

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 OPPOSITION TO MOTION TO AMEND CLAIMS
UNDER 37 C.F.R. § 42.121**

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<i>Pfaff v. Wells Elecs., Inc.</i> , 525 U.S. 55 (1998).....	14

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37 C.F.R. § 42.12	1
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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 – A New Class of Key Intermediates for 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

Exhibit No.	Title	Abbreviation
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-alkyloigoribonucleotides Synthesis and Applications in Studying RNA Splicing</u> , Nucleosides and Nucleotides (1991) 10:1-3, 25-36	Sproat (1991)

Exhibit No.	Title	Abbreviation
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	Updated 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	

Exhibit No.	Title	Abbreviation
1037	Paul Gaytán, <i>BioTechniques</i> 47:701-702 (August 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	
1041	Dimitrios Stefanidis, et al., General Base Catalysis of Ester Hydrolysis, <i>J. Am. Chem. Soc.</i> 1993, 115, 6045-6050	
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	

Petitioner Shanghai Hongene Biotech Corporation respectfully submits this brief in opposition to Patent Owner's Motion to Amend Claims Under 37 C.F.R. § 42.121.

Petitioner also submits herewith as Exhibit 1044, the Declaration of Phil S. Baran, Ph.D. in Support of Petitioner's Opposition to Patent Owner's Motion to Amend Claims Under 37 C.F.R. § 42.121.

INTRODUCTION

Patent Owner moves to substitute Claim 6 for current Claim 1 of the '885 Patent, and substitute Claim 7 for current Claim 5 of the '885 Patent. The Board should deny this motion because each substitute claim is unpatentable in view of prior art, including prior art known to and owned by Patent Owner.

ARGUMENT

A. Substitute Claim 6 is Anticipated by U.S. Patent No. 5,525,719

Substitute Claim 6 is the same as current Claim 1, except that Patent Owner has deleted "cytosine-N-acetyl" from the Markush group of nucleobases for "B." Accordingly, the Markush group of Substitute Claim 6 is "where B is selected from the group consisting of guanine-N-acetyl, adenine-N-acetyl, cytosine-N-isobutyryl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl." (Motion to Amend at Appx. A; Ex. 1044 ¶¶10-14.)

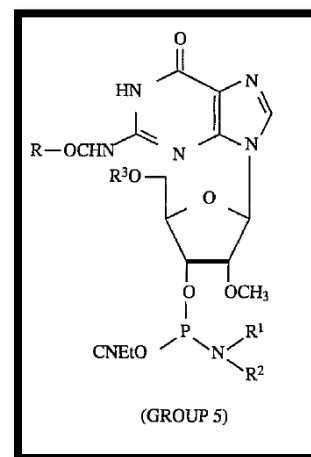
U.S. Patent No. 5,525,719 ("the '719 Patent") (Ex. 1043) discloses three compounds of Substitute Claim 6: (1) where B is guanine-N-acetyl; (2) where B is

adenine-N-acetyl; and (3) where B is cytosine-N-isobutyryl. (Ex. 1044 ¶18.) The '719 Patent issued on June 11, 1996, and is assigned to Patent Owner. (*Id.* ¶16.)

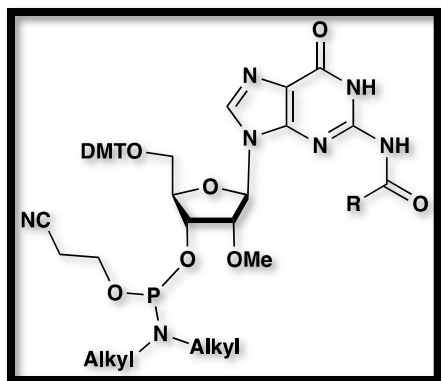
**1. The '719 Patent Discloses Substitute Claim 6
Where "B" is Guanine-N-Acetyl**

The '719 Patent discloses the same compound of Substitute Claim 6, where B is guanine-N-acetyl. This compound belongs to a group named "Group 5," directed to phosphoramidite compounds having a 2' O-methyl group and a 1' N²-protected guanine residue. (Ex. 1044 ¶¶20-21.)

The disclosed structure of Group 5 is at right. (Ex. 1043 at 6:48-65; Ex. 1044 ¶21.) This group contains four substituents: R¹ and R²; R³; and R. (Ex. 1043 at 6:48-65; Ex. 1044 ¶22.)



The '719 Patent discloses that R¹ and R² are each alkyl (N,N-dialkyl), and that R³ is DMT (5'-dimethoxytrityl). (Ex. 1044 ¶¶23-24.) Specifically, the '719 Patent refers to Group 5 as "N²-protected-2'-O-methyl-**5'-dimethoxytrityl**-guanosine cyanoethyl **N,N-dialkyl** phosphoramidite." (Ex. 1043 at 16:66-17:1 (emphasis added); Ex. 1044 ¶¶23-24.)



The '719 Patent therefore discloses that Group 5 is the N²-protected guanosine depicted at left, where the protecting group is represented by R. (Ex. 1044 ¶25.) Group 5 in the '719 Patent has the same structure of Formula 1 in Substitute

Claim 6 where Z is Oxygen, W is methyl, and X is cyanoethyl dialkyl phosphoramidite. (*Id.* ¶26.)

