

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SHANGHAI HONGENE BIOTECH CORPORATION,

Petitioner,

v.

CHEMGENES CORPORATION,

Patent Owner.

IPR2023-00862
U.S. Patent No. 8,541,569

**PATENT OWNER'S MOTION TO AMEND CLAIMS
UNDER 37 C.F.R. § 42.121**

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I. INTRODUCTION

The challenged Claims of U.S. Patent No. 8,541,569 (“the ’569 Patent”) are directed to innovative compounds that facilitate efficient synthesis of high-purity RNA in the 5' → 3' direction, and convenient and efficient introduction of various modifications at the 3'-end. Independent Claims 1 and 2 encompasses a genus of compounds. This Motion to Amend proposes to narrow the scope of Claims 1 and 2 to delete species from the recited genera. Such narrowing amendments are fully supported by the ’569 Patent and are not anticipated by or rendered obvious by Petitioner’s cited prior art.

II. STATEMENT OF RELIEF REQUESTED

Patent Owner respectfully requests that the Board grant this Motion to Amend and substitute challenged Claims 1 and 2 with the claims presented in **Appendix A**.

Further, Patent Owner requests that the Board issue preliminary guidance on this Motion. *See* Notice Regarding a New Pilot Program Concerning Motion to Amend Practice and Procedures in Trial Proceedings under the America Invents Act before the Patent Trial and Appeal Board, 84 Fed. Reg. 9,497 (Mar. 15, 2019) (providing a patent owner with the option to receive preliminary guidance from the Board on its motion to amend) (“Notice”); *see also* 35 U.S.C. § 316(d) (2018); 37 C.F.R. § 42.121 (2019).

III. THE SUBSTITUTE CLAIMS SATISFY 37 C.F.R. § 42.121

Patent Owner hereby respectfully submits and requests admittance and entry of this Motion to Amend and “Substitute Claims” 33 and 34 are presented herewith under the provisions of 35 U.S.C. § 316(d) and 37 C.F.R. 42.121. Specifically, Patent Owner has submitted: (1) only a single respective Substitute Claim for each of the two challenged claims (Claims 1 and 2) that were originally issued; (2) Substitute Claims that narrow the scope of the originally issued claims, and thus meet the requirement of not enlarging the scope of the claims; (3) proposed Substitute Claims that are fully supported by the original disclosure of the patent as shown herein; and (4) amended Substitute Claims responsive to grounds of unpatentability set forth by both the Petitioner in its Petition as well as the same or very similar grounds set forth by the Board in its Decision to Institute.

A. The Number of Substitute Claims is Reasonable.

Petitioner has challenged the patentability of issued Claims 1 and 2 in the '569 Patent. Substitute Claims 33 and 34 correspond to issued Claims 1 and 2, respectively. Consequently, Patent Owner has satisfied the “presumption...that only one substitute claim would be needed to replace each challenged claim.” See 37 C.F.R. § 42.121 (a)(3).

B. The Substitute Claims Do Not Enlarge the Scope of the Claims.

Appendix A is a claim listing showing the amendments made to the originally-issued '569 Patent's claims. As shown Substitute Claim 33 retains all limitations of original independent Claim 1, but narrows the Claim by making the following amendments:

Substitute Claim 33		'569 Patent (Ex. 1001)
R¹	Removes "NR ⁷ " from the options of "intervening heteroatoms."	111:61; 112:25
R²	Removes "NR ⁷ " from the options of "intervening heteroatoms."	111:67; 112:25
R⁴	Removes "—NR ⁷ R ⁸ " and "SR ¹⁰ " from the options for R ⁴ .	112:27
R⁵	Removes "—NR ⁷ R ⁸ " and "SR ¹⁰ " from the options for R ⁵ .	113:5, 7
R⁶	Removes "H" from the options for R ⁶ .	113:9
R⁷; R⁸; R¹⁰	Removed entirely in view of narrowing of R ⁵ .	113:10-20, 24-27
Bⁿ	Removes "8-alkylaminopurine," "thymine," "5-(C ₁)alkyluracil," and " $=\text{CR}^8\text{N}(\text{C}_1\text{-C}_6)\text{alkyl}_2$; —C(=O)—NR ⁸ —(CH ₂) ₁₋₁₆ NR ⁸ C(=O)CF ₃ ; —C(=O)—(CH ₂) ₁₋₁₆ NR ⁸ C(=O)CF ₃ ; —C(=O)—NR ⁸ (CH ₂) ₁₋₁₆ NR ⁸ C(=O)-phthalimide" from the options for B ⁿ .	113:56, 57; 114:2, 14-17

As also shown in Appendix A, Substitute Claim 34 retains all limitations of original independent Claim 2, but narrows the Claim by making the following amendments:

Substitute Claim 34		'569 Patent (Ex. 1001)
R¹	Removes “NR ⁷ ” from the options of “intervening heteroatoms.”	114:67; 115:11
R²	Removes “NR ⁷ ” from the options of “intervening heteroatoms.”	115:6, 11
R⁴	Removes “—NR ⁷ R ⁸ ” and “SR ¹⁰ ” from the options for R ⁴ .	115:14
R⁵	Removes “—NR ⁷ R ⁸ ” and “SR ¹⁰ ” from the options for R ⁵ .	115:58, 60
R⁶	Removes “H” from the options for R ⁶ .	115:62
R⁷; R⁸; R¹⁰	Removed entirely in view of narrowing of R ⁵ .	115:63-116:6; 116:10-13
Bⁿ	Removes thymine, N ² -isobutyryl guanine, N ⁴ -benzoyl 5-methyl cytosine, N ⁴ -benzoyl cytosine, N ⁶ -benzoyl adenine, and uracil from the options for B ⁿ .	Additional limitation: See Appendix A at A-12.

In view of these amendments, each of Substitute Claims 33 and 34 is narrower in scope than corresponding Claims 1 and 2. *See* 37 C.F.R. § 42.121 (a)(2)(ii).

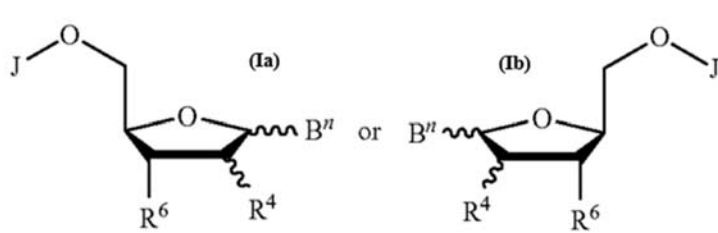
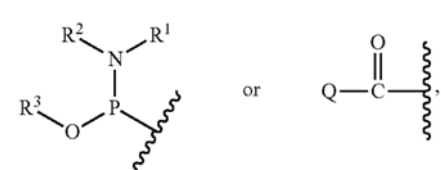
C. The Substitute Claims Are Fully Supported by the '569 Patent and the '827 Application.

The '569 Patent issued from U.S. Application No. 12/708,827 (“the '827 Application”) (Ex. 1002, 2-181), which is a continuation-in-part of PCT/US2009/005063, and claims priority to U.S. provisional Appl. No. 61/191,065 (“the '065 Provisional”) (Ex. 2002). Because Patent Owner does not currently seek the benefit of the filing date of the disclosure set forth in the earlier-filed PCT/US2009/005063 Application or in the earlier-filed '065 Provisional Application, this Motion is not required to identify support for the proposed Substitute Claims in either of those applications. *See* 37 C.F.R. § 42.121(b)(2).

Patent Owner identifies the following portions of the '827 Application that provide 35 U.S.C. § 112 support for the proposed substituted claims. As demonstrated below, a person of ordinary skill in the art (“POSA”) would have understood that the Substitute Claims are fully described by the '827 Application. *See* 37 C.F.R. §§ 42.121(a)(2)(ii), 42.121(b); Ex. 2001, ¶¶74-75, 83-84.

