

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

**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**

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I, Phil S. Baran, declare as follows:

1. I am the same Phil S. Baran who submitted a declaration dated January 18, 2023 in the above-captioned IPR proceeding, which I understand became Exhibit 1003 in this proceeding.

2. I submit this declaration to respond to the “Patent Owner’s Motion to Amend Claims under 37 C.F.R. § 42.121” (“Motion to Amend”) and the portions of the Declaration of Dr. Hrdlicka (Ex. 2008) concerning the Motion to Amend.

I. LEGAL STANDARDS

3. I have used the same legal standards described in connection with my opening declaration. (Ex. 1003 at ¶¶ 19-39.)

4. In addition, I have been informed that a reference can anticipate a patent claim even if it does not expressly disclose all the limitations arranged or combined as in the claim, if a POSA, reading the reference, would “at once envisage” the claimed arrangement or combination.

5. I have also been informed that a claimed invention is anticipated (and thus invalid) if the claimed invention was on sale in the United States more than one year before the effective filing date. As stated in my opening declaration, I have been asked to treat the effective filing date of U.S. Patent No. 9,884,885 (“the ’885 Patent”) as May 18, 2009. (Ex. 1003 at ¶ 27.) I have been informed that this basis of anticipation is known as the “on-sale bar.” I have been informed that the

on-sale bar has two requirements: (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.

II. SUMMARY

6. In my opinion, Substitute Claim 6 of the '885 Patent is anticipated by each of the following three prior art references: (1) U.S. Patent No. 5,525,719 ("the '719 Patent") (Ex. 1043), issued on June 11, 1996; (2) U.S. Patent No. 5,606,049 ("the '049 Patent") (Ex. 1045), issued on February 25, 1997; and (3) Vol. 8, No. 1 of the Glen Report, published by the Glen Research Corporation in June 1995 ("Glen Report") (Ex. 1046).

7. In my opinion, Substitute Claim 6 also would have been obvious based on each of the following four combinations of prior art references:

- The '719 Patent alone (Ex. 1043)
- The '719 Patent (Ex. 1043) and Pitsch (Ex. 1018)
- The '049 Patent alone (Ex. 1045)
- The '049 Patent (Ex. 1045) and Pitsch (Ex. 1018)

8. Finally, in my opinion, Substitute Claim 7 would have been obvious based on each of the following five combinations of prior art references:

- The '719 Patent (Ex. 1043) and Scaringe (Ex. 1022)
- The '719 Patent (Ex. 1043), Pitsch (Ex. 1018), and Scaringe (Ex. 1022)

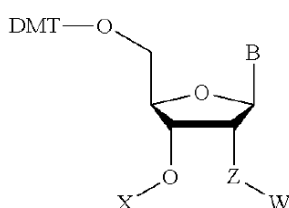
- The '049 Patent (Ex. 1045) and Scaringe (Ex. 1022)
- The '049 Patent (Ex. 1045), Pitsch (Ex. 1018), and Scaringe (Ex. 1022)
- The Glen Report (Ex. 1046) and Scaringe (Ex. 1022)

III. SUBSTITUTE CLAIM 6 IS ANTICIPATED BY EACH OF NUMEROUS PIECES OF PRIOR ART, INCLUDING PATENT OWNER'S OWN PRIOR ART

9. In my opinion, Substitute Claim 6 is anticipated by each of several references: (1) the '719 Patent (Ex. 1043), issued on June 11, 1996; (2) the '049 Patent (Ex. 1045), issued on February 25, 1997; and (3) the Glen Report (Ex. 1046), published in June 1995.

10. Substitute Claim 6, which is a proposed substitute for claim 1 of the '885 Patent, recites:

Derivatized nucleoside and phosphoramidite of general formula 1,



Formula 1

where B is selected from the group consisting of Guanine-N-acetyl, adenine-N-acetyl, ~~cytosine-N-acetyl~~, cytosine-N-isobutyryl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl;

Z is Oxygen and W is methyl; and

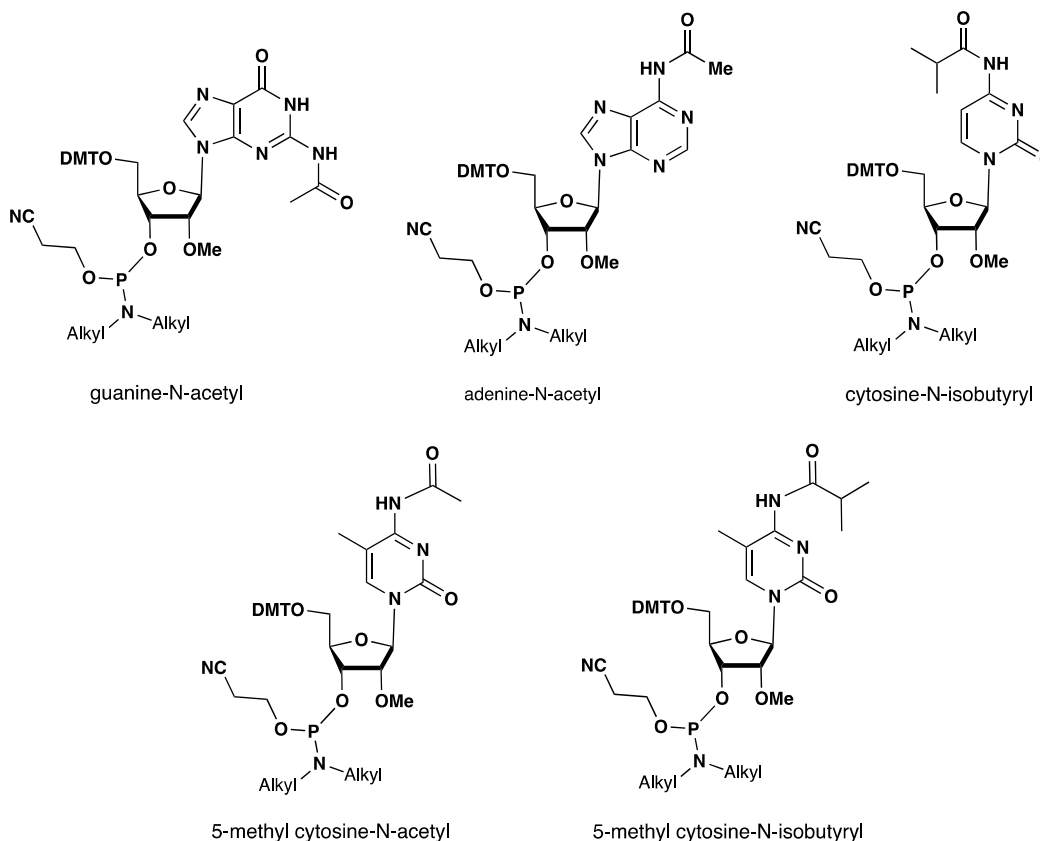
X is cyanoethyl dialkyl phosphoramidite.

(Motion to Amend at Appx. A.)

11. Substitute Claim 6 is identical to Claim 1 of the '885 Patent, except that it omits the "cytosine-N-acetyl" species of B as reflected in strikethrough text above.

12. Like Claim 1 of the '885 Patent, Substitute Claim 6 is directed to a group of phosphoramidite compounds that differ only with respect to the identity of the substituent "B" of Formula 1. "B" is used in Formula 1 to denote a nucleobase or modified nucleobase, consistently with its customary use in the field of nucleic acid chemistry.

