (*Supra* Section VII.B.4; Ex. 1033¶¶88-89.)

Fourth, Chemgenes incorrectly suggests that their result was unexpected because the prior art avoided degradation by changing the deprotection conditions, whereas Chemgenes changed the PG while still using methylamine, which Chemgenes asserts was problematic according to Sinha (2013). (POR59-60.) But first, Sinha is not prior art, did not establish that methylamine was a problem. (Ex. 1033¶91.) And second, deprotection conditions and PGs go hand-in-hand. (Ex. 1033¶91.) It was known that (a) mild and shorter base deprotection was preferred when synthesizing RNA, (b) using labile protecting groups facilitates RNA synthesis and allows incorporation of modified and base sensitive nucleosides, and (c) acetyl PG was useful in making RNA oligonucleotides because it permitted

rapid deprotection under mild conditions. (*Id.*) POSAs looking to make oligonucleotides containing 2'-F-monomers would naturally have used an acetyl PG along with the mild, short deprotection conditions it facilitated. (*Id.*)

Fifth, Chemgenes' result of obtaining "high quality, full length RNA," is not commensurate in scope with the claimed invention. *Daikin Indus., Ltd. v. Chemours Co. FC, LLC*, 846 Fed. Appx. 907, 914 (Fed. Cir. 2021). Claim 2 claims phosphoramidites *per se*, not oligonucleotides, RNA, synthetic steps, or any quality or length of RNA. (Ex. 1033¶92.)

Finally, Chemgenes has not shown that anyone tried but failed to make the claimed phosphoramidite. (Ex. 1033¶93.)

VIII. GROUND III

A. Chemgenes' motivation arguments are meritless.

POSAs would have been motivated by the disclosure of Compound 5 to make the corresponding D-configured guanosine homolog of Claim 2.

Chemgenes' incorrectly argues that Compound 5 and the compound of Claim 2 "would have had to have been prepared completely differently." (POR63.) POSAs would use the same procedures, simply using D-guanosine as starting material instead of L-cytosine. (Ex. 1033¶97.)

Chemgenes' argues that the two compounds "would have reacted completely differently during SPOS..." (POR63-64.) This is vague, baseless, and incorrect.

(Ex. 1033¶98.) If Chemgenes is arguing that they would react differently during protection/deprotection, that is incorrect. (*Id.*) The PG is the same in both, and protection/deprotection conditions for cytosine and guanosine are often identical, as exemplified in Iyer. (*Id.*) If Chemgenes is arguing that they would react differently because of their different stereochemistry, that is incorrect.

Enantiomers react identically in achiral environments. (Ex. 1033¶99.)

Chemgenes' incorrectly suggests that the structural differences between Compound 5 and Claim 2 demonstrates non-obviousness of Claim 2. (POR61-64.) But the two are closely structurally related. (Ex. 1033¶100.) Both are phosphoramidite building blocks for SPOS that are identical except for the nucleobase they carry and their stereochemistry. Motivation to create homologs can be provided by structural relationships. *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995). Thus, POSAs encountering the cytosine phosphoramidite (Compound 5) would have been immediately motivated to make its guanosine homolog (Claim 2), so that both nucleosides could be incorporated into an oligonucleotide, which typically requires all four nucleobases. (Ex. 1033¶100.) The stereochemical difference would not change this. As detailed below, both enantiomers of any given phosphoramidite were known to be potentially useful in certain applications, as explained in the '991 Patent itself.

Chemgenes incorrectly argues that Hongene provided no reason to select Compound 5. (POR64.) But as explained above, 2'-fluoro-substituted oligonucleotides were famously useful, and so was the utility of Compound 5 for synthesizing such oligonucleotides. This alone was sufficient reason to select it and consider making and using a guanosine version of it for use in SPOS. (Ex. 1033¶101.) Further, the '991 Patent highlights Compound 5 by describing its synthesis at length in Example 6 and illustrating that synthesis in Figure 16. (Ex. 1033¶102.)

Chemgenes incorrectly argues that the '991 Patent discloses a preference for 2'-fluoro-modified *pyrimidines* over *purines*. (POR65-67.) Chemgenes misinterprets the cited passage, which is *silent* as to purines. At most, it conveys a preference that the pyrimidines *in the nucleic acids being made* be 2'-F-modified. (Ex. 1033¶104.)

Chemgenes incorrectly argues that the '991 Patent would have discouraged POSAs from making the claimed compound because it “is directed to L-configured nucleic acids, not D-configured phosphoramidites” and “teaches instability of D-configured nucleic acids...” (POR66.) But the '991 Patent expressly contemplates (a) using *either or both* D-configured or L-configured nucleotides, and (b) that nucleic acids can be wholly D-configured, wholly L-configured, or partially D-,

partially L, depending on the desired function. (Ex. 1033¶105.) For example, the '991 Patent states:

- “The nucleic acids according to the present invention can either be D nucleic acids or L nucleic acids.”
- “[P]arts of these longer nucleic acids can be either a D nucleic acid or an L nucleic acid[, and such parts] can have a function, [such as] immobilizing, cross-linking, proof or amplification.”