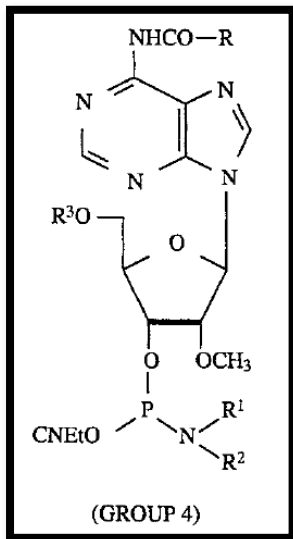
Finally, the '719 Patent discloses an acetyl group for protecting the N² position of guanine in Group 5, which is the same as in Substitute Claim 6 where “B” is guanine-N-acetyl. (Ex. 1044 ¶27.) Specifically, the '719 Patent discloses that “N²-Protection of guanosine is meant to include isobutyryl, acetyl, substituted acetyls, phenoxyacetyl, and related compounds.” (Ex. 1043 at 4:35-37; Ex. 1044 ¶27.) Acetyl is specifically identified in this list. (Ex. 1044 ¶27.)

Thus, the '719 Patent discloses, and a POSA would have at once envisaged, acetyl for the N²-protection of guanosine in Group 5 (*i.e.*, when R above is CH₃). (Ex. 1044 ¶27.) This is the same compound claimed in Substitute Claim 6 where “B” is guanine-N-acetyl. (*Id.* ¶¶28-29.)

2. The '719 Patent Discloses Substitute Claim 6 Where “B” is Adenine-N-Acetyl

The '719 Patent discloses the same compound of Substitute Claim 6, where B is adenine-N-acetyl. This compound belongs to a group named “Group 4,”

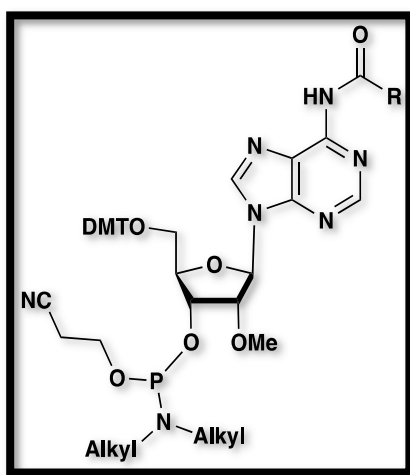
directed to phosphoramidite compounds having a 2' O-methyl group and a 1' N⁶-protected adenosine residue. (Ex. 1044 ¶¶31-32.)



The disclosed structure of Group 4 is at left. (Ex. 1043 at 6:32-45; Ex. 1044 ¶32.) This group contains four substituents: R¹ and R²; R³; and R. (Ex. 1043 at 6:32-45; Ex. 1044 ¶33.)

As with Group 5 described above, in Group 4 the '719 Patent discloses that R¹ and R² are each alkyl (N,N-dialkyl), and that R³ is DMT (5'-dimethoxytrityl). (Ex.

1044 ¶¶34-35.) Specifically, the '719 Patent refers to Group 4 as “N⁶-protected-2'-O-methyl-5'-dimethoxytrityl-adenosine cyanoethyl N,N-dialkyl-phosphoramidite.” (Ex. 1043 at 16:63-65 (emphasis added); Ex. 1044 ¶¶34-35.)



The '719 Patent therefore discloses that Group 4 is the N⁶-protected adenosine depicted at left, where the protecting group is represented by R. (Ex. 1044 ¶36.) Group 4 in the '719 Patent has the same structure of Formula 1 in Substitute Claim 6 where Z is Oxygen, W is methyl, and X is

cyanoethyl dialkyl phosphoramidite. (*Id.* ¶37.)

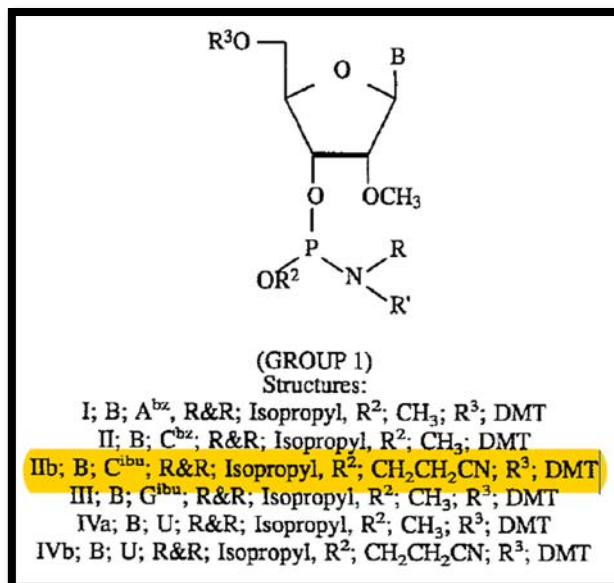
The '719 Patent also discloses an acetyl group for protecting the N⁶ position of adenine in Group 4, which is the same structure in Substitute Claim 6 where “B” is adenine-N-acetyl. (Ex. 1044 ¶38.) Specifically, the '719 Patent discloses that “‘N⁶-Protection of adenosine’ is meant to include benzoyl, substituted benzoyl, other aroyls (such as naphthoyl), acetyl, substituted acetyl, phenoxyacetyl, and related compounds.” (Ex. 1043 at 4:29-31; Ex. 1044 ¶38.) Acetyl is specifically identified in this list. (Ex. 1044 ¶38.)