13. The "B" group in Substitute Claim 6 contains five members: guanine-N-acetyl; adenine-N-acetyl; cytosine-N-isobutyryl; 5-methyl cytosine-N-acetyl; and 5-methyl cytosine-N-isobutyryl. When incorporated into Substitute Claim 6, these five members have the following chemical structures:



14. The remainder of Substitute Claim 6 is identical to Claim 1 of the '885 Patent, which I discussed in my opening declaration. (Ex. 1003 at ¶¶ 91-94.)

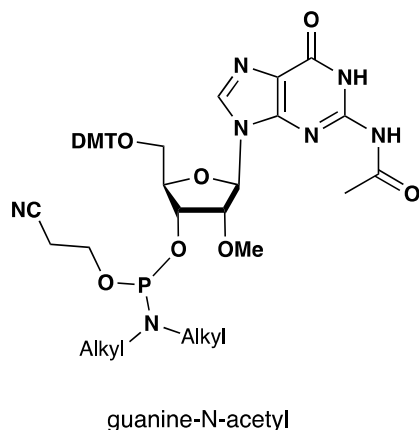
A. Substitute Claim 6 Is Anticipated by the '719 Patent

15. In my opinion, Substitute Claim 6 is anticipated by U.S. Patent No. 5,525,719 ("the '719 Patent") (Ex. 1043).

16. The '719 Patent issued on June 11, 1996, over ten years before the priority date of the '885 Patent. (Ex. 1043 at Cover; Ex. 1001 at Cover.) The '719 Patent and the '885 Patent are both assigned to Patent Owner ChemGenes Corporation. (Ex. 1043 at Cover; Ex. 1001 at Cover.)

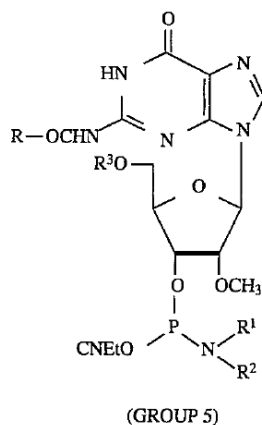
18. As described below, the '719 Patent anticipates Substitute Claim 6 where B is (1) guanine-N-acetyl, (2) adenine-N-acetyl, and (3) cytosine-N-isobutyryl.

19. When “B” is **guanine-N-acetyl**, Substitute Claim 6 claims the following compound:



20. The '719 Patent discloses the same compound of Substitute Claim 6, where B is guanine-N-acetyl. The '719 Patent describes this compound as belonging to a group of compounds named “group 5 (N²-protected-2'-O-methyl-5'-dimethoxytrityl-guanosine cyanoethyl N,N-dialkyl phosphoramidite)[.]” (Ex. 1043 at 16:66-17:1.) I refer to this group of compounds in the '719 Patent as “Group 5” in this declaration.

21. The '719 Patent further discloses the structure of compounds in Group 5 as follows:



(Ex. 1043 at 6:48-65.) Group 5 is directed to phosphoramidite compounds having an O-methyl group at the 2' position of the sugar ring and an N²-protected guanine residue at the 1' position of the sugar ring.

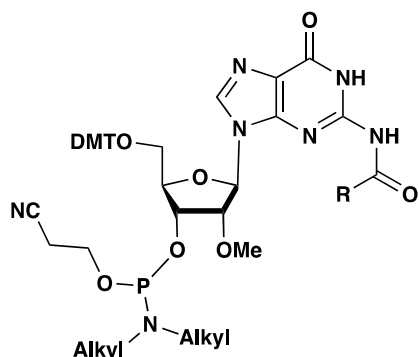
22. Group 5 contains four substituent groups: R¹ and R² (referring to the groups attached to nitrogen of the phosphoramidite); R³ (referring to the group attached to the oxygen at the 5' position of the sugar ring); and R (referring to the

group attached to the carbonyl (CO) group protecting the N² position of guanosine). (*Id.*)

23. The '719 Patent discloses that the identities of R¹ and R² are each alkyl. The '719 Patent refers to the compounds in 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).) A POSA would have understood that “N,N-dialkyl” refers to alkyl groups attached to the nitrogen of the phosphoramidite, as reflected in R¹ and R² of the figure above. (Ex. 1043 at 6:48-65.) A POSA also would have understood that the most well-known “cyanoethyl N,N-dialkyl phosphoramidite” is 2-cyanoethyl N,N-di-isopropyl phosphoramidite, which has “been used virtually exclusively in phosphoramidite-based solid phase nucleotide synthesis.” (Ex. 1009 at 3857.)

24. The '719 Patent discloses that the identity of R³ is DMT (dimethoxytrityl). The '719 Patent refers to the compounds in 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).) A POSA would have understood that “5'-dimethoxytrityl” refers to a dimethoxytrityl group attached to the oxygen at the 5' position of the sugar ring, as reflected in R³ of the figure above. (Ex. 1043 at 6:48-65.)

25. The '719 Patent therefore discloses that Group 5 is the N²-protected guanosine depicted below, where the guanosine protecting group is represented by R.

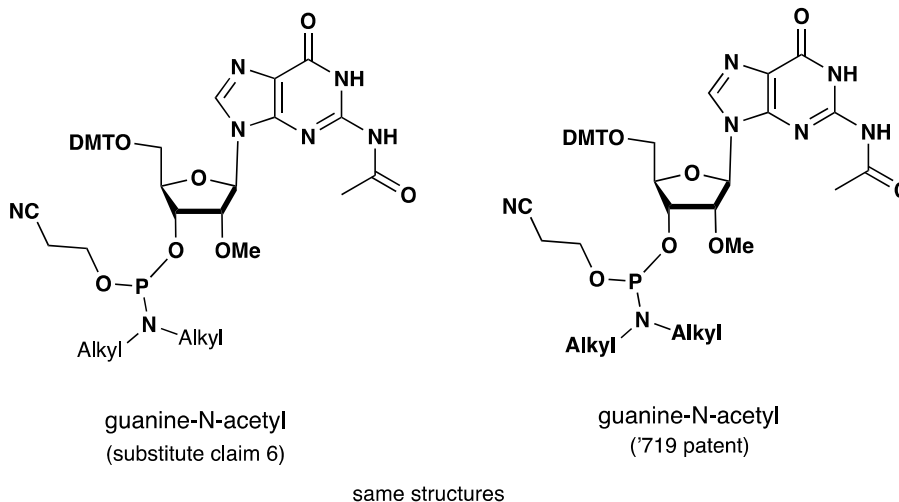


26. As shown above, Group 5 in the '719 Patent has the same structure of Formula 1 in Substitute Claim 6 where Z is Oxygen, W is methyl, and X is cyanoethyl dialkyl phosphoramidite.

27. The '719 Patent also discloses an acetyl group for protecting the N² position of guanine in Group 5, which is the same structure in Substitute Claim 6 where “B” is guanine-N-acetyl. 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.) Acetyl is specifically identified in this list. Thus, a POSA would have at once envisaged acetyl for the N²-protection of guanosine in Group 5, which is the same compound claimed in Substitute Claim 6. Given that the figure associated with Group 5 in the '719 Patent already depicts the carbonyl (CO) part of an acetyl protecting group

(COCH₃), a POSA would have understood that the '719 Patent discloses acetyl-protected guanosine in Group 5 when R is CH₃.