1. Substitute Claim 33 is Fully Supported.

Substitute Claim 33 is directed to:

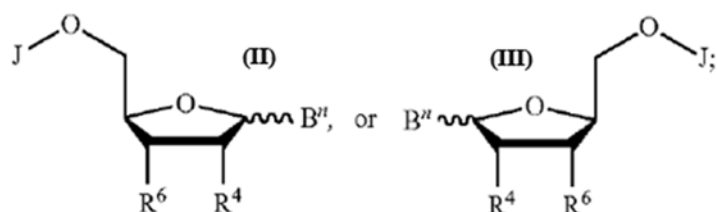
Substitute Claim 33	
A compound of Formula Ia or Ib:	
 or a salt thereof, wherein:	
J is H,  wherein  indicates where J is attached to the O atom;	
Q is a support comprised of: a) a linking group and a spacer that can be cleaved to form a hydroxy group; or b) an aliphatic chain, aromatic group, substituted or unsubstituted aromatic, a substituted or unsubstituted phenoxy, or levulinyl;	
R ¹ is a substituted or unsubstituted (C ₁ -C ₁₂)alkyl group, a substituted or unsubstituted (C ₃ -C ₂₀)cycloalkyl group, or a substituted or unsubstituted (C ₃ -C ₂₀)cycloalkyl(C ₁ -C ₁₂)alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, O and S;	
R ² is a substituted or unsubstituted (C ₁ -C ₁₂)alkyl group, a substituted or unsubstituted (C ₃ -C ₂₀)cycloalkyl group, or a substituted or unsubstituted (C ₃ -	

C₂₀)cycloalkyl(C₁-C₁₂)alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, O and S;

or R¹ and R² taken together with the nitrogen atom to which they are bound form a 4-7 membered non-aromatic heterocyclyl, wherein the heterocyclyl formed may optionally include intervening heteroatoms independently selected from NH, O and S;

R³ is a phosphate protecting group;

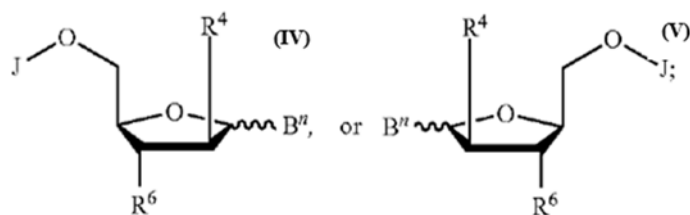
R⁴ is a -halo, —R⁵, —OR⁹, or 2'-blocking group; or when Structural Formula Ia



or Ib is:

wherein R⁴ is further

selected from O—Si(R¹¹)₃ or O—CH₂—Si(R¹¹)₃; or when Structural Formula Ia



or Ib is:

R⁴ is further selected

from —OC(=O)R¹²;

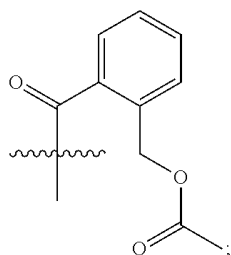
each R ⁵ is independently a substituted or unsubstituted (C ₁ -C ₁₂)alkyl group, a substituted or unsubstituted (C ₂ -C ₁₂)alkenyl group, a substituted or unsubstituted (C ₂ -C ₁₂)alkynyl group, or a substituted or unsubstituted phenyl, wherein the alkyl, alkenyl, alkynyl and the phenyl groups optionally includes intervening heteroatoms independently selected from NH, NR ⁵ , O and S; and may optionally terminate with (C ₁ -C ₄)alkylamino, di(C ₁ -C ₄)alkylamino, —OR ⁹ , (C ₁ -C ₆)alkoxy, benzyl or substituted benzyl; or —S—(C ₁ -C ₆)alkyl group;
R ⁶ is —O—Z;
each R ⁹ is independently —C(=O)—(CH ₂) ₁₋₁₆ CH ₃ ; a substituted or unsubstituted (C ₂ -C ₁₂)alkenyl group, or a substituted or unsubstituted (C ₂ -C ₁₂)alkynyl group;
each R ¹¹ is independently a substituted or unsubstituted (C ₁ -C ₁₂)alkyl group, a substituted or unsubstituted (C ₂ -C ₁₂)alkenyl group, or a substituted or unsubstituted (C ₂ -C ₁₂)alkynyl group;
each R ¹² is independently a substituted or unsubstituted (C ₁ -C ₁₂)alkyl group, a substituted or unsubstituted (C ₂ -C ₁₂)alkenyl group, or a substituted or unsubstituted (C ₂ -C ₁₂)alkynyl group, or a substituted or unsubstituted aryl group;
Z is an unsubstituted or substituted aryl group, an unsubstituted or substituted triarylmethyl group, an unsubstituted or substituted trityl group, an unsubstituted

or substituted tetrahydropyranyl group, or an unsubstituted or substituted 9-phenylxanthyl;

Bⁿ is hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group, wherein the nucleobase is selected from: N6,N6-dimethyl adenine, N-1 methyladenine, 7-deazaadenine, 7-deaza-8-azaadenine, 3-deazaadenine, ethenoadenine, isoguanine, N1-methylguanine, 7-iodo-7-deazaguanine, 7-deaza-7-iodoadenine, 7-deaza-7-iodo-6-oxopurine, 5-iodo-5-methyl-7-deazaguanine, 7-deazaguanine substituted with —C≡C(CH₂)₁₋₈-phthlamide, 7-deaza-8-azaguanine, 8-methylguanine, 8-bromoguanine, 8-aminoguanine, hypoxanthine, 6-methoxypurine, 7-deaza-6-oxopurine, 6-oxopurine, 2-aminopurine, 2,6-diaminopurine, 8-bromopurine, 8-aminopurine, 8-alkylaminopurine, N-3 methyl thymine, 5-acetoxymethylcytosine, 5-azacytosine, isocytosine, N-4(C₁-C₆)alkylcytosine, N-3(C₁-C₆)alkylcytidine, 5-propynylcytosine, 5-iodo-cytosine, 5-(C₁-C₆)alkylcytosine, 5-aryl(C₁-C₆)alkylcytosine, 5-trifluoromethylcytosine, 5-methylcytosine, ethenocytosine, cytosine and uracil substituted with —CH=CH—C(=O)NH(C₁-C₆)alkyl, cytosine and uracil substituted with —C≡C—CH₂-phthalimide, NH(C₁-C₆)alkyl, 4-thiouracil, 2-thiouracil, N³-thiobenzoyl ethyluracil, 5-propynyluracil, 5-acetoxymethyluracil, 5-fluorouracil,

5-chlorouracil, 5-bromouracil, 5-iodouracil, thiouracil, N-3-(C₁-C₆)alkyluracil, 5-(3-aminoallyl)-uracil, 5-(C₂-C₆)alkyluracil, 5-aryl(C₁-C₆)alkyluracil, 5-trifluoromethyluracil, 4-triazolyl-5-methyluracil, 2-pyridone, 2-oxo-5-methylpyrimidine, 2-oxo-4-methylthio-5-methylpyrimidine, 2-thiocarbonyl-4-oxo-5-methylpyrimidine, and 4-oxo-5-methylpyrimidine;

wherein any substitutable nitrogen atom within the nucleobase or on the exocyclic amine is optionally substituted with fluorenylmethyloxycarbonyl; —C(=O)OPh; —C(=O)(C₁-C₁₆)alkyl; —C(=O)CH₂CH₂CH=CH₂—; —C(=O)(C₁-

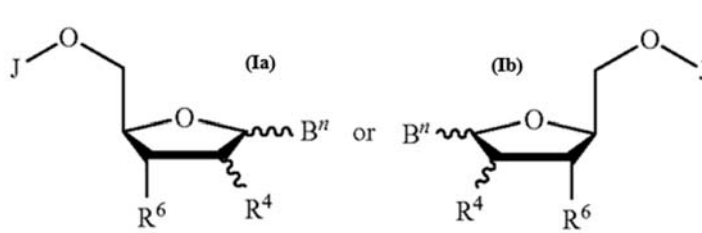
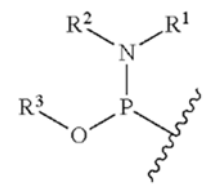


C₁₆)alkylene-C(=O)OH; —C(=O)(C₁-C₁₆)alkylene-C(=O)O(C₁-C₆)alkyl; —C(=O)—(CH₂)₁₋₁₆-phthalimide; and wherein any substitutable oxygen atom within the nucleobase is optionally substituted with —C(=O)N(C₁-C₆alkyl)₂ or —C(=O)N(phenyl)₂.

Each of these elements is recited in original Claim 1 of the '569 Patent (Ex. 1001, 111:21-114:34), and is supported by, *inter alia*, pages 3:10-7:17, 14:22-19:4, 33:6-15, 118:1-122:11 (Claim 1), 126:5-9 (Claim 5) of the '827 Application. Ex. 1002, 4:10-8:17, 15:23-20:4, 34:6-10, 119:1-123:11, 127:5-9; Ex. 2001, ¶75.