Thus, the '719 Patent discloses, and a POSA would have at once envisaged, acetyl for the N⁶-protection of adenosine in Group 4 (*i.e.*, when R above is CH₃). (Ex. 1044 ¶38.) This is the same compound claimed in Substitute Claim 6 where “B” is adenine-N-acetyl. (*Id.* ¶¶39-40.)

3. The '719 Patent Discloses Substitute Claim 6 Where "B" is Cytosine-N-Isobutyryl

The '719 Patent discloses the same compound of Substitute Claim 6, where B is cytosine-N-isobutyryl. The '719 Patent describes this compound as "structure IIb" in a series of compounds named "Group 1" depicted at right. (Ex. 1043 at 5:50-65 (highlighting added); Ex. 1044 ¶42.)

Group 1 contains five substituent groups: B (referring to the base group); R and R'; R²; and R³.

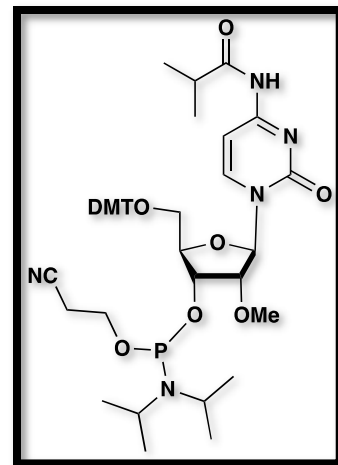


(Ex. 1043 at 5:50-65 (highlighting added); Ex. 1044 ¶43.)

The '719 Patent discloses the identity of these constituents for structure IIb. Specifically, the '719 Patent discloses that "B" is "C^{ibu}", which means cytosine-N-isobutyryl. (Ex. 1044 ¶44.) A POSA also would have understood that "R&R; Isopropyl" refers to isopropyl groups attached to the nitrogen at R and R', and that "R²; CH₂CH₂CN" refers to a 2-cyanoethyl group attached to the oxygen at R². (Id.) A POSA also would have understood that "R³; DMT" refers to a dimethoxytrityl protecting group (DMT) bound to the oxygen at R³. (Id.)

Thus, a POSA would have understood that the '719 patent discloses that "structure IIb" has the structure at right. (*Id.* ¶¶45-46.) This "structure IIb" the '719 Patent is identical to Substitute Claim 6 where B is cytosine-N-isobutyryl. (Ex. 1044 ¶¶47-48.)

4. The '719 Patent is Enabling



An anticipatory prior art patent is presumed to be enabling. *Impax Labs. v. Aventis Pharms, Inc.*, 545 F.3d 1312, 1316 (Fed. Cir. 2008). Regardless of this presumption, the '719 Patent would have enabled a POSA to make, without undue experimentation, three compounds of Substitute Claim 6 (where "B" is guanine-N-acetyl, adenine-N-acetyl, and cytosine-N-isobutyryl). (Ex. 1044 ¶¶50-56.)

With respect to "guanine-N-acetyl" and "adenine-N-acetyl" in Substitute Claim 6, the '719 Patent discloses acetyl-protected guanosine and adenosine in Group 5 and 4, respectively. It further discloses that "[t]he compounds of group 4 and 5 are produced using the process disclosed for producing compounds of group II of parent patent application, Ser. No. 07/753,077," (Ex. 1043 at 3:10-12), and which "issued as U.S. Patent No. 5,214,135 on May 25, 1993, which is herein incorporated by reference." (*id.* at 1:9-12). (Ex. 1044 ¶51.)

Thus, a POSA would have understood that the compounds of group 4 and 5 of the '719 Patent could be prepared by using the process for producing the

compounds of group II in the '135 Patent. (Ex. 1047 at 4:1-17 (depicting Group II) and 5:2-6:53 (synthesis of compounds in Group II); Ex. 1044 ¶52.) A POSA would have been able to use that incorporated '135 Patent process to make two molecules of Substitute Claim 6 – where “B” is guanine-N-acetyl and adenine-N-acetyl, without much, if any, experimentation. (Ex. 1044 ¶53.)

With respect to “cytosine-N-isobutyryl” in Substitute Claim 6, the '719 Patent discloses that structure IIb is part of Group 1. The '719 Patent includes a section named “[p]rocedure for the preparation of 2' and 3'-phosphoramidites [with] purity greater than 99.54 (groups 1-2, and 7)” that discloses a synthesis scheme for compounds in Group 1. (Ex. 1043 at 4:56-5:48; Ex. 1044 ¶54.) A POSA would have been able to follow this process to make the molecule of Substitute Claim 6 – where “B” is cytosine-N-isobutyryl, without much, if any, experimentation. (Ex. 1044 ¶55.)

Indeed, a POSA would have been able to make all three compounds above without undue experimentation based on a general knowledge of synthetic organic chemistry because the '719 Patent discloses that its compounds “demonstrate the generality of the synthetic processes.” (Ex. 1043 at 15:54-57; Ex. 1044 ¶¶53-54.)

B. Substitute Claim 6 is Anticipated by U.S. Patent No. 5,606,049

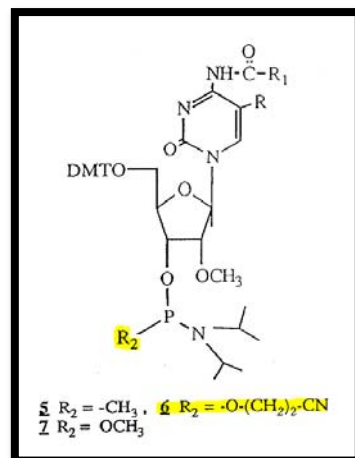
U.S. Patent No. 5,606,049 (“the ‘049 Patent”) (Ex. 1045) issued on February 25, 1997. As described below, the ‘049 Patent anticipates Substitute Claim 6 where B is (1) cytosine-N-isobutyryl and (2) 5-methyl cytosine-N-isobutyryl.