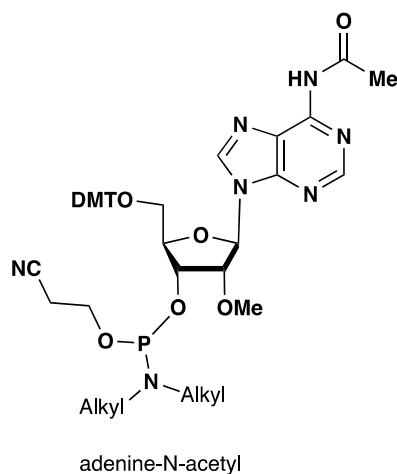
28. For comparison, both (a) the molecule claimed in Substitute Claim 6 where “B” is guanine-N-acetyl and (b) the molecule disclosed in Group 5 (N²-protected-2'-O-methyl-5'-dimethoxytrityl-guanosine cyanoethyl N,N-dialkyl phosphoramidite where acetyl is the protecting group) are arranged side-by-side below.



29. Thus, the molecule claimed in Substitute Claim 6 where “B” is guanine-N-acetyl and the acetyl-protected guanosine compound of Group 5 in the '719 Patent are identical.

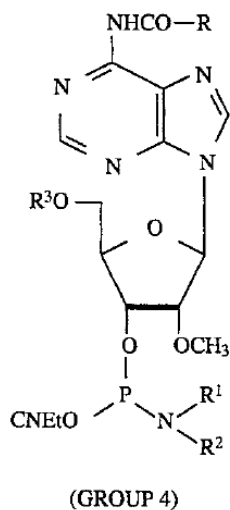
2. The '719 Patent Discloses the Identical Molecule as Substitute Claim 6 of the '885 Patent Where “B” Is Adenine-N-Acetyl

30. When “B” is **adenine-N-acetyl**, Substitute Claim 6 claims the following compound:



31. The '719 Patent discloses the same compound of Substitute Claim 6, where B is adenine-N-acetyl. The '719 Patent describes this compound as belonging to a group of compounds named “group 4 (N⁶-protected-2'-O-methyl-5'-dimethoxytrityl-adenosine cyanoethyl N,N-dialkyl-phosphoramidite)[.]” (Ex. 1043 at 16:63-65.) I refer to this group of compounds in the '719 Patent as “Group 4” in this declaration.

32. The '719 Patent further discloses the structure of compounds in Group 4 as follows:



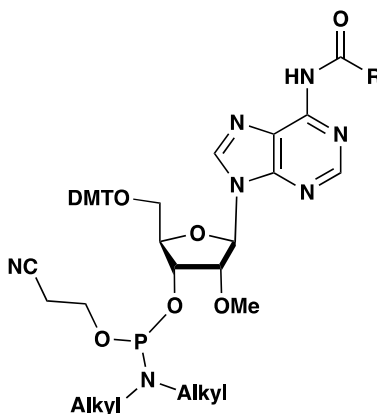
(Ex. 1043 at 6:32-45.) Group 4 is directed to phosphoramidite compounds having an O-methyl group at the 2' position of the sugar ring and an N⁶-protected adenosine residue at the 1' position of the sugar ring.

33. Group 4 contains four substituent groups: R¹ and R² (referring to the groups attached to nitrogen of the phosphoramidite); R³ (referring to the group attached to the oxygen at the 5' position of the sugar ring); and R (referring to the group attached to the carbonyl (CO) group protecting the N⁶ position of adenosine). (*Id.*)

34. As with Group 5 described above, the '719 Patent discloses that the identities of R¹ and R² are each alkyl in Group 4. The '719 Patent refers to the compounds in Group 4 as “N⁶-protected-2'-O-methyl-5'-dimethoxytrityl-adenosine cyanoethyl **N,N-dialkyl**-phosphoramidite.” (Ex. 1043 at 16:63-65 (emphasis added).) A POSA would have understood that “N,N-dialkyl” refers to alkyl groups attached to the nitrogen of the phosphoramidite, as reflected in R¹ and R² of the figure above. (Ex. 1043 at 6:32-45.) A POSA also would have understood that the most well-known “cyanoethyl N,N-dialkyl phosphoramidite” is 2-cyanoethyl N,N-di-isopropyl phosphoramidite, which has “been used virtually exclusively in phosphoramidite-based solid phase nucleotide synthesis.” (Ex. 1009 at 3857.)

35. The '719 Patent discloses that the identity of R³ is DMT (dimethoxytrityl). The '719 Patent refers to the compounds in Group 4 as “N⁶-protected-2'-O-methyl-5'-**dimethoxytrityl**-adenosine cyanoethyl N,N-dialkyl-phosphoramidite.” (Ex. 1043 at 16:63-65 (emphasis added).) A POSA would have understood that “5'-dimethoxytrityl” refers to a dimethoxytrityl group attached to the oxygen at the 5' position of the sugar ring, as reflected in R³ of the figure above. (Ex. 1043 at 6:32-45.)

36. The '719 Patent therefore discloses that Group 4 is the N⁶-protected adenosine depicted below, where the adenosine protecting group is represented by R.

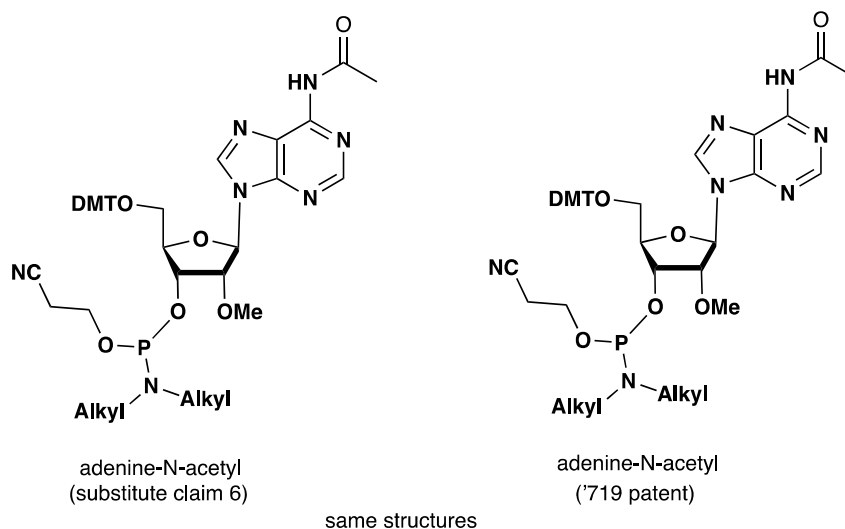


37. As shown above, Group 4 in the '719 Patent has the same structure of Formula 1 in Substitute Claim 6 where Z is Oxygen, W is methyl, and X is cyanoethyl dialkyl phosphoramidite.

38. 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. 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.) Acetyl is specifically identified in this list. Thus, a POSA would have at once envisaged acetyl for the N⁶-protection of adenosine in Group 4, which is the same compound claimed in Substitute Claim 6. Given that the disclosure of Group 4 in the ’719 Patent already depicts the carbonyl (CO) part of an acetyl protecting group (COCH₃), a POSA would have understood that the ’719 Patent discloses acetyl-protected adenosine when R is CH₃.

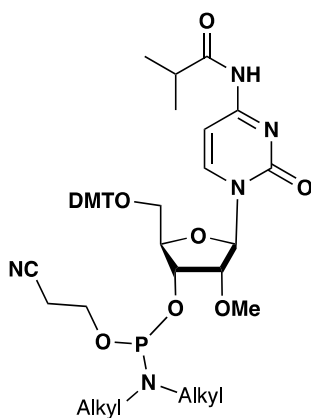
39. For comparison, both (a) the molecule claimed in Substitute Claim 6 where “B” is adenine-N-acetyl and (b) the molecule disclosed in Group 4 (N⁶-protected-2’-O-methyl-5’-dimethoxytrityl-adenosine cyanoethyl N,N-dialkyl-phosphoramidite where acetyl is the protecting group) are arranged side-by-side below.