(*Id.*) Thus, the '991 Patent would have motivated POSAs to develop *both* D-configured and L-configured phosphoramidites. (*Id.*) The '991 Patent also discusses ways to improve stability of D-configured nucleic acids. (Ex. 1003¶106.)

B. Expectation of success

Citing no authority, Chemgenes implies that Hongene failed to provide evidence of a reasonable expectation of success that is “based on the '991 Patent or Compound 5.” (POR67.) Ground II addresses the *same compound* as Ground III, and Hongene provided ample evidence of a reasonable expectation of success in making that compound. (Ex. 1033¶107-09.) Nothing more is required.

C. Secondary considerations

Chemgenes relies on the same meritless arguments as it does for Ground II. Hongene's response is above. (*Supra* Section VII.D.)

IX. GROUND IV

To the extent Chemgenes relies on its arguments regarding Claim 2 (POR69), as explained above, those arguments are meritless.

Chemgenes also asserts that Compound 5c in Scaringe is “different from the molecules covered by Claim 3 and the various molecules disclosed in the ’031 Patent, Pitsch, and Fan...” and does not disclose deprotection rates. (POR70.) Chemgenes does not explain *why* that leads to lack of motivation or reasonable expectation of success. (POR70.) To the extent this constitutes a barebones reprise of analogous arguments offered in response to Ground II, as explained above, those arguments are meritless. (*Supra* Section VII.)

Scaringe shows how to convert nucleosides to their corresponding phosphoramidites or succinylated derivatives and attach a LCAA-CPG. (Ex. 1033¶113.) This worked for Scaringe with the larger 2’-OTBDMS present, so it would be expected to work better with the 2’-F-substituted species, because fluorine is smaller, providing less steric hindrance, rendering the 3’-OH site more reactive. (*Id.*) And as explained above, the nucleobase PG would not affect the reactivity of the chemically-distant ribose-OH site. (*Supra* Section VII.B.3.)

Finally it does not matter whether Scaringe itself discusses deprotection rates. As discussed above, the ’031 Patent, Pitsch, and Fan provide that information. (Ex. 1033¶114.)

X. GROUND V

A. Chemgenes' arguments against selecting Compound 5(c) are meritless.

As explained above (Section VI), the “lead compound” analysis is not appropriate here, and Chemgenes' suggestion that Hongene was required to identify a *single* “most promising” compound is erroneous. (POR73; Ex. 1033¶115.)

Regardless, ample reason existed to select Compound 5(c). Scaringe discloses that it can be attached to LCAA-CPG to prepare a solid support for SPOS. This alone was reason sufficient to select Compound 5(c). (Ex. 1033¶116.)

Chemgenes incorrectly argues that the Scaringe did not use Compound 5(c) to attach guanosine to the solid support. (POR73-74.) But Scaringe *did* that, reporting:

Syntheses were conducted...using derivatized solid supports. These supports were prepared by the coupling of compounds **5a-d** to LCAA-CPG. Other reagents and details are described in the experimental section.

(Ex. 1033¶117.) Scaringe also provides data from that synthesis:

Derivatization of Controlled Pore Glass Supports

1000 Å LCAA-CPG (CPG Inc., NJ) was derivatized with compounds **5a-d** following a published protocol (23). Final nucleoside loadings of 10–15 $\mu\text{mol g}^{-1}$ were obtained.

(*Id.*)

B. Chemgenes' motivation arguments are meritless.

Chemgenes relies on its arguments made in connection with Ground 2 to argue against motivation. (POR75.) As explained above, those arguments are meritless. (*Supra* Section VII.B.)

C. Chemgenes' expectation of success arguments are meritless.

Chemgenes does not argue that POSAs would not have had a reasonable expectation of success in making the compound of Claim 4. Instead, Chemgenes incorrectly asserts that Hongene provided no basis to establish a reasonable expectation of success for Claim 4. (POR76.) But Hongene provided those bases in connection with Claim 3. (Ex. 1033¶¶123-24.)

Respectfully submitted,
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Dated: January 19, 2024

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CERTIFICATE OF COMPLIANCE

I, the undersigned, hereby certify that the above Petitioner's Reply to Patent Owner Response complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a)(1), this Reply, including footnotes, contains 5,595 words as counted by the word count function of Microsoft Word.

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CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that a copy of the above Petitioner's Reply to Patent Owner Response, along with all exhibits supporting and filed with the Motion, were served on January 19, 2024 via electronic mail to counsel of record for Patent Owner ChemGenes Corporation at the following addresses:

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