2. Substitute Claim 34 is Fully Supported.

Substitute Claim 34 is directed to:

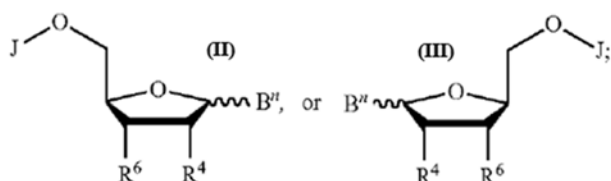
Substitute Claim 34	
A compound of Formula Ia or Ib:	
 or a salt thereof, wherein:	
	J is H or
R^1 is a substituted or unsubstituted (C₁-C₁₂)alkyl group, a substituted or unsubstituted (C₃-C₂₀)cycloalkyl group, or a substituted or unsubstituted (C₃-C₂₀)cycloalkyl(C₁-C₁₂)alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, O and S;	
R^2 is a substituted or unsubstituted (C₁-C₁₂)alkyl group, a substituted or unsubstituted (C₃-C₂₀)cycloalkyl group, or a substituted or unsubstituted (C₃-C₂₀)cycloalkyl(C₁-C₁₂)alkyl group, wherein the alkyl or cycloalkyl groups	

optionally include intervening heteroatoms independently selected from NH, O and S;

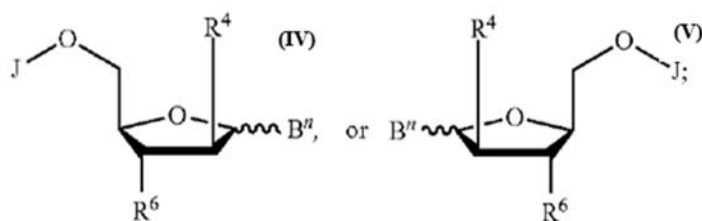
or R^1 and R^2 taken together with the nitrogen atom to which they are bound form a 4-7 membered non-aromatic heterocyclyl, wherein the heterocyclyl formed may optionally include intervening heteroatoms independently selected from NH, O and S;

R^3 is a phosphate protecting group;

R^4 is a -halo, $-R^5$, $-OR^9$, or 2'-blocking group; or when Structural Formula Ia or Ib is:



wherein R^4 is further selected from $O-Si(R^{11})_3$ or $O-CH_2-Si(R^{11})_3$; or when Structural Formula Ia or Ib is:



R^4 is further selected from $-OC(=O)R^{12}$;

each R⁵ is independently a substituted or unsubstituted (C₁-C₁₂)alkyl group, a substituted or unsubstituted (C₂-C₁₂)alkenyl group, a substituted or unsubstituted (C₂-C₁₂)alkynyl group, or a substituted or unsubstituted phenyl, wherein the alkyl, alkenyl, alkynyl and the phenyl groups optionally includes intervening heteroatoms independently selected from NH, NR⁵, O and S; and may optionally terminate with (C₁-C₄)alkylamino, di(C₁-C₄)alkylamino, —OR⁹, (C₁-C₆)alkoxy, benzyl or substituted benzyl; or —S—(C₁-C₆)alkyl group;

R⁶ is —O—Z;

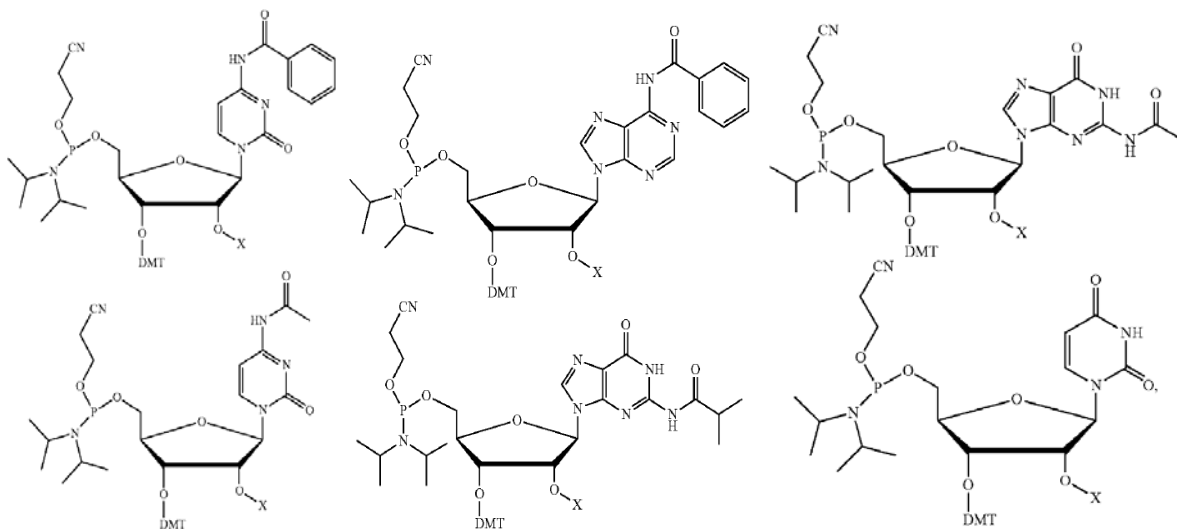
each R⁹ is independently —C(=O)—(CH₂)₁₋₁₆CH₃; a substituted or unsubstituted (C₂-C₁₂)alkenyl group, or a substituted or unsubstituted (C₂-C₁₂)alkynyl group;

each R¹¹ is independently a substituted or unsubstituted (C₁-C₁₂)alkyl group, a substituted or unsubstituted (C₂-C₁₂)alkenyl group, or a substituted or unsubstituted (C₂-C₁₂)alkynyl group; provided that if R⁴ is —O—Si(R¹¹)₃, and two R¹¹ groups are both methyl, the other is not t-butyl or if R⁴ is —O—CH₂—Si(R¹¹)₃, then the three R¹¹ groups cannot all be isopropyl;

each R¹² is independently a substituted or unsubstituted (C₁-C₁₂)alkyl group, a substituted or unsubstituted (C₂-C₁₂)alkenyl group, or a substituted or unsubstituted (C₂-C₁₂)alkynyl group, or a substituted or unsubstituted aryl group;

Z is an unsubstituted or substituted aryl group, an unsubstituted or substituted triarylmethyl group, an unsubstituted or substituted trityl group, an unsubstituted or substituted tetrahydropyranyl group, or an unsubstituted or substituted 9-phenylxanthyl;

B^n is hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group, wherein B^n is not thymine, N²-isobutyryl guanine, N⁴-benzoyl 5-methyl cytosine, N⁴-benzoyl cytosine, N⁶-benzoyl adenine, or uracil, and provided that the compound is not represented by one of the following structural formulas:



wherein X is tert-butyldimethylsilyl or triisopropylsiloxymethyl.

Each of these elements is recited in original Claim 2 of the '569 Patent (Ex. 1001, 114:34-117:52), and is supported by, *inter alia*, pages 7:19-10:23, 33:6-10, 99:20-100:4, 122:13-125:23 (Claim 2), 126:5-9 (Claim 5) of the '827 Application.

Ex. 1002, 8:19-11:23, 34:6-10, 100:20-101:4, 123:13-126:23, 127:5-9. Ex. 2001, ¶83.

The '827 Application discloses and supports many alternative nucleoside bases including, *inter alia*, where Bⁿ is thymine (6:17; 18:2; 31:3; 40:15; 51:24), N²-isobutyryl guanine (55:9-16; 59:1 (structure ix); 111:6; 113:1), N⁴-benzoyl 5-methyl cytosine (52:9-10; 54:25-55:1; 69:10 (structure 1), N⁴-benzoyl cytosine (55:9-16; 68:16-17), N⁶-benzoyl adenine (6:7; 17:21; 30:25), and uracil (51:23-24). Ex. 1002, 7:17; 19:2; 32:3; 41:15; 52:24; 56:9-16; 60:1 (structure ix); 112:6; 114:1; 53:9-10; 55:25-56:2; 70:10 (structure 1); 56:9-16; 69:16-17; 7:7; 18:21; 31:25; 52:23-24; Ex. 2001, ¶84.

Accordingly, the amendment does not present any issues of new matter because Substitute Claim 34 is only claiming less than Applicant has a right to claim. *See In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA 1977) (“[the] specification, having described the whole, necessarily described the part remaining.”); *see also* M.P.E.P. § 2173.05(i) *citing In re Johnson* (“If alternative elements are positively recited in the specification, they may be explicitly excluded in the claims.”).

D. The Substitute Claims Are Responsive to the Instituted Grounds.

The proposed Substitute Claims are responsive to the Grounds at issue in this IPR because they each respond to a ground of unpatentability involved in the trial.

Specifically, proposed Substitute Claim 33 deletes the species in Claim 1 that Petitioner alleged was anticipated in Ground I, and proposed Substitute Claim 34 deletes the species in Claim 2 that Petitioner alleged was anticipated in Ground II. For at least these reasons, and as further explained in Section IV below, the Substitute Claims are patentable over the instituted Grounds. *See* 37 C.F.R. §42.121(a)(2)(i).