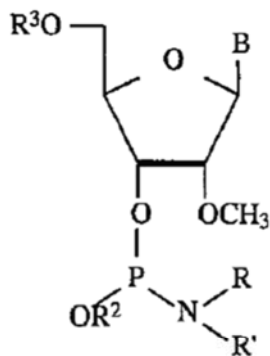
40. Thus, the molecule claimed in Substitute Claim 6 where “B” is adenine-N-acetyl and the acetyl-protected adenosine compound of Group 4 in the '719 Patent are identical.

3. The '719 Patent Discloses the Identical Molecule as Substitute Claim 6 of the '885 Patent Where “B” Is Cytosine-N-Isobutyryl

41. When “B” is **cytosine-N-isobutyryl**, Substitute Claim 6 claims the following compound:



42. 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,” which is depicted as “IIb” below.



(GROUP 1)

Structures:

I; B; A^{bz}, R&R; Isopropyl, R²; CH₃; R³; DMT
 II; B; C^{bz}, R&R; Isopropyl, R²; CH₃; DMT
 IIb; B; C^{ibu}, R&R; Isopropyl, R²; CH₂CH₂CN; R³; DMT
 III; B; G^{ibu}, R&R; Isopropyl, R²; CH₃; R³; DMT
 IVa; B; U; R&R; Isopropyl, R²; CH₃; R³; DMT
 IVb; B; U; R&R; Isopropyl, R²; CH₂CH₂CN; R³; DMT

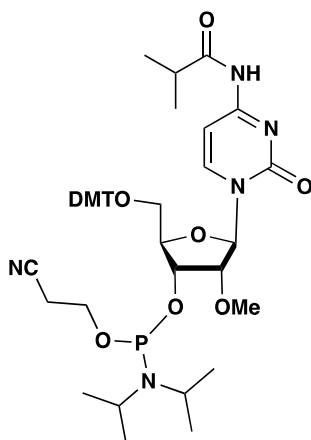
(Ex. 1043 at 5:50-65 (highlighting added).) The '719 Patent discloses the general phosphoramidite structure above and describes this structure as belonging to a series of compounds labeled group 1. (*Id.*) I refer to this group of compounds in the '719 Patent as “Group 1” in this declaration.

43. This general structure of Group 1 contains five substituent groups: B (referring to the base group); R and R' (referring to the groups attached to nitrogen of the phosphoramidite); R² (referring to the group attached to the oxygen in the

phosphoramidite); and R³ (referring to the group attached to the oxygen at the 5' position of the sugar ring). (*Id.*)

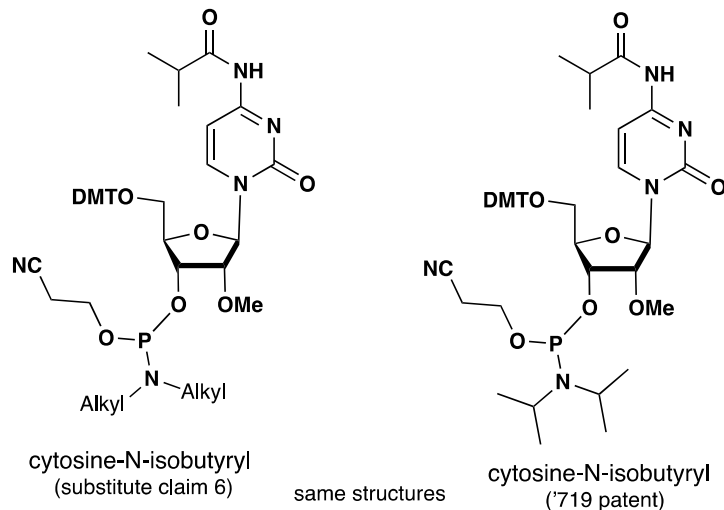
44. The '719 Patent discloses the identity of these constituents for structure IIb. (*Id.*) Specifically, a POSA would have understood that “B; C^{ibu}” refers to the base as cytosine-N-isobutyryl, which is consistent with the conventional naming of cytosine (C) with an isobutyryl protecting group (^{ibu}). A POSA also would have understood that “R&R; Isopropyl” refers to isopropyl groups attached to the nitrogen at R and R' in the figure, and that “R²; CH₂CH₂CN” refers to a 2-cyanoethane group attached to the oxygen at R² in the figure. A POSA also would have understood that “R³; DMT” refers to a dimethoxytrityl protecting group (DMT) bound to the oxygen at R³ in the figure.

45. Thus, a POSA would have understood that the '719 patent discloses that “structure IIb” has the following structure:



46. Consistent with this understanding, the '719 Patent also describes “Structure IIb” as “N⁴-Isobutyryl-2'-O-methyl-5'-dimethoxytrityl-cytidine-3'-CNEt, N,N-diisopropylphosphoramidite.” (Ex. 1043 at 15 (Table 9).) This compound is identical to the compound depicted above as structure IIb.

47. For comparison, both (a) the molecule claimed in Substitute Claim 6 where “B” is cytosine-N-isobutyryl and (b) the molecule disclosed as compound IIb in the '719 Patent are arranged side-by-side below.



48. Thus, the molecule claimed in Substitute Claim 6 where “B” is cytosine-N-isobutyryl and the molecule disclosed as compound IIb in the '719 Patent are identical.

4. The '719 Patent Is Enabling

49. As mentioned in my opening declaration, I was informed that a prior art reference which expressly anticipates a claimed invention is presumed to be enabling, *i.e.*, that the prior art reference would have enabled a POSA to make the

claimed invention. Thus, I understand that the '719 Patent is presumptively enabling.

50. Irrespective of the foregoing presumption, in my opinion, the '719 Patent would have enabled a POSA to make and use the molecules claimed in Substitute Claim 6 (where "B" is guanine-N-acetyl, adenine-N-acetyl, and cytosine-N-isobutyryl) as of its priority date without undue experimentation.

51. With respect to "guanine-N-acetyl" and "adenine-N-acetyl" in Substitute Claim 6, the '719 Patent discloses acetyl-protected guanosine and adenosine as part of Group 5 and Group 4, respectively. The '719 Patent states that "[t]he compounds of group 4 and group 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.) The '719 Patent further indicates that application Ser. No. 07/753,077 "issued as U.S. Pat. No. 5,214,135 on May 25, 1993, which is herein incorporated by reference." (Ex. 1043 at 1:9-12.) This passage is referring to the '135 Patent (Ex. 1047). Thus, a POSA would have understood that the compounds of Groups 4 and 5 could be prepared using the process for producing the compounds of group II in the '135 Patent.

52. The '135 Patent, which the '719 Patent incorporates by references and is the parent of the '719 Patent, discloses a synthesis scheme for compounds of group II. Specifically, the '135 Patent discloses that group II includes compounds

VIIa-d, and further discloses a synthesis scheme for these compounds. (Ex. 1047 at 4:1-17 (depicting Group II) and 5:2-6:53 (synthesis of compounds in Group II).)

53. Based on this disclosure in the '719 Patent that the “compounds of group 4 and group 5 are produced using the process disclosed for producing compounds of group II” of the '135 Patent, (Ex. 1043 at 3:10-12), and a general knowledge of synthetic organic chemistry, a POSA would not have had to engage in very much, if any, experimentation to make the molecules claimed in Substitute Claim 6 (where “B” is guanine-N-acetyl and adenine-N-acetyl). Even without the '135 Patent, however, a POSA would not have had to engage in very much, if any, experimentation to make these molecules because the '719 Patent discloses that its compounds “demonstrate the generality of the synthetic processes.” (Ex. 1043 at 15:54-57.)