1. The ‘049 Patent Discloses Substitute Claim 6 Where “B” is Cytosine-N-Isobutyryl

The ‘049 Patent discloses the same compound of Substitute Claim 6, where B is cytosine-N-isobutyryl. The ‘049 Patent describes this compound in Figure 2, below. (Ex. 1045 at Fig. 2 (highlighting added); Ex. 1044 ¶61.)

This structure is directed to a phosphoramidite having a 2’ O-methyl group and a 1’ N-protected cytosine residue. It contains three substituents: R_2 ; R_1 ; and R. (Ex. 1045 at Fig. 2; Ex. 1044 ¶62.)

The ‘049 Patent discloses that R_2 is cyanoethyl (-O-(CH₂)₂-CN) in compound 6 in Figure 2, as recited



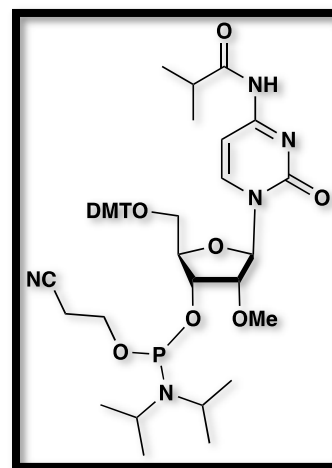
at the X position in Substitute Claim 6, as recited at the X position in Substitute Claim 6. (Ex. 1045 at Fig. 2; Ex. 1044 ¶63.)

The ‘049 Patent discloses that R_1 includes an isobutyryl protecting group on the cytosine group. (Ex. 1044 ¶64.) The ‘049 Patent discloses that R_1 is “alkyl of about 1 to 6 carbon atoms”. (Ex. 1045 at 1:64.) A POSA would have understood that this alkyl group includes the three-carbon isopropyl alkyl group, CH(CH₃)₂,

which would have resulted in an isobutyryl protecting group when attached at R₁ in Figure 2. (Ex. 1044 ¶64.) Furthermore, the '049 Patent describes Figure 2 as “depict[ing] the synthesis of nucleoside monomers from N⁴-isobutyryl-2'-O-methylcytidine.” (Ex. 1045 at 5:13-14 (emphasis added); *id.* at 2:50-53.) A POSA would have understood that “N⁴-isobutyryl” refers to an isobutyryl protecting group attached at the 4 position of cytosine. (Ex. 1044 ¶64.)

The '049 Patent discloses that R includes hydrogen. (Ex. 1044 ¶65.) The '049 patent discloses that “R is hydrogen, fluorine or alkyl of 1 to 4 carbon atoms” at this position. (Ex. 1045 at 1:48-65; *id.* at claims 1 and 2.) The '049 Patent further discloses that it is “directed to certain novel N⁴-alkanoyl 2'-O-methyl cytidine derivatives, especially N⁴-isobutyryl-2'-O-methyl cytidine (**i.e., where R is hydrogen**).” (Ex. 1045 at 2:39-42 (emphasis added); Ex. 1044 ¶65.)

Thus, the '049 Patent discloses, and a POSA would have at once envisaged, the compound at right from Figure 2 of the '049 Patent. (Ex. 1044 ¶66.) The molecule claimed in Substitute Claim 6 where “B” is cytosine-N-isobutyryl and the isobutyryl-protected compound in Figure 2 of the '049 Patent where R is hydrogen (right) are identical. (*Id.* ¶¶67-68.)

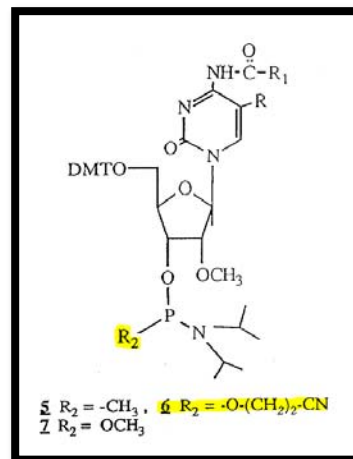


2. The '049 Patent Discloses Substitute Claim 6 Where “B” is 5-Methyl Cytosine-N-Isobutyryl

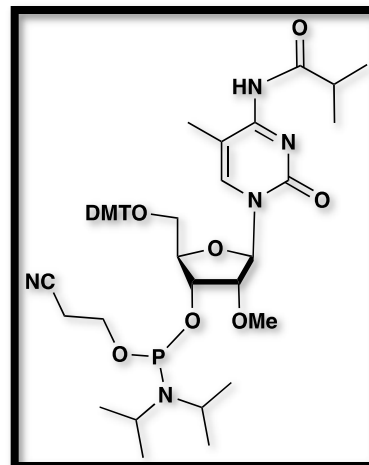
The only difference between “cytosine-N-isobutyryl” and “5-methyl cytosine-N-isobutyryl” in Substitute Claim 6 is that the latter has a methyl (CH₃) group at the 5 position of the cytosine ring. (Ex. 1044 ¶70.)