Patent Owner also amended Claim 1 to remove compounds from Claim 1's Markush Groups (where Bⁿ is, thymine and 5-(C₁)alkyluracil) and Claim 2 to remove certain compounds (where Bⁿ is not thymine, N²-isobutyryl guanine, N⁴-benzoyl 5-methyl cytosine, N⁴-benzoyl cytosine, N⁶-benzoyl adenine, or uracil), based on prior sales of those compounds.

IV. THE SUBSTITUTE CLAIMS ARE PATENTABLE OVER THE INSTITUTED GROUNDS

Patent Owner does not bear the burden of proving the patentability of Substitute Claims 33 and 34. *See Lectrosonics, Inc. v. Zaxcom, Inc.*, IPR2018-01129, Paper 15 at 3-4 (PTAB Feb. 25, 2019); *Aqua Prods., Inc. v. Matal*, 872 F. 3d 1290, 1295-96, 1327 (Fed. Cir. 2017) (*en banc*). Rather, Petitioners must prove unpatentability by a preponderance of the evidence. *See Lectrosonics*, Paper 15 at 4. However, Patent Owner provides the following comments regarding the Substitute Claims 33 and 34.

A. Level of Ordinary Skill in the Art.

Patent Owner notes that the Institution Decision adopted the following definition of a POSA:

an ordinarily skilled artisan would have had a Ph.D. (or equivalent degree) in organic or medicinal chemistry, and two to three years of post-graduate work experience in medicinal chemistry, synthetic organic chemistry, and nucleic acid chemistry, including the development of oligonucleotide therapeutics, diagnostics, or building blocks. Alternatively, . . . an individual holding a Bachelor's or Master's degree in organic chemistry or medicinal chemistry, who had extensive work experience in these fields, and who had gained a thorough understanding of the development of nucleic acid-based materials, would also have qualified as an ordinarily skilled artisan.

Paper 6, at 5 (internal citation omitted).

For the reasons explained in Section V of the Patent Owner's Response, Patent Owner disagrees and proposes the following definition of a POSA:

a POSA would have had a Ph.D. (or equivalent degree) in organic chemistry, and at least 2 to 3 years of post-graduate work experience in the development and syntheses of nucleosides, nucleotides, and nucleic acids, including, but not limited to, the syntheses of oligonucleotides through solid phase oligonucleotide synthesis ("SPOS") pursuant to P(III) chemistry.

Alternatively, someone with a Ph.D. (or equivalent degree) in organic chemistry, and who focused on the development and syntheses of

nucleosides, nucleotides, and nucleic acids, including, but not limited to, the syntheses of oligonucleotides through SPOS during his or her Ph.D. studies.

Alternatively, someone with a Bachelor's or Master's degree in organic chemistry who had at least 5 years of extensive work experience in these fields, and who had gained a thorough understanding of the syntheses of nucleic acid-based materials pursuant to P(III) chemistry, would also have qualified as a POSA.

Ex. 2001, ¶¶64. This definition would not exclude medicinal chemists so long as the medicinal chemist in question met the above requirements. *Id.*, ¶¶65.

Patent Owner contends that the Substitute Claims are patentable over the instituted grounds under either definition of a POSA. *Id.*

B. Claim Construction.

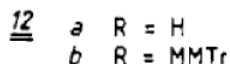
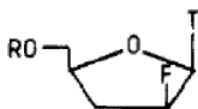
The proposed Substitute Claims should be construed in accordance with “the ordinary and customary meaning of such claim[s] as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” 37 C.F.R. § 42.100.

C. Petitioner's References Do Not Anticipate or Render Substitute Claim 33 Obvious.

Petitioner's cited references do not disclose the limitations of Substitute Claim 33 (shown above in § III.C.1). Ex. 2001, ¶¶67-73.

Petitioner cites Aerschot¹ (Ex. 1004) as anticipating Claim 1 alleging that Aerschot's compound 12a is a species of Claim 1 where in compound 12a, R = H:

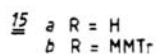
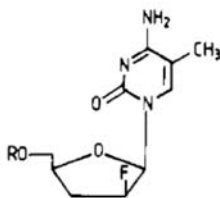
Aerschot compound 12a:



and the Institution Decision adopted this position. Paper 6, at 7; Ex. 2001, ¶¶69-70.

Petitioner also cites Aerschot as anticipating Claim 1 alleging that Aerschot's compound 15a is a species of Claim 1 where in compound 15a, R = H:

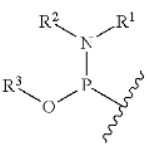
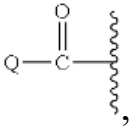
Aerschot Compound 15a



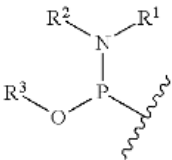
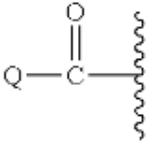
and the Institution Decision adopted this position. Paper 6, at 8; Ex. 2001, ¶¶69-70.

¹ Aerschot et. al., 3'-Fluoro-2',3'-dideoxy-5-chlorouridine: Most Selective Anti-HIV1 Agent among a Series of New 2'- and 3'-Fluorinated 2',3'-Dideoxynucleoside Analogues, 32 J. MED. CHEM. 1742-49 (1989) ("Aerschot") (Ex. 1004).

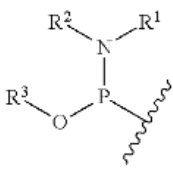
Substitute Claim 33 limits “R⁶” such that it excludes “H.” Ex. 2001, ¶67. Aerschot does not disclose a compound having the claimed structure including, *inter*

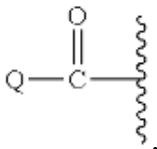
alia, “R⁶” limited to “—O—Z” and “J” limited to H,  or , as recited in Substitute Claim 33 and therefore does not disclose the compounds that are claimed in Substitute Claim 33. Ex. 2001, ¶71.

All of the compounds disclosed in Aerschot have H, F, =O, N₃, O-Bz, or OH at the “R⁶” position. *Id.*, ¶72. Aerschot does not disclose “—O—Z” at the “R⁶”

position when “J” is H,  or . *Id.*

Substitute Claim 33 requires Z to be “an unsubstituted or substituted aryl group, an unsubstituted or substituted triarylmethyl group, an unsubstituted or substituted trityl group, an unsubstituted or substituted tetrahydropyranyl group, or

an unsubstituted or substituted 9-phenylxanthyl” and also that “J” is H, 

or . *Id.* Thus, Aerschot does not anticipate the compound of Substitute

Claim 33 including the amended definition of “R⁶” in combination with the definition of “J” as well as the other structural features of Substitute Claim 33. *Id.*

Further, nothing in Aerschot alone or in combination with any of the other references of record in this IPR would have provided a POSA with a reason or motivation to modify the compounds of Aerschot to arrive at the compounds claimed in Substitute Claim 33, including to modify the Aerschot compounds to have chemical groups at positions corresponding to “J” and “R⁶” to be those recited in Substitute Claim 33, with a reasonable expectation of success. *Id.*, ¶73.

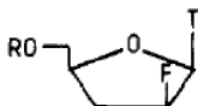
For at least these reasons, Substitute Claim 33 is patentable over Aerschot and this Motion is responsive to the Petition’s Ground I.

D. Petitioner’s References Do Not Anticipate or Render Substitute Claim 34 Obvious.

Petitioner’s cited references do not disclose the limitations of Substitute Claim 34 (shown above in § III.C.2). Ex. 2001, ¶¶76-82.

Petitioner alleges Aerschot (Ex. 1004) anticipates Claim 2 because Aerschot’s compound 12a is a species of Claim 2 where in compound 12a, R = H:

Aerschot compound 12a:

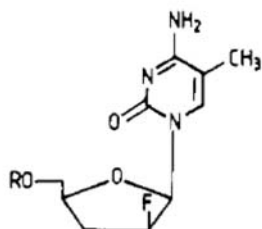


12
a R = H
b R = MMTr

and the Institution Decision adopted this position. Paper 6, at 9; Ex. 2001, ¶¶78-79.

Petitioner also cites Aerschot as anticipating Claim 2 because Aerschot's compound 15a is a species of Claim 2 where in compound 15a, R = H:

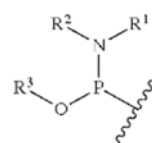
Aerschot Compound 15a

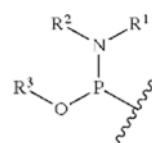


15 a R = H
 b R = MMTf

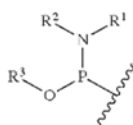
and the Institution Decision adopted this position. Paper 6, at 9; Ex. 2001, ¶¶78-79.