54. 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.) The '719 Patent also discloses that “[c]ertain additional 2'-O-methyl-5'-dimethoxytritylnucleosides were added in the present investigation, as to increase the further usefulness of these products, as well as to **demonstrate generality of**

the synthetic processes. This includes the compound N4-isobutyryl-2'-O-methyl-5'-dimethoxytrityl cytidine (structure XIX), and its subsequent conversion to the corresponding 3'-CNEt phosphoramidite (structure IIb)." (Ex. 1043 at 15:54-61 (emphasis added).)

55. Based on this disclosure, and a general knowledge of synthetic organic chemistry, a POSA following the '719 Patent would not have had to engage in very much, if any, experimentation to make the molecule claimed in Substitute Claim 6 (where "B" is cytosine-N-isobutyryl).

56. A POSA further would have understood that the '719 Patent taught a POSA how to use the acetyl-protected guanosine compound of Group 5, the acetyl-protected adenosine compound of Group 4, and structure IIb in Group 1. For example, the '719 Patent discloses that its compounds can be used in oligonucleotide synthesis. (Ex. 1043 at 17:24-37.) In fact, the use of these compounds as building blocks in oligonucleotide synthesis would have been known to even less experienced chemists or technicians, who would simply have had to load such a building block into an automated oligonucleotide synthesizer following standard parameters.

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

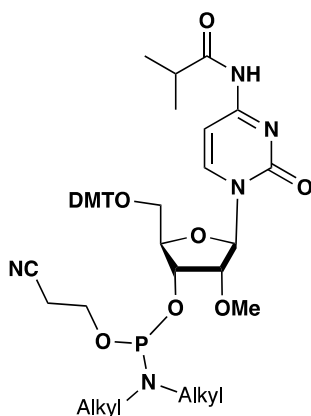
57. In my opinion, Substitute Claim 6 is anticipated by U.S. Patent No. 5,606,049 ("the '049 Patent") (Ex. 1045).

58. The '049 Patent issued on February 25, 1997, over ten years before the priority date of the '885 Patent. (Ex. 1045 at Cover; Ex. 1001 at Cover.)

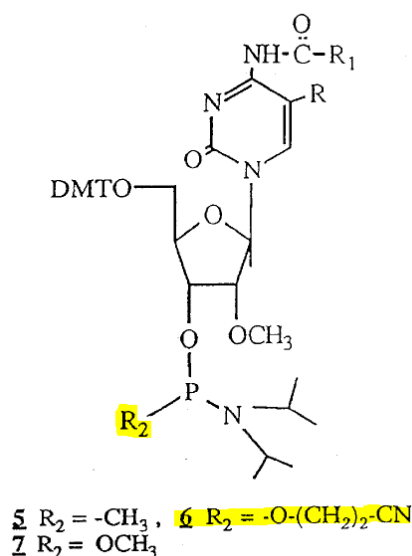
59. As described below, the '049 Patent anticipates Substitute Claim 6 where B is (1) cytosine-N-isobutyryl and (2) 5-methyl cytosine-N-isobutyryl.

1. The '049 Patent Discloses the Identical Molecule as Substitute Claim 6 of the '885 Patent Where “B” Is Cytosine-N-Isobutyryl

60. When “B” is **cytosine-N-isobutyryl**, Substitute Claim 6 claims the following compound:



61. 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).) This structure is directed to a phosphoramidite having an O-methyl group at the 2' position of the sugar ring and an N-protected cytosine residue at the 1' position of the sugar ring.

62. This structure in Figure 2 contains three substituent groups: R_2 (referring to the group attached to the phosphorous in the phosphoramidite); R_1 (referring to the group attached to the carbonyl (CO) group protecting the N position of the cytosine residue); and R (referring to the group attached at the 5-position of cytosine). (*Id.*)

63. The '049 Patent discloses that R_2 is cyanoethyl. With respect to compound 6 identified in Figure 2, the '049 Patent discloses that R_2 is “-O-(CH₂)₂-CN”. (Ex. 1045 at Fig. 2.) A POSA would have understood that “-O-(CH₂)₂-CN” refers to cyanoethyl, as recited at the X position in Substitute Claim 6.

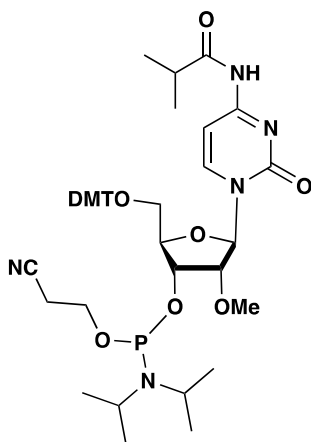
Furthermore, the '049 patent discloses that Compound 6 in Example 6 is “**3'-β-cyanoethyl-diisopropylphosphoramidite-5'-dimethoxytrityl-N⁴-isobutyryl-2'-O-methyl-cytidine**”, which similarly has cyanoethyl at this position. (Ex. 1045 at 10:62-63 (emphasis added).)

64. The '049 Patent discloses that R₁ includes an isobutyryl protecting group on the cytosine group. The '049 Patent discloses that R₁ includes “alkyl of about 1 to 6 carbon atoms”. (Ex. 1045 at 1:64.) A POSA would have understood that this alkyl group included the three-carbon isopropyl alkyl group, CH(CH₃)₂, which would have resulted in an isobutyryl protecting group when attached to the carbonyl (CO) part of the protecting group depicted in Figure 2. 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.) 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); *id.* at 6:26-27.) A POSA would have understood that “N⁴-isobutyryl” refers to an isobutyryl protecting group attached at the 4 position of cytosine.

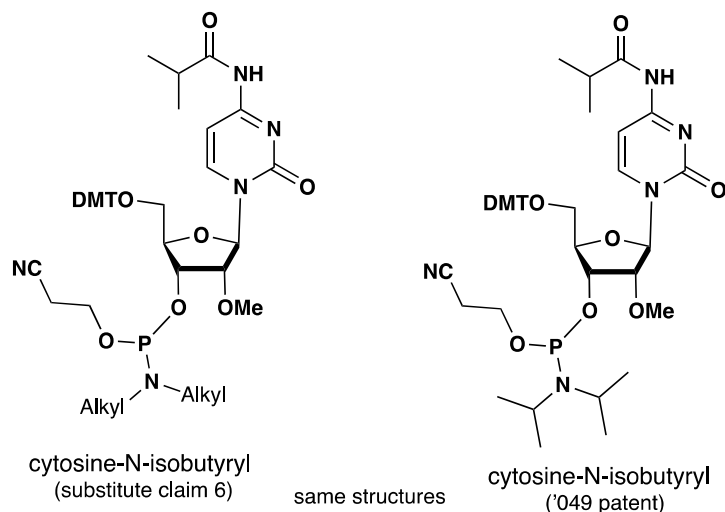
65. The '049 Patent discloses that R includes hydrogen. The '049 patent discloses that “R is hydrogen, fluorine or alkyl of 1 to 4 carbon atoms” at this

position. (Ex. 1045 at 1:63-65; *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).) In the corresponding disclosure of Compound 6, the '049 Patent discloses that Compound 6 is “3'-β-cyanoethyl-diisopropylphosphoramidite-5'-dimethoxytrityl-N⁴-isobutyryl-2'-O-methyl-cytidine.” (Ex. 1045 at 10:21-62 (describing Example 6).) A POSA would have understood that, in Compound 6 in this example, the R group attached at the 5-position of cytosine is hydrogen.