Based on Figure 2 again (right), the '049 Patent also discloses the same compound of Substitute Claim 6, where B is 5-methyl cytosine-N-isobutyryl. (Ex. 1045 at Fig. 2 (highlighting added); Ex. 1044 ¶71.)

In addition to disclosing cytosine-N-isobutyryl (where R is hydrogen) described above, Figure 2 also discloses 5-methyl cytosine-N-isobutyryl (where R is CH₃). (Ex. 1044 ¶72.) Specifically, the '049 Patent states that “R is hydrogen, fluorine or alkyl of 1 to 4 carbon atoms” at this position. (Ex. 1045 at 1:48-65; Ex. 1044 ¶72.) A POSA would have understood that an alkyl group of 1 carbon atom at this position would be a methyl (CH₃) group. (Ex. 1044 ¶72.)



Thus, the '049 Patent discloses, and a POSA would have at once envisaged, the compound at right from Figure 2 of the '049 Patent. (Ex. 1044 ¶¶73.) The molecule claimed in Substitute Claim 6 where “B” is 5-methyl cytosine-N-isobutyryl and the isobutyryl-protected compound in Figure 2 of the '049 Patent where R is methyl (right) are identical. (Ex. 1044 ¶¶74-75.)



3. The '049 Patent is Enabling

Regardless of the presumption of enablement, the '049 Patent would have enabled a POSA to make and use the molecules claimed in Substitute Claim 6 (where “B” is cytosine-N-isobutyryl and 5-methyl cytosine-N-isobutyryl) as of its priority date without undue experimentation. (Ex. 1044 ¶¶77-81.)

With respect to “cytosine-N-isobutyryl” in Substitute Claim 6, the '049 Patent discloses a detailed synthesis for this compound, described as Compound 6 in Example 6. (Ex. 1045 at 10:59-11:2; Ex. 1044 ¶¶78.) The '049 Patent also discloses the synthesis of the precursor compounds for Example 6 in Examples 1-4. (Ex. 1045 at 8:44-10:32; Ex. 1044 ¶¶78.)

With respect to “5-methyl cytosine-N-isobutyryl” in Substitute Claim 6, a POSA would have understood to follow the same Examples 1-4 and 6 as in the

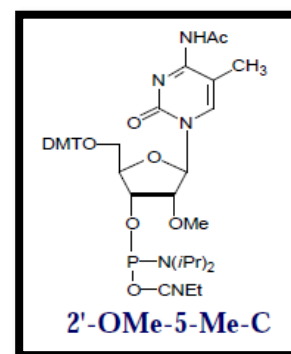
'049 Patent, except replacing the starting cytosine material with 5-methyl cytosine material. (Ex. 1045 at 8:44-10:32, 10:59-11:2; Ex. 1044 ¶79.)

Based on these disclosures and a general knowledge of synthetic organic chemistry, a POSA would not have had to engage in much, if any, experimentation to make the molecules claimed in Substitute Claim 6 (where "B" is cytosine-N-isobutyryl and 5-methyl cytosine-N-isobutyryl). (Ex. 1044 ¶80.)

C. Substitute Claim 6 is Anticipated by the Glen Report

Substitute Claim 6 is anticipated by Vol. 8, No. 1 of the Glen Report, published by the Glen Research Corporation ("Glen Report") (Ex. 1046). The Glen Report published in June 1995, over ten years before the priority date of the '885 Patent. (Ex. 1046 at 1; Ex. 1001 at Cover; Ex. 1044 ¶¶83-84.)

The Glen Report anticipates Substitute Claim 6 where B is 5-methyl cytosine-N-acetyl. (Ex. 1044 ¶85.) The Glen Report describes this compound as "2'-OMe-5-Me-C" and discloses its structure, at right. (Ex. 1046 at 6; Ex. 1044 ¶¶87-88.) The Glen Report discloses that this compound is



"the 5-methyl analogue of protected 2'-OMe-Cytidine which also has acetyl protection and is compatible with UltraFAST deprotection." (Ex. 1046 at 6; Ex. 1044 ¶89.) This is the same structure of Formula 1 in Substitute Claim 6 where Z

is Oxygen, W is methyl, X is cyanoethyl dialkyl phosphoramidite, and B is 5-methyl cytosine-N-acetyl. (Ex. 1044 ¶¶90-92.)

Further, the Glen Report would have enabled a POSA to make and use the molecule claimed in Substitute Claim 6 (where “B” is 5-methyl cytosine-N-acetyl) as of its priority date without undue experimentation. (Ex. 1044 ¶¶93-95.) Based on the disclosure of the structure and a general knowledge of synthetic organic chemistry, a POSA would not have had to engage in much, if any, experimentation to make the molecule claimed in Substitute Claim 6 (where “B” is 5-methyl cytosine-N-acetyl). (Ex. 1044 ¶94.)

Finally, the Glen Report anticipates Substitute Claim 6 where B is 5-methyl cytosine-N-acetyl for the additional reason that the claimed compound was offered for sale in 1995. (Ex. 1044 ¶¶96-99.) Substitute Claim 6 is therefore invalid as anticipated under the on-sale bar, which requires that (1) the claimed invention is the subject of a commercial offer for sale more than one year before the effective filing date and (2) the claimed invention was ready for patenting. *Pfaff v. Wells Elecs., Inc.*, 525 U.S. 55, 67-68 (1998). The Glen Report discloses a commercial offer for sale of 2'-OMe-5-Me-C in 1995, along with the quantity and price of that compound. (Ex. 1046 at 6; Ex. 1044 ¶98.) Specifically, the Glen Report discloses that 2'-OMe-5-Me-C is available under catalog number 10-3160-90 in a quantity of 100 μ mole and price of \$150, and under catalog number 10-3160-02) in a

quantity of 0.25 g and price of \$360. (Ex. 1046 at 6; Ex. 1044 ¶¶98.) Nothing about this offer for sale suggests it was experimental. (Ex. 1044 ¶¶99.)