Substitute Claim 34 limits “R⁶” such that it excludes “H.” Ex. 2001, ¶80. Aerschot does not disclose a compound having the claimed structure including, *inter*

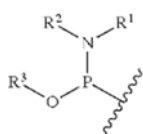


alia, “R⁶” limited to “—O—Z” and “J” limited to H or , as recited in Substitute Claim 34 and therefore does not disclose the compounds that are claimed in Substitute Claim 34. Ex. 2001, ¶80.

All of the compounds disclosed in Aerschot have H, F, =O, N₃, O-Bz, or OH at the “R⁶” position. Ex. 2001, ¶81. Aerschot does not disclose “—O—Z” at the “R⁶”

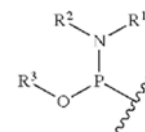


position when “J” is H or . *Id.* Substitute Claim 34 requires Z to be “an unsubstituted or substituted aryl group, an unsubstituted or substituted triarylmethyl group, an unsubstituted or substituted trityl group, an unsubstituted or substituted tetrahydropyranyl group, or an unsubstituted or substituted 9-phenylxanthyl” and



also that “J” is H or . *Id.* Thus, Aerschot does not anticipated the compound of Substitute Claim 34 including the amended definition of “R⁶” in combination with the definition of “J” as well as the other structural features of Substitute Claim 34. *Id.*

Further, nothing in Aerschot alone or in combination with any of the other references of record in this IPR would have provided a POSA with a reason or



motivation to modify the “R⁶” group to be “—O—Z” when “J” is H or with a reasonable expectation of success. *Id.*, ¶82.

For at least these reasons, Substitute Claim 34 is patentable over Aerschot and this Motion is responsive to the Petition’s Ground II.

V. INFORMATION DISCLOSURE

With the submission of this Motion to Amend, Patent Owner is submitting an Information Disclosure Statement in Appendix B disclosing certain ChemGenes invoices.

VI. CONCLUSION

For at least all the above and foregoing reasons, Patent Owner respectfully submits that Substitute Claims 33 and 34 are patentable, and respectfully requests a Final Written Decision confirming the patentability of these claims.

Dated: February 5, 2024

Respectfully submitted,

/Daniel L. Shores/

Daniel L. Shores (Reg. No. 74,571)
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
10 Post Office Square, Suite 800
Boston, MA 02109
Tel: (617) 312-3101
Fax: (202) 783-6031
Email: dshores@rfem.com

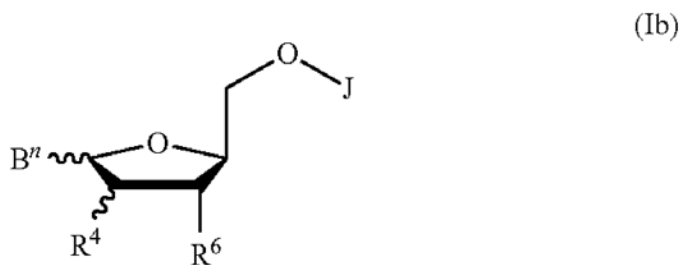
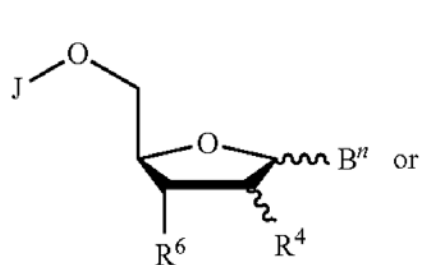
Joseph A. Hynds (Reg. No. 34,627)
Aydin H. Harston, Ph.D. (Reg. No. 65,249)
Melissa C. Santos, Ph.D. (Reg. No. 78,314)
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
901 New York Ave., N.W.,
Suite 900 East
Washington, DC 20001
Tel: (202) 783-6040
Fax: (202) 783-6031
Email: jhynds@rfem.com
Email: aharston@rfem.com
Email: msantos@rfem.com

**Counsel for Patent Owner,
ChemGenes Corporation**

APPENDIX A
CLAIM LISTING

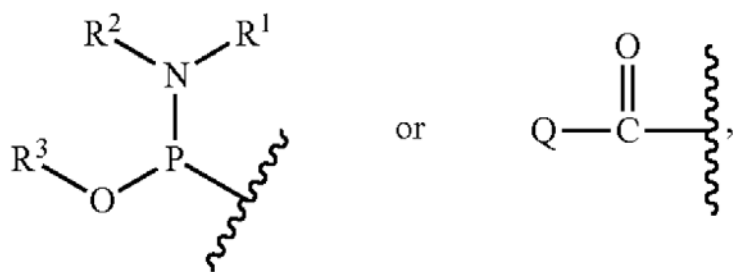
Proposed amended claims are shown in marked-up form below.

Claim 33 (proposed substitute for Claim 1). A compound of Formula Ia or Ib:



or a salt thereof, wherein:

J is H,



wherein  indicates where J is attached to the O atom;

Q is a support comprised of: a) a linking group and a spacer that can be cleaved to form a hydroxy group; or b) an aliphatic chain, aromatic group, substituted or unsubstituted aromatic, a substituted or unsubstituted phenoxy, or levulinyl;

R¹ is a substituted or unsubstituted (C₁-C₁₂)alkyl group, a substituted or unsubstituted (C₃-C₂₀)cycloalkyl group, or a substituted or unsubstituted (C₃-C₂₀)cycloalkyl(C₁-C₁₂)alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, ~~NR⁷~~, O and S;

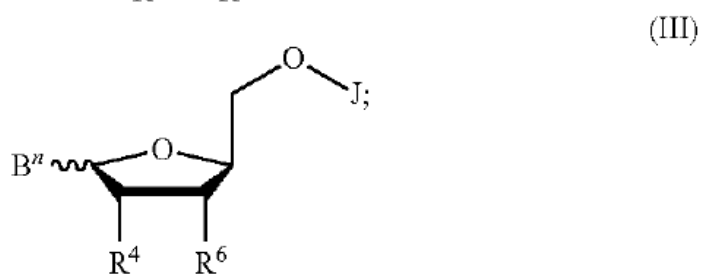
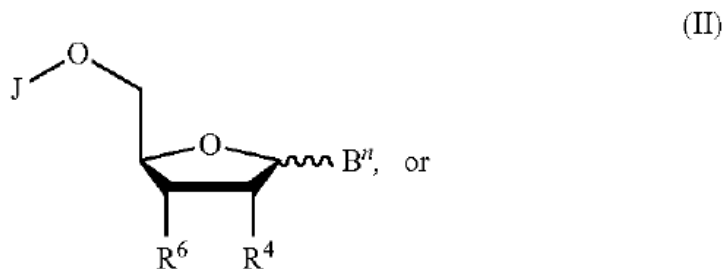
R² is a substituted or unsubstituted (C₁-C₁₂)alkyl group, a substituted or unsubstituted (C₃-C₂₀)cycloalkyl group, or a substituted or unsubstituted (C₃-C₂₀)cycloalkyl(C₁-C₁₂)alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, ~~NR⁷~~, O and S;

or R¹ and R² taken together with the nitrogen atom to which they are bound form a 4-7 membered non-aromatic heterocyclyl, wherein the heterocyclyl formed may optionally include intervening heteroatoms independently selected from NH, ~~NR⁷~~, O and S;

R³ is a phosphate protecting group;

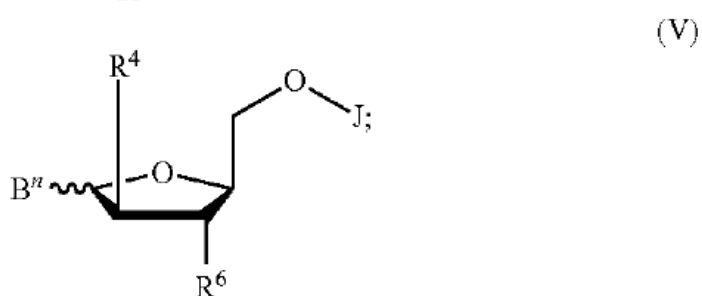
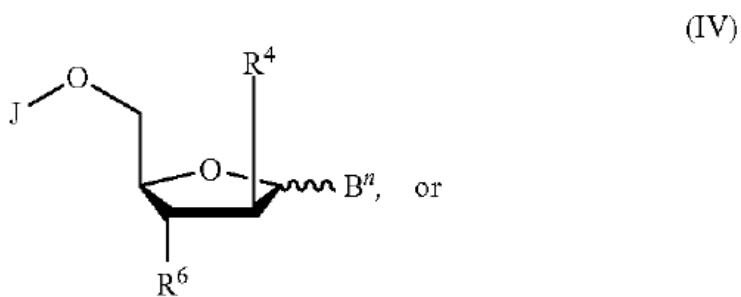
R^4 is a -halo, $-R^5$, $-NR^7R^8$, $-OR^9$, $-SR^{10}$, or 2'-blocking group; or when