66. A POSA therefore would have at once envisaged the following compound in Figure 2 of the '049 Patent:



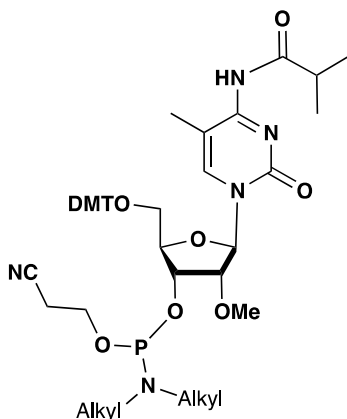
67. For comparison, both (a) the molecule claimed in Substitute Claim 6 where “B” is cytosine-N-isobutyryl and (b) the isobutyryl-protected compound in Figure 2 of the '049 Patent where R is hydrogen are arranged side-by-side below.



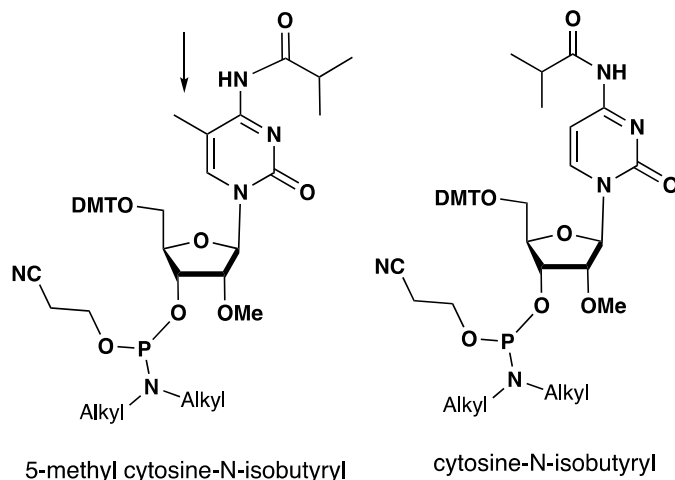
68. Thus, the molecule claimed in Substitute Claim 6 where “B” is cytosine-N-isobutyryl and the isobutyryl-protected compound in Figure 2 of the '049 Patent where R is hydrogen are identical.

2. The '049 Patent Discloses the Identical Molecule as Substitute Claim 6 of the '885 Patent Where “B” Is 5-Methyl Cytosine-N-Isobutyryl

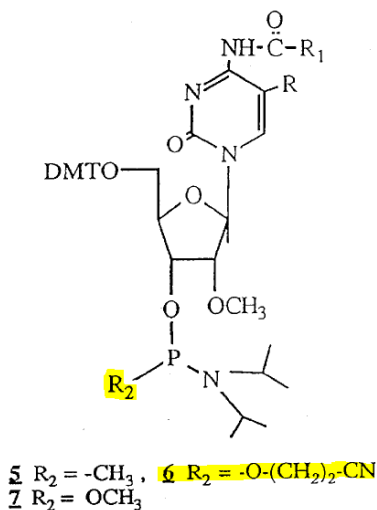
69. When “B” is **5-methyl cytosine-N-isobutyryl**, Substitute Claim 6 claims the following compound:



70. 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, depicted below.



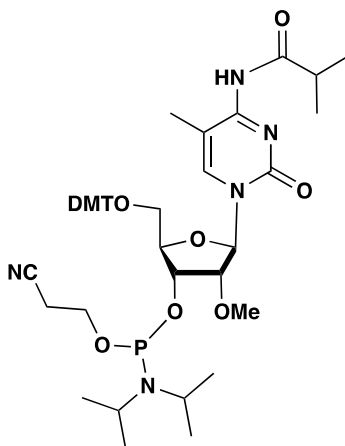
71. Based on the same disclosure described in the previous section with respect to cytosine-N-isobutyryl, the '049 Patent also discloses the same compound of Substitute Claim 6, where B is 5-methyl cytosine-N-isobutyryl. The '049 Patent describes this compound as in Figure 2 below.



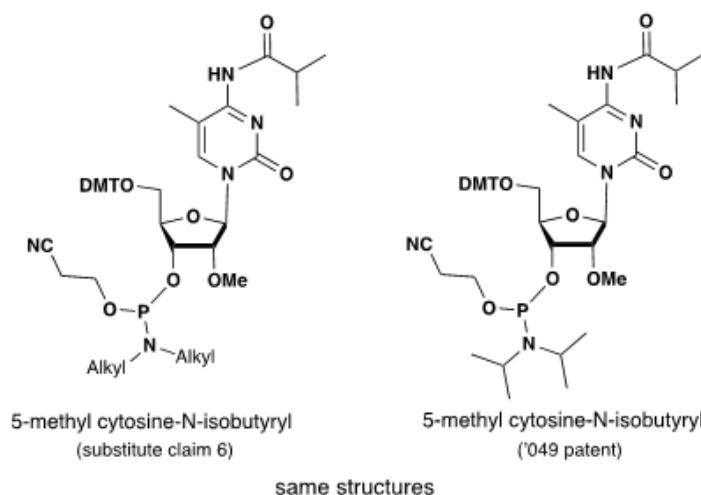
(Ex. 1045 at Fig. 2 (highlighting added).)

72. In addition to the disclosure of cytosine-N-isobutyryl (where R is hydrogen) described above, Figure 2 also discloses 5-methyl cytosine-N-isobutyryl (where R is CH₃). Specifically, the '049 Patent states that “R is hydrogen, fluorine or alkyl of 1 to 4 carbon atoms” at this position. (Ex. 1045 at 1:63-64; *id.* at claim 1.) A POSA would have understood that an alkyl group of 1 carbon atom at this position would be a methyl (CH₃) group.

73. A POSA therefore would have at once envisaged the following compound in Figure 2 of the '049 Patent:



74. For comparison, both (a) the molecule claimed in Substitute Claim 6 where “B” is 5-methyl cytosine-N-isobutyryl and (b) the isobutyryl-protected compound in Figure 2 of the '049 Patent where R is methyl are arranged side-by-side below.



75. Thus, 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 are identical.

3. The '049 Patent Is Enabling

76. As mentioned above with respect to the '719 Patent, I understand that the '049 Patent is presumptively enabling.

77. Irrespective of the foregoing presumption, in my opinion, 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.

78. 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.) 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.)

79. 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.)

80. Based on these disclosures and a general knowledge of synthetic organic chemistry, a POSA would not have had to engage in very 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).

81. A POSA further would have understood that the ’049 Patent taught a POSA how to use the cytosine-N-isobutyryl and 5-methyl cytosine-N-isobutyryl compounds. For example, the ’049 Patent discloses that its compounds “are useful in the synthesis of Oligomers.” (Ex. 1045 at 6:6-7.) In fact, the use of these compounds as building blocks in oligonucleotide synthesis would have been known to even less experienced chemists or technicians, who would simply have had to load such a building block into an automated oligonucleotide synthesizer following standard parameters.

C. Substitute Claim 6 Is Anticipated by the Glen Report

82. In my opinion, Substitute Claim 6 is anticipated by Vol. 8, No. 1 of the Glen Report, published in June 1995 (“Glen Report”) (Ex. 1046).

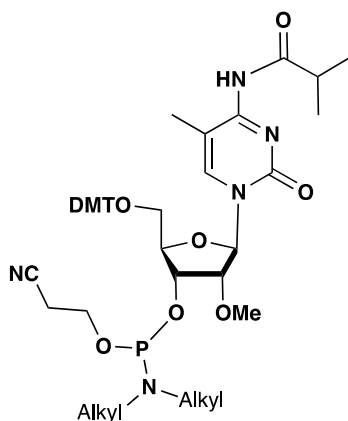
83. The Glen Report published in June 1995, over ten years before the priority date of the ’885 Patent. (Ex. 1046 at 1; Ex. 1001 at Cover.)