Furthermore, the Glen Report also discloses that this compound was ready for patenting because the claimed compound was reduced to practice and available for sale without restriction in 1995. (Ex. 1044 ¶¶99.)

D. Substitute Claim 6 Would Have Been Obvious in View of the '719 Patent Alone or with Pitsch

1. The '719 Patent Alone

Substitute Claim 6 of the '885 Patent (where B is **guanine-N-acetyl** and **adenine-N-acetyl**) would have been obvious in view of the '719 Patent alone. As described above, the '719 Patent discloses the compounds in Substitute Claim 6 where B is guanine-N-acetyl and adenine-N-acetyl (*i.e.*, the N-protected guanine (Group 5) and N-protected adenine (Group 4) compounds with acetyl as the protecting group). (See Sections II.A.1 and II.A.2.)

A POSA also would have been motivated to make these compounds with a reasonable expectation of success based on the '719 Patent. (Ex. 1044 ¶¶104.) The '719 Patent lists acetyl as a suitable protecting group for both N-protected guanine (Group 5) and N-protected adenine (Group 4). (Ex. 1043 at 4:29-37; Ex. 1044 ¶¶104.) A POSA therefore would have been motivated to use acetyl to protect the guanine (Group 5) and adenine (Group 4) compounds in the '719 Patent. (Ex. 1044 ¶¶104.) A POSA also would have had a reasonable expectation of success in

making these compounds because the synthesis of protected phosphoramidites such as those claimed was a routine procedure for a POSA. (Ex. 1044 ¶104.)

Furthermore, a POSA would have had a reasonable expectation of success in making these compounds based on the '719 Patent. As described above, the '719 Patent's disclosure of these compounds is enabling. (See Section II.A.4.) That same disclosure would have given a POSA a reasonable expectation of success. (Ex. 1044 ¶105.)

2. The '719 Patent and Pitsch

Further, substitute Claim 6 of the '885 Patent (where B is **guanine-N-acetyl** and **adenine-N-acetyl**) also would have been obvious in view of the '719 Patent and Pitsch. As described above, a POSA would have been motivated to make the compounds in Substitute Claim 6 where B is guanine-N-acetyl and adenine-N-acetyl based on the '719 Patent alone.

Pitsch (Ex. 1018) would have strengthened this motivation. (Ex. 1044 ¶110.) Pitsch discloses acetyl-protecting groups on both adenosine and guanosine phosphoramidites. (Ex. 1018 at 3775; Ex. 1044 ¶110.) Furthermore, Pitsch explains that the acetyl protecting group was chosen for its fast deprotection speed, concluding that "the Ac [acetyl] group, in combination with MeNH₂, is indeed suited for a labile universal nucleobase protection." (Ex. 1018 at 3778; Ex. 1044 ¶110; Ex. 1003 at ¶ 119.) A POSA therefore would have been motivated to use

acetyl from the suitable protecting groups that the '719 Patent discloses for N-protected guanine (Group 5) and N-protected adenine (Group 4). (Ex. 1044 ¶110.)

Furthermore, a POSA would have had a reasonable expectation of success in making these compounds in view of Pitsch. (Ex. 1044 ¶111.) Pitsch would have provided a POSA with more than a reasonable expectation of success, as it not only discloses acetyl protection of both guanine and adenine but also concludes that acetyl in combination with MeNH₂ is suitable for “universal nucleobase protection.” (Ex. 1018 at 3778; Ex. 1044 ¶111.) Furthermore, the acetylation of these compounds would have been routine. (Ex. 1044 ¶111.)

E. Substitute Claim 6 Would Have Been Obvious in View of the '049 Patent Alone or with Pitsch

1. The '049 Patent Alone

Substitute Claim 6 of the '885 Patent (where B is **cytosine-N-isobutyryl** and **5-methyl cytosine-N-isobutyryl**) would have been obvious in view of the '049 Patent alone. As described above, the '049 Patent discloses the compounds in Substitute Claim 6 where B is cytosine-N-isobutyryl and 5-methyl cytosine-N-isobutyryl (*i.e.*, the isobutyryl-protected compounds in Figure 2 of the '049 Patent where R is hydrogen and methyl, respectively). (See Sections II.B.1 and II.B.2.)

A POSA also would have been motivated to make these compounds with a reasonable expectation of success based on the '049 Patent. (Ex. 1044 ¶115.) For example, the '049 Patent discloses both hydrogen and methyl (CH₃) as suitable

options for the R group at the 5-position of cytosine. Specifically, the '049 patent discloses that the R group at the 5-position of cytosine can be “hydrogen, fluorine or alkyl of 1 to 4 carbon atoms.” (Ex. 1045 at 1:48-65; Ex. 1044 ¶115.) A POSA would have understood that methyl (CH₃) is the simplest member of the “alkyl of 1 to 4 carbon atoms” group. (Ex. 1044 ¶115.)