Structural Formula Ia or Ib is:



wherein R^4 is further selected from $\text{O}-\text{Si}(\text{R}^{11})_3$ or $\text{O}-\text{CH}_2-\text{Si}(\text{R}^{11})_3$; or

when Structural Formula Ia or Ib is:



R^4 is further selected from $-\text{OC}(=\text{O})\text{R}^{12}$;

each R^5 is independently a substituted or unsubstituted (C_1 - C_{12})alkyl group, a substituted or unsubstituted (C_2 - C_{12})alkenyl group, a substituted or unsubstituted (C_2 - C_{12})alkynyl group, or a substituted or unsubstituted phenyl, wherein the alkyl, alkenyl, alkynyl and the phenyl groups optionally includes intervening heteroatoms independently selected from NH, NR^5 , O and S; and may optionally terminate with $—NR^7R^8$, $—(C_1-C_4)$ alkylamino, di(C_1 - C_4)alkylamino, $—OR^9$, (C_1-C_6) alkoxy, benzyl or substituted benzyl, $—SR^{10}$; or $—S—(C_1-C_6)$ alkyl group;

R^6 is $—H$ or $—O—Z$;

~~each R^7 is independently a fluorenylmethyloxycarbonyl; $—C(=O)—(CH_2)_{1-16}$ NR⁸C(=O)CF₃; $—C(=O)—(CH_2)_{1-16}$ NR⁸C(=O)-phthalimide; $—C(=O)—(CH_2)_{1-16}$ -phthalimide; NR⁸C(=O)-phthalimide; a substituted or unsubstituted (C_4 - C_{12})alkyl group, a substituted or unsubstituted (C_2 - C_{12})alkenyl group, or a substituted or unsubstituted (C_2 - C_{12})alkynyl group;~~

~~each R^8 is H or a substituted or unsubstituted (C_1 - C_{12})alkyl group, a substituted or unsubstituted (C_2 - C_{12})alkenyl group, or a substituted or unsubstituted (C_2 - C_{12})alkynyl group;~~

each R^9 is independently $—C(=O)—(CH_2)_{1-16}CH_3$; a substituted or unsubstituted (C_2 - C_{12})alkenyl group, or a substituted or unsubstituted (C_2 - C_{12})alkynyl group;

~~each R¹⁰ is independently —S(C₄-C₆)alkyl, —C(=O)—(CH₂)₁₋₁₆CH₃; a substituted or unsubstituted (C₂-C₁₂)alkenyl group, or a substituted or unsubstituted (C₂-C₁₂)alkynyl group;~~

each R¹¹ is independently a substituted or unsubstituted (C₁-C₁₂)alkyl group, a substituted or unsubstituted (C₂-C₁₂)alkenyl group, or a substituted or unsubstituted (C₂-C₁₂)alkynyl group;

each R¹² is independently a substituted or unsubstituted (C₁-C₁₂)alkyl group, a substituted or unsubstituted (C₂-C₁₂)alkenyl group, or a substituted or unsubstituted (C₂-C₁₂)alkynyl group, or a substituted or unsubstituted aryl group;

Z is an unsubstituted or substituted aryl group, an unsubstituted or substituted triarylmethyl group, an unsubstituted or substituted trityl group, an unsubstituted or substituted tetrahydropyranyl group, or an unsubstituted or substituted 9-phenylxanthyl;

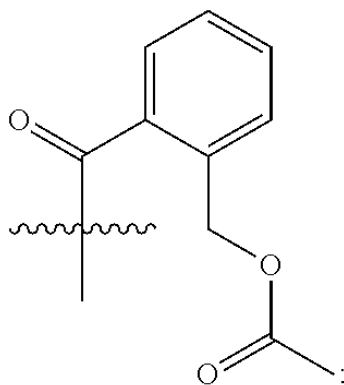
Bⁿ is hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group, wherein the nucleobase is selected from:

N6,N6-dimethyl adenine, N-1 methyladenine, 7-deazaadenine, 7-deaza-8-azaadenine, 3-deazaadenine, ethenoadenine, isoguanine, N1-methylguanine, 7-iodo-7-deazaguanine, 7-deaza-7-iodoadenine, 7-deaza-7-iodo-6-oxopurine, 5-iodo-5-methyl-7-deazaguanine, 7-deazaguanine substituted with —C≡C(CH₂)₁₋₈-

phthalamide, 7-deaza-8-azaguanine, 8-methylguanine, 8-bromoguanine, 8-aminoguanine, hypoxanthine, 6-methoxypurine, 7-deaza-6-oxopurine, 6-oxopurine, 2-aminopurine, 2,6-diaminopurine, 8-bromopurine, 8-aminopurine, 8-alkylaminopurine, 8-alkylaminopurine, thymine, N-3 methyl thymine, 5-acetoxymethylcytosine, 5-azacytosine, isocytosine, N-4(C₁-C₆)alkylcytosine, N-3(C₁-C₆)alkylcytidine, 5-propynylcytosine, 5-iodo-cytosine, 5-(C₁-C₆)alkylcytosine, 5-aryl(C₁-C₆)alkylcytosine, 5-trifluoromethylcytosine, 5-methylcytosine, ethenocytosine, cytosine and uracil substituted with —CH=CH—C(=O)NH(C₁-C₆)alkyl, cytosine and uracil substituted with —C≡C—CH₂-phthalimide, NH(C₁-C₆)alkyl, 4-thiouracil, 2-thiouracil, N³-thiobenzoylthiouracil, 5-propynyluracil, 5-acetoxymethyluracil, 5-fluorouracil, 5-chlorouracil, 5-bromouracil, 5-iodouracil, thiouracil, N-3-(C₁-C₆)alkyluracil, 5-(3-aminoallyl)-uracil, 5-(C₁-C₆)alkyluracil, 5-aryl(C₁-C₆)alkyluracil, 5-trifluoromethyluracil, 4-triazolyl-5-methyluracil, 2-pyridone, 2-oxo-5-methylpyrimidine, 2-oxo-4-methylthio-5-methylpyrimidine, 2-thiocarbonyl-4-oxo-5-methylpyrimidine, and 4-oxo-5-methylpyrimidine;

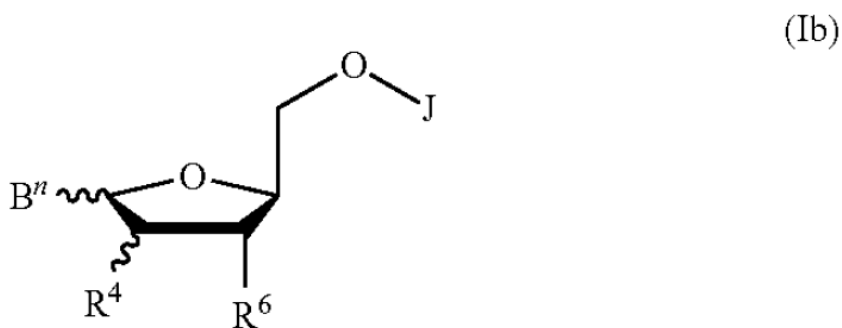
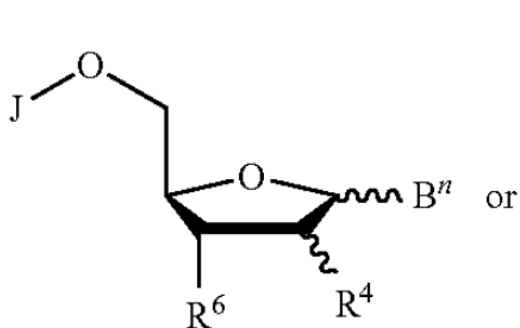
wherein any substitutable nitrogen atom within the nucleobase or on the exocyclic amine is optionally substituted with fluorenylmethyloxycarbonyl; —C(=O)OPh; —C(=O)(C₁-C₁₆)alkyl; —C(=O)CH₂CH₂CH=CH₂—; —C(=O)(C₁-C₁₆)alkylene-C(=O)OH; —C(=O)(C₁-C₁₆)alkylene-C(=O)O(C₁-C₆)alkyl;

$=\text{CR}^8\text{N}(\text{C}_1\text{-C}_6\text{alkyl})_2$; $-\text{C}(=\text{O})-\text{NR}^8-(\text{CH}_2)_{1-16}\text{NR}^8\text{C}(=\text{O})\text{CF}_3$; $-\text{C}(=\text{O})-(\text{CH}_2)_{1-16}\text{NR}^8\text{C}(=\text{O})\text{CF}_3$; $-\text{C}(=\text{O})-\text{NR}^8(\text{CH}_2)_{1-16}\text{NR}^8\text{C}(=\text{O})$ -phthalimide; $-\text{C}(=\text{O})-(\text{CH}_2)_{1-16}$ -phthalimide; and



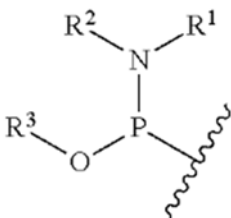
wherein any substitutable oxygen atom within the nucleobase is optionally substituted with $-\text{C}(=\text{O})\text{N}(\text{C}_1\text{-C}_6\text{alkyl})_2$ or $-\text{C}(=\text{O})\text{N}(\text{phenyl})_2$.