84. The Glen Report is part of a series of publications by the Glen Research Corporation (“Glen Research”). Glen Research was (and still is a) well-known manufacturer of reagents for oligonucleotide synthesis. A POSA would have been aware of Glen Research and the Glen Report, which Glen Research distributed to interested persons, including POSAs. In my experience with companies I have worked with, Glen Research is the “gold standard” in terms of the quality of their products, their constant participation in oligonucleotide conferences, and the state-of-the-art products they have available.

85. As described below, the Glen Report anticipates Substitute Claim 6 where B is 5-methyl cytosine-N-acetyl.

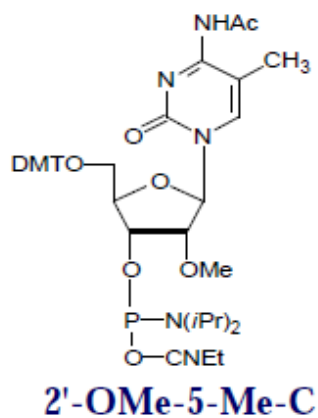
1. The Glen Report Discloses the Identical Molecule as Substitute Claim 6 of the ’885 Patent Where “B” Is 5-Methyl Cytosine-N-Acetyl

86. When “B” is **5-methyl cytosine-N-acetyl**, Substitute Claim 6 claims the following compound:



87. The Glen Report discloses the same compound of Substitute Claim 6, where B is 5-methyl cytosine-N-acetyl. The Glen Report describes this compound as “2’-OMe-5-Me-C.” (Ex. 1046 at 6.) I refer to this compound as “2’-OMe-5-Me-C” in this declaration.

88. The Glen Report further discloses the structure of 2’-OMe-5-Me-C as follows:

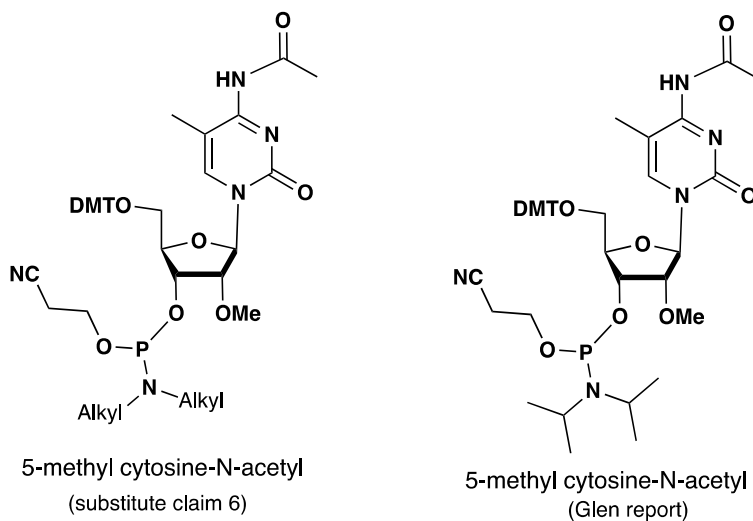


(Ex. 1046 at 6.)

89. 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.)

90. 2’-OMe-5-Me-C in the Glen Report has 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.

91. For comparison, both (a) the molecule claimed in Substitute Claim 6 where “B” is 5-methyl cytosine-N-acetyl and (b) 2’-OMe-5-Me-C in the Glen Report are arranged side-by-side below.



92. Thus, the molecule claimed in Substitute Claim 6 where “B” is 5-methyl cytosine-N-acetyl and 2’-OMe-5-Me-C in the Glen Report are identical.

2. The Glen Report Is Enabling

93. In my opinion, 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.

94. Based on the disclosure of the structure and a general knowledge of synthetic organic chemistry, a POSA would not have had to engage in very much, if any, experimentation to make the molecule claimed in Substitute Claim 6 (where “B” is 5-methyl cytosine-N-acetyl).

95. A POSA further would have understood that the Glen Report taught a POSA how to use the 5-methyl cytosine-N-acetyl compound. For example, the Glen Report discloses that 2'-OMe-5-Me-C is a building block for oligonucleotide synthesis and states that “[o]ligonucleotides containing 2'-OMe-5-Me-C . . . would be of interest to researchers involved in triplex and antisense studies using 2'-OMe-RNA.” (Ex. 1046 at 6.) In fact, the use of this compound as a building block in oligonucleotide synthesis would have been known to even less experienced chemists or technicians, who would simply have had to load such a building block into an automated oligonucleotide synthesizer following standard parameters.

**3. The Glen Report Discloses That
Substitute Claim 6 Where “B” Is 5-Methyl
Cytosine-N-Acetyl Was Offered for Sale in 1995**

96. As explained above, I have been informed that, under the on-sale bar, a claimed invention is anticipated (and thus invalid) if the claimed invention was on sale in the United States more than one year before the effective filing date. I have been informed that the on-sale bar has two requirements: (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.

97. In my opinion, the Glen Report discloses that both conditions are met for the compound of Substitute Claim 6 where “B” is 5-methyl cytosine-N-acetyl.

98. First, the Glen Report discloses that Glen Research offered to sell the compound in Substitute Claim 6 where B is 5-methyl cytosine-N-acetyl in 1995. With respect to 2'-OMe-5-Me-C, the Glen Report discloses the quantity and price of that compound. (Ex. 1046 at 6.) 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.) These prices, quantities, and catalog numbers show that Glen Research had commercially offered to sell the claimed compound more than one year before the effective filing date of May 18, 2009.

99. Second, the Glen Report discloses that the compound in Substitute Claim 6 where B is 5-methyl cytosine-N-acetyl was ready for patenting. The Glen Report discloses that Glen Research added the compound 2'-OMe-5-Me-C to its catalog. (Ex. 1046 at 6.) The two quantities offered of 100 μ mole and 0.25 g indicate that Glen Research was able to synthesize this compound at a repeatable, commercial scale. (*Id.*) And nothing in the Glen Report suggests that the offer for sale was experimental.

IV. SUBSTITUTE CLAIM 6 WOULD HAVE BEEN OBVIOUS IN LIGHT OF THE PRIOR ART

100. In my opinion, in addition to anticipation above, Substitute Claim 7 is obvious in view of each of the following four combinations of references:

- The '719 Patent alone (Ex. 1043)
- The '719 Patent (Ex. 1043) and Pitsch (Ex. 1018)
- The '049 Patent alone (Ex. 1045)
- The '049 Patent (Ex. 1045) and Pitsch (Ex. 1018)

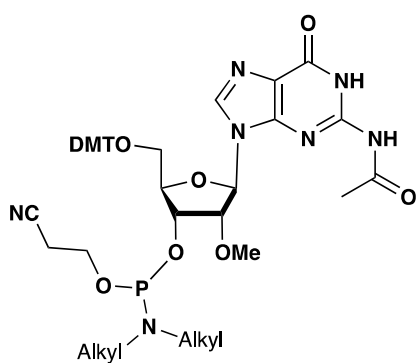
A. Substitute Claim 6 Would Have Been Obvious in View of the '719 Patent Alone or with Pitsch

101. As I described above, the '719 Patent anticipates Substitute Claim 6. In addition to anticipation, Substitute Claim 6 of the '885 Patent would have been obvious in view of the '719 Patent alone or with Pitsch (Ex. 1018).