Furthermore, a POSA would have had a reasonable expectation of success in making these compounds based on the '049 Patent. As described above, the '049 Patent's disclosure of these compounds is enabling. (See Section II.B.3.) That same disclosure would have given a POSA a reasonable expectation of success. (Ex. 1044 ¶116.)

2. The '049 Patent and Pitsch

Substitute Claim 6 of the '885 Patent (where B is **5-methyl cytosine-N-acetyl**) would have been obvious in view of the '049 Patent and Pitsch. As described above, a POSA would have been motivated to make the compound in Substitute Claim 6 where B is 5-methyl cytosine-N-isobutyryl.

A POSA would have been motivated to make the compound of Substitute Claim 6 where B is 5-methyl cytosine-N-acetyl with a reasonable expectation of success in view of the '049 Patent with Pitsch. (Ex. 1044 ¶120.) As described above, Pitsch discloses that an acetyl protecting group was chosen for its fast deprotection speed, concluding that acetyl in combination with MeNH₂ is suitable

for “universal nucleobase protection.” (Ex. 1018 at 3778; Ex. 1044 ¶121.) This disclosure also includes acetyl-protected cytosine. (Ex. 1018 at 3775; Ex. 1044 ¶121.) Thus, Pitsch would have motivated a POSA to make the compound of Substitute Claim 6 where B is 5-methyl cytosine-N-acetyl with a reasonable expectation of success. (Ex. 1044 ¶122.)

F. Substitute Claim 7 Would Have Been Obvious in View of (1) the '719 Patent and Scaringe or (2) the '719 Patent, Pitsch, and Scaringe

The respective chemical structures in Substitute Claims 6 and 7 of the '885 Patent differ only with respect to (1) the omission of “cytosine-N-isobutyryl” as an option for B in Substitute Claim 7 and (2) the moiety bound to the 3'-O position of the sugar ring. (Ex. 1044 ¶131.) In Substitute Claim 6, the 3'-O “X” is cyanoethyl dialkyl phosphoramidite, whereas in Substitute Claim 7, the 3'-O “Z” can be a succinyl-NH group, which is capable of being attached to a solid support with a one of the enumerated spacers. (*Id.*)

As explained above, the '719 Patent anticipates Substitute Claim 6 and renders that claim obvious over the '719 Patent alone or with Pitsch. (*See* Sections II.A and II.D.) For those same reasons and the reasons explained in this section, Substitute Claim 7 of the '885 Patent would have been obvious in view of either (1) the '719 Patent and Scaringe or (2) the '719 Patent, Pitsch, and Scaringe.

1. The '719 Patent and Scaringe

Substitute Claim 7 of the '885 Patent (where B is **guanine-N-acetyl** and **adenine-N-acetyl**) would have been obvious in view of the '719 Patent and Scaringe. As explained above with respect to Substitute Claim 6 of the '885 Patent, the '719 Patent anticipates and renders obvious the compounds in Substitute Claim 6 where B is guanine-N-acetyl and adenine-N-acetyl. (See Sections II.A.1, II.A.2, and II.D.1.)

The only difference between these two compounds and the compounds in Substitute Claim 7 of the '885 Patent is the identity of the moiety bound to the 3'-O position of the sugar ring. (Ex. 1044 ¶135.) The two compounds in the '719 Patent contain a phosphoramidite at this position; Substitute Claim 7 recites a group of linkers that includes a succinyl group, which in turn is capable of being attached to a solid support with a spacer group. (*Id.*)

A POSA would have been motivated to substitute the phosphoramidite in these two compounds in the '719 Patent and replace it with a succinyl group, which in turn is capable of being attached to a solid support with a spacer selected from the group in Substitute Claim 7. (Ex. 1044 ¶¶136-39.)

It was well known to a POSA that in solid phase oligonucleotide synthesis using phosphoramidite chemistry, the side group bound to the O at the 3' position of a nucleoside (i.e., "X" in Substitute Claim 6 and "Z" in Substitute Claim 7)

could be either a phosphoramidite (as recited in Substitute Claim 6) or a succinate (as recited in Substitute Claim 7). (Ex. 1044 ¶137.)

It was also well known to a POSA that the choice between these options (i.e., phosphoramidite or succinate) depended on the desired location of the nucleoside during synthesis. (Ex. 1044 ¶138.) A POSA would have understood that, in general, a nucleoside attached to a phosphoramidite could be added at any position during oligonucleotide synthesis except as the 3'-terminal nucleoside residue, while a nucleoside attached to a succinate could be added at this position. (Ex. 1044 ¶138.) In other words, a POSA would have understood that a phosphoramidite could represent any building block along the oligonucleotide except the first one, which was most commonly a succinate. (Ex. 1044 ¶138.)

A POSA would have had a reasonable expectation of success in making the change described above to both of these compounds in the '719 Patent. (Ex. 1044 ¶140.) A POSA would have known that succinate was “very popular because of low cost and ease of incorporation,” and would have reasonable expected the same ease here. (Pon (2000) (Ex. 2031) at 11; Ex. 1044 ¶140.) A POSA also would have known how to switch between a phosphoramidite group and a succinate group based on the prior art. (Ex. 1044 ¶140.)

As one of many examples, Scaringe (Ex. 1022) explains how to convert each of the four canonical RNA nucleosides – including an N2-isobutyryl, 2'-O-

TBDMS protected guanosine – to either its corresponding phosphoramidite or succinylated derivative. (Ex. 1022, 5434 & 5440; Ex. 1044 ¶141.) Scaringe further explains that the succinylated derivatives are coupled to LCAA-CPG to prepare the solid supports for SPOS. (Ex. 1044 ¶142.)