Claim 34 (proposed substitute for Claim 2). A compound of Formula Ia or Ib:



or a salt thereof, wherein:

J is H or



R¹ is a substituted or unsubstituted (C₁-C₁₂)alkyl group, a substituted or unsubstituted (C₃-C₂₀)cycloalkyl group, or a substituted or unsubstituted (C₃-C₂₀)cycloalkyl(C₁-C₁₂)alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, ~~NR⁷~~, O and S;

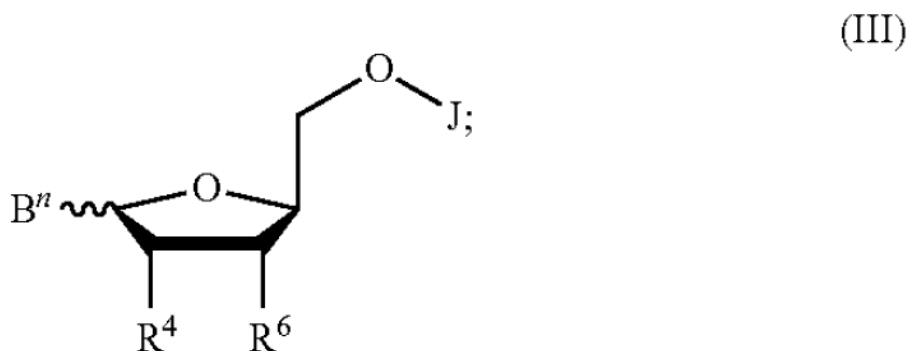
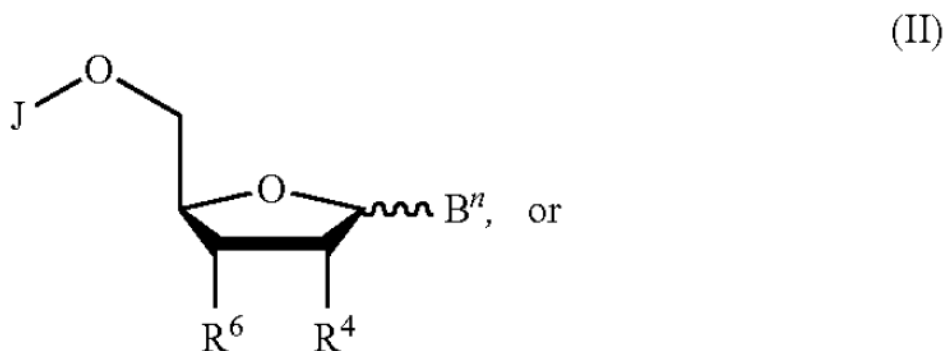
R² is a substituted or unsubstituted (C₁-C₁₂)alkyl group, a substituted or unsubstituted (C₃-C₂₀)cycloalkyl group, or a substituted or unsubstituted (C₃-C₂₀)cycloalkyl(C₁-C₁₂)alkyl group, wherein the alkyl or cycloalkyl groups optionally include intervening heteroatoms independently selected from NH, ~~NR⁷~~, O and S;

or R¹ and R² taken together with the nitrogen atom to which they are bound form a 4-7 membered non-aromatic heterocyclyl, wherein the heterocyclyl formed may optionally include intervening heteroatoms independently selected from NH, ~~NR⁷~~, O and S;

R^3 is a phosphate protecting group;

R^4 is a -halo, $-R^5$, $-NR^7R^8$, $-OR^9$, $-SR^{10}$, or 2'-blocking group; or when

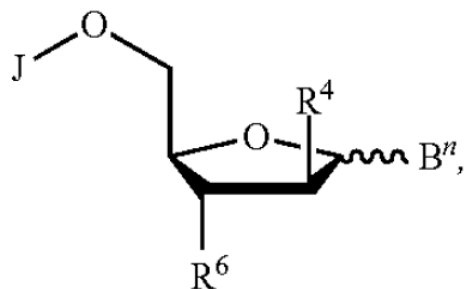
Structural Formula Ia or Ib is:



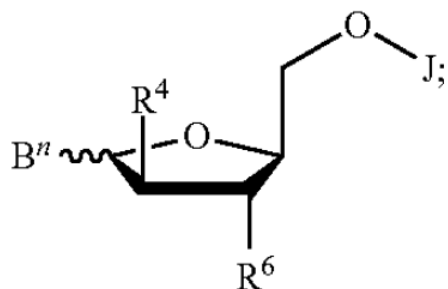
wherein R^4 is further selected from $\text{O}-\text{Si}(\text{R}^{11})_3$ or $\text{O}-\text{CH}_2-\text{Si}(\text{R}^{11})_3$; or

when Structural Formula Ia or Ib is:

(IV)



(V)



R^4 is further selected from —OC(=O)R^{12} ;

each R^5 is independently a substituted or unsubstituted $(C_1\text{--}C_{12})$ alkyl group, a substituted or unsubstituted $(C_2\text{--}C_{12})$ alkenyl group, a substituted or unsubstituted $(C_2\text{--}C_{12})$ alkynyl group, or a substituted or unsubstituted phenyl, wherein the alkyl, alkenyl, alkynyl and the phenyl groups optionally includes intervening heteroatoms independently selected from NH, NR^5 , O and S; and may optionally terminate with $\text{—NR}^7\text{R}^8$; $(C_1\text{--}C_4)$ alkylamino, $\text{di}(C_1\text{--}C_4)$ alkylamino, —OR^9 , $(C_1\text{--}C_6)$ alkoxy, benzyl or substituted benzyl, —SR^{10} ; or $\text{—S—}(C_1\text{--}C_6)$ alkyl group;

R^6 is —H or —O—Z ;

each R^7 is independently a fluorenylmethyloxycarbonyl; $\text{—C(=O)—(CH}_2\text{)}_{1\text{--}16}$
 $\text{NR}^8\text{C(=O)CF}_3$; $\text{—C(=O)—(CH}_2\text{)}_{1\text{--}16}\text{NR}^8\text{C(=O)—phthalimide}$; $\text{—C(=O)—(CH}_2\text{)}_{1\text{--}16}$

~~+6-phthalimide; NR⁸C(=O)-phthalimide; a substituted or unsubstituted (C₄-C₁₂)alkyl group, a substituted or unsubstituted (C₂-C₁₂)alkenyl group, or a substituted or unsubstituted (C₂-C₁₂)alkynyl group;~~

~~each R⁸ is H or a substituted or unsubstituted (C₄-C₁₂)alkyl group, a substituted or unsubstituted (C₂-C₁₂)alkenyl group, or a substituted or unsubstituted (C₂-C₁₂)alkynyl group;~~

each R⁹ is independently —C(=O)—(CH₂)₁₋₁₆CH₃; a substituted or unsubstituted (C₂-C₁₂)alkenyl group, or a substituted or unsubstituted (C₂-C₁₂)alkynyl group;