A POSA would have known that LCAA-CPG stands for “long chain alkylamine controlled pore glass,” a commonly used solid support used in solid phase oligonucleotide synthesis, in which the “long chain alkyl” functions as a spacer attaching the “amine” group (i.e., -NH-) to the “controlled pore glass,” i.e., the solid support. (Ex. 1044 ¶143.) A POSA would also have regarded a C6 alkyl as a suitable long chain alkyl spacer. (*Id.*) A C6 alkyl falls within the claimed “C1-C20 alkyl” recited in Substitute Claim 6. (*Id.*) Thus, Scaringe demonstrates that a POSA would have had a reasonable expectation of success to (a) synthesize the molecule claimed in Substitute Claim 6 of the ’885 Patent (where “B” is guanine-N-acetyl and adenine-N-acetyl), and to (b) attach that molecule to a “long chain alkylamine controlled pore glass.” (*Id.*)

2. The ’719 Patent, Pitsch, and Scaringe

Substitute Claim 7 of the ’885 Patent (where B is **guanine-N-acetyl** and **adenine-N-acetyl**) would have been obvious in view of the ’719 Patent, Pitsch, and Scaringe. As explained above with respect to Substitute Claim 6 of the ’885

Patent, the '719 Patent and Pitsch render obvious the compounds in Substitute Claim 6 where B is guanine-N-acetyl and adenine-N-acetyl. (See Section II.D.2.)

For the same reasons explained above in Section II.F.1 that Substitute Claim 7 of the '885 Patent would have been obvious in view of the '719 Patent and Scaringe, this claim would have been obvious in view of the '719 Patent, Pitsch, and Scaringe as well. (Ex. 1044 ¶147.)

G. Substitute Claim 7 Would Have Been Obvious in View of (1) the '049 Patent and Scaringe or (2) the '049 Patent, Pitsch, and Scaringe

As explained above, the '049 Patent anticipates Substitute Claim 6 and renders this claim obvious over the '049 Patent alone or with Pitsch. See Sections II.B and II.E.) For those same reasons and the reasons explained in this section, Substitute Claim 7 of the '885 Patent would have been obvious in view of either (1) the '049 Patent and Scaringe or (2) the '049 Patent, Pitsch, and Scaringe.

1. The '049 Patent and Scaringe

Substitute Claim 7 of the '885 Patent (where B is **5-methyl cytosine-N-isobutyryl**) would have been obvious in view of the '049 Patent and Scaringe. As explained above with respect to Substitute Claim 6 of the '885 Patent, the '049 Patent anticipates and renders obvious the compound in Substitute Claim 6 where B is 5-methyl cytosine-N-isobutyryl. (See Sections II.B.2 and II.E.1.)

The only difference between this compound and the compounds in Substitute Claim 7 of the '885 Patent is the identity of the moiety bound to the 3'-O position of the sugar ring. (Ex. 1044 ¶151.)

For the same reasons discussed above in Section II.F.1 with respect to the obviousness of this claim in view of the '719 Patent and Scaringe, a POSA would have been motivated to substitute the phosphoramidite on this compound of the '049 patent to a succinyl group with a reasonable expectation of success, which would result in a compound within Substitute Claim 7. (Ex. 1044 ¶152.)

2. The '049 Patent, Pitsch, and Scaringe

Substitute Claim 7 of the '885 Patent (where B is **5-methyl cytosine-N-acetyl**) would have been obvious in view of the '049 Patent, Pitsch, and Scaringe. As explained above with respect to Substitute Claim 6 of the '885 Patent, the '049 Patent and Pitsch render obvious the compound in Substitute Claim 6 where B is 5-methyl cytosine-N-acetyl. (See Section II.E.2.)

For the same reasons explained above in Section II.F.1 that Substitute Claim 7 of the '885 Patent would have been obvious in view of the '719 Patent and Scaringe, this claim would have been obvious in view of the '049 Patent, Pitsch, and Scaringe as well. (Ex. 1044 ¶ 155.)

H. Substitute Claim 7 Would Have Been Obvious in View of the Glen Report and Scaringe

Substitute Claim 7 of the '885 Patent (where B is **5-methyl cytosine-N-acetyl**) would have been obvious in view of the Glen Report and Scaringe. As explained above with respect to Substitute Claim 6 of the '885 Patent, the Glen Report anticipates the compound in Substitute Claim 6 where B is 5-methyl cytosine-N-acetyl. (See Section II.C.)

The only difference between this compound and the compounds in Substitute Claim 7 of the '885 Patent is the identity of the moiety bound to the 3'-O position of the sugar ring. (Ex. 1044 ¶159.)

For the same reasons discussed above in Section II.F.1 with respect to the obviousness of this claim in view of the '719 Patent and Scaringe, a POSA would have been motivated to substitute the phosphoramidite on this compound of the Glen Report to a succinyl group with a reasonable expectation of success, which would result in a compound within Substitute Claim 7. (Ex. 1044 ¶160.)

CONCLUSION

For these reasons, the Board should deny Patent Owner's Motion to Amend Claims Under 37 C.F.R. § 42.121.

Respectfully submitted,
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CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that a copy of the above Petitioner's Opposition to Motion to Amend claims Under 37 C.F.R. § 42.121, 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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