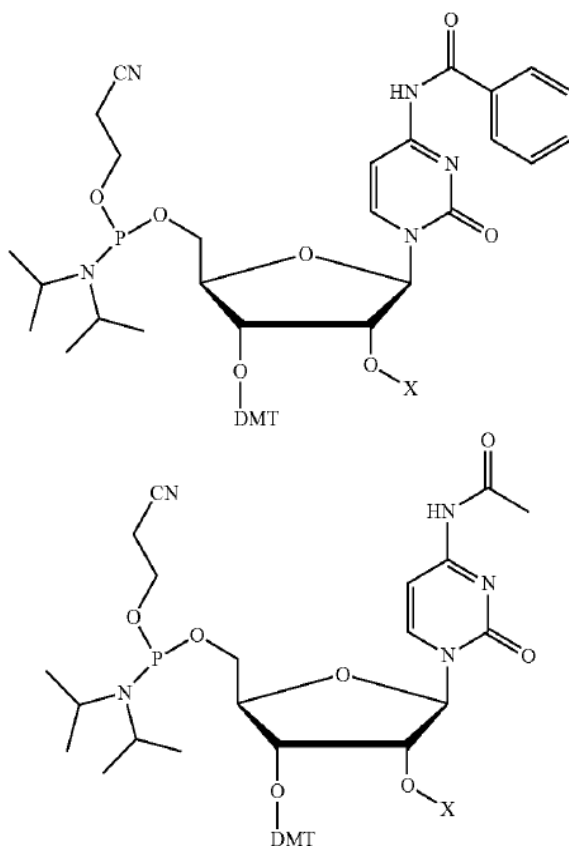
~~each R¹⁰ is independently —S(C₄-C₆)alkyl, —C(=O)—(CH₂)₁₋₁₆CH₃; a substituted or unsubstituted (C₂-C₁₂)alkenyl group, or a substituted or unsubstituted (C₂-C₁₂)alkynyl group;~~

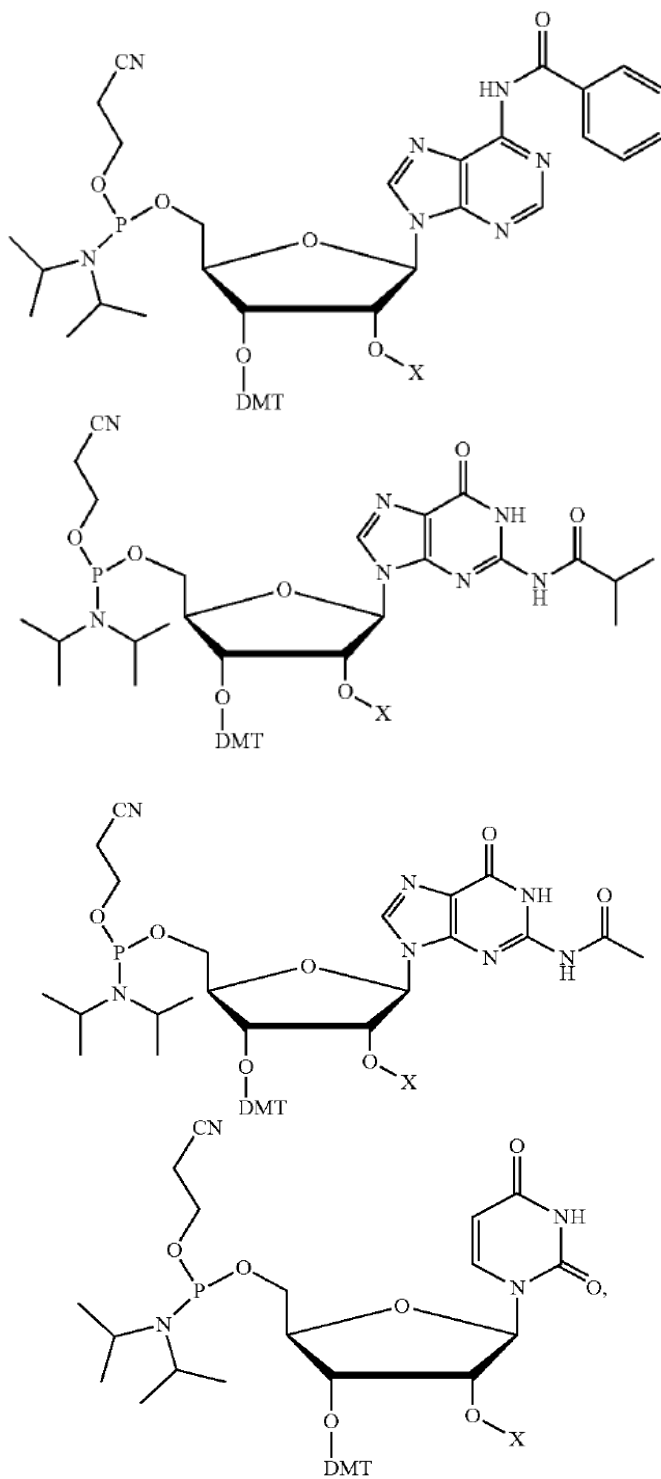
each R¹¹ is independently a substituted or unsubstituted (C₁-C₁₂)alkyl group, a substituted or unsubstituted (C₂-C₁₂)alkenyl group, or a substituted or unsubstituted (C₂-C₁₂)alkynyl group; provided that if R⁴ is —O—Si(R¹¹)₃, and two R¹¹ groups are both methyl, the other is not t-butyl or if R⁴ is —O—CH₂—Si(R¹¹)₃, then the three R¹¹ groups cannot all be isopropyl;

each R¹² is independently a substituted or unsubstituted (C₁-C₁₂)alkyl group, a substituted or unsubstituted (C₂-C₁₂)alkenyl group, or a substituted or unsubstituted (C₂-C₁₂)alkynyl group, or a substituted or unsubstituted aryl group;

Z is an unsubstituted or substituted aryl group, an unsubstituted or substituted triarylmethyl group, an unsubstituted or substituted trityl group, an unsubstituted or substituted tetrahydropyranyl group, or an unsubstituted or substituted 9-phenylxanthyl;

Bⁿ is hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group, wherein Bⁿ is not thymine, N²-isobutyryl guanine, N⁴-benzoyl 5-methyl cytosine, N⁴-benzoyl cytosine, N⁶-benzoyl adenine, or uracil, and provided that the compound is not represented by one of the following structural formulas:





wherein X is tert-butyldimethylsilyl or triisopropylsiloxymethyl.

APPENDIX B

INFORMATION DISCLOSURE STATEMENT

Patent Owner submits the following exhibits which are also listed on the Exhibit List in Patent Owner's Response being filed contemporaneously herewith.

Ex. No.	Description
2004	ChemGenes Corporation Invoice 28401 dated 6/2/2004
2005	ChemGenes Corporation Invoice 43871 dated 3/3/2008
2006	ChemGenes Corporation Invoice 35809 dated 5/16/2006
2007	ChemGenes Corporation Invoice 35778 dated 6/13/2006
2008	ChemGenes Corporation Invoice 36382 dated 6/22/2006
2009	ChemGenes Corporation Invoice 37774 dated 12/4/2006
2010	ChemGenes Corporation Catalog, Bio Technology Products & Manufacturer of DNA-RNA Intermediates (1999)
2011	ChemGenes Corporation Catalog, Bio Technology Products & Manufacturer of DNA-RNA Intermediates (Feb. 2009)
2012	ChemGenes Corporation Catalog, Bio Technology Products & Manufacturer of DNA-RNA Intermediates, E-Catalog Version 6.0, (Release Date 10-12-2009)
2013	ChemGenes Corporation Catalog, Bio Technology Products & Manufacturer of DNA-RNA Intermediates, E-Catalog Version 7.0, (Release Date 12-12-2009)

CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing PATENT OWNER'S MOTION TO AMEND CLAIMS UNDER 37 C.F.R. § 42.121 was served on February 5, 2024, to the following counsel for Petitioner via electronic mail at Hongene@procopio.com:

Jeremy J. Edwards (Reg. No. 60,982)
PROCOPIO, CORY, HARGREAVES & SAVITCH, LLP
1050 Connecticut Ave., NW, Suite 500
Washington, DC 20036
Tel.: 202-830-0707
E-mail: Hongene@procopio.com

Raymond K. Chan (Reg. No. 66,164)
PROCOPIO, CORY, HARGREAVES & SAVITCH, LLP
200 Spectrum Center Dr., Suite 1650
Irvine, CA 92618
Tel.: 949-383-2997
E-mail: Hongene@procopio.com

Xiaofan Yang (Reg. No. 61,459)
PROCOPIO, CORY, HARGREAVES & SAVITCH, LLP
12544 High Bluff Dr., Suite 400
San Diego, CA 92310
Tel.: 858-720-6300
E-mail: Hongene@procopio.com

Jack Shaw (Reg. No. 72,262)
PROCOPIO, CORY, HARGREAVES & SAVITCH, LLP
3000 El Camino Real, Suite 5-400
Palo Alto, CA 94306
Tel.: 650-645-9000
E-mail: Hongene@procopio.com

Counsel for Petitioner Shanghai Hongene Biotech Corporation

/Daniel L. Shores/

Daniel L. Shores (Reg. No. 74,571)
ROTHWELL, FIGG, ERNST & MANBECK, P.C.
10 Post Office Square, Suite 800
Boston, MA 02109
Tel: (617) 312-3101
Fax: (202) 783-6031
Email: dshores@rfem.com

**Counsel for Patent Owner,
ChemGenes Corporation**