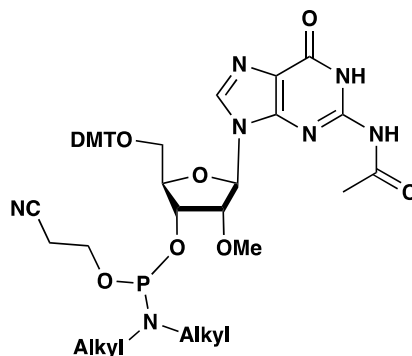
1. The '719 Patent Alone

102. 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.

103. 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). These structures are reproduced below.

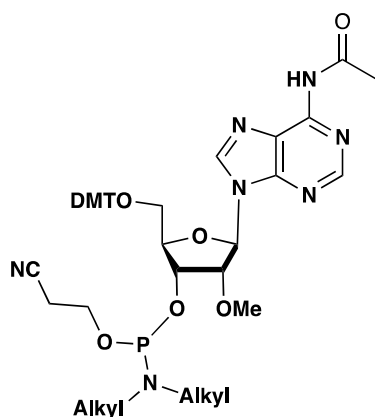


guanine-N-acetyl
(substitute claim 6)

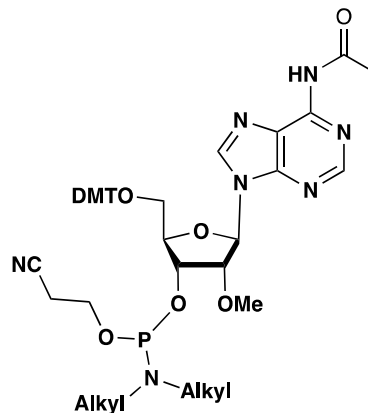


guanine-N-acetyl
('719 patent)

same structures



adenine-N-acetyl
(substitute claim 6)



adenine-N-acetyl
('719 patent)

same structures

104. A POSA also would have been motivated to make these compounds with a reasonable expectation of success based on the '719 Patent. 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.) 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. 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.

105. Furthermore, a POSA would have had a reasonable expectation of success in making these compounds based on the '719 Patent. As described above with respect to anticipation, the '719 Patent's disclosure of these compounds is enabling. That same disclosure would have given a POSA a reasonable expectation of success in making these compounds.

106. Finally, to the extent Chemgenes or Dr. Hrdlicka contend that the "lead compound" framework is required for Substitute Claim 6, I disagree. As I explained further in my reply declaration submitted with this declaration, that framework is not consistent with how a POSA would have approached the selection of building blocks for oligonucleotide synthesis. (Ex. 1033.) Nevertheless, a POSA would have been motivated to select the N-protected

guanine (Group 5) and N-protected adenine (Group 4) from the '719 Patent for the reasons provided above, including that the '719 Patent discloses that its compounds can be used in oligonucleotide synthesis. (Ex. 1043 at 17:24-37.)

2. The '719 Patent and Pitsch

107. 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.

108. 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).

109. A POSA would have been motivated to make the compounds in Substitute Claim 6 where B is guanine-N-acetyl and adenine-N-acetyl with a reasonable expectation of success in view of Pitsch (Ex. 1018).

110. Pitsch discloses acetyl-protecting groups on both adenosine and guanosine phosphoramidites. (Ex. 1018 at 3775.) Furthermore, as I explained my opening declaration, Pitsch explains that the acetyl protecting group was chosen for its fast deprotection speed, concluding that “the Ac [acetyl] group, in combination with MeNH_2 , is indeed suited for a labile universal nucleobase protection.” (Ex. 1018 at 3778; 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).

111. A POSA would have had a reasonable expectation of success in making these compounds in view of Pitsch. 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 concludes that acetyl in combination with MeNH₂ is suitable for “universal nucleobase protection.” (Ex. 1018 at 3778.) Furthermore, the acetylation of these compounds would have been a routine process for a POSA.

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

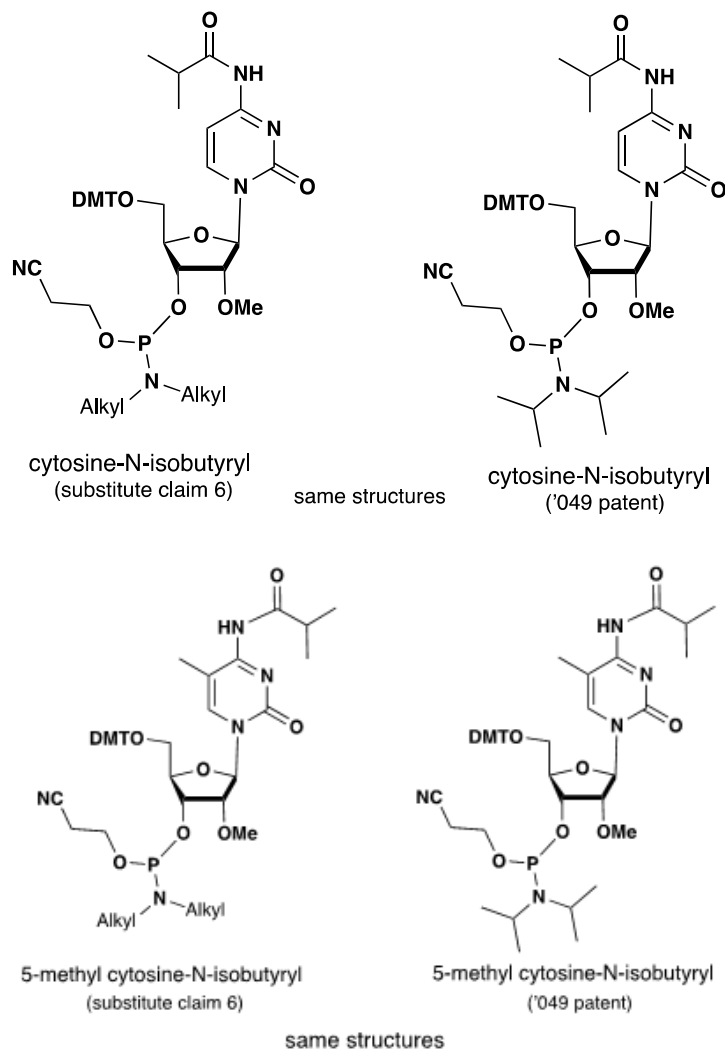
112. As I described above, the '049 Patent anticipates Substitute Claim 6. In addition to anticipation, Substitute Claim 6 of the '885 Patent would have been obvious in view of the '049 Patent alone or with Pitsch (Ex. 1018).

1. The '049 Patent Alone

113. 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.

114. 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). These structures are reproduced below.



115. A POSA also would have been motivated to make these compounds with a reasonable expectation of success based on the '049 Patent. For example, with the R group attached at the 5-position of cytosine in the '049 Patent, a POSA would have been motivated to use hydrogen and methyl (CH₃), as the '049 Patent disclosed both as suitable options. Specifically, the '049 patent discloses that the R

group attached at the 5-position of cytosine can be “hydrogen, fluorine or alkyl of 1 to 4 carbon atoms.” (Ex. 1045 at 1:48-65; *id.* at claims 1 and 2.) A POSA would have understood that methyl (CH₃) is the simplest member of the “alkyl of 1 to 4 carbon atoms” group.

116. Furthermore, a POSA would have had a reasonable expectation of success in making these compounds based on the '049 Patent. As described above with respect to anticipation, the '049 Patent's disclosure of these compounds is enabling. That same disclosure would have given a POSA a reasonable expectation of success in making these compounds.

117. Finally, to the extent Chemgenes or Dr. Hrdlicka contend that the “lead compound” framework is required for Substitute Claim 6, I disagree. As I explained further in my reply declaration submitted with this declaration, that framework is not consistent with how a POSA would have approached the selection of building blocks for oligonucleotide synthesis. (Ex. 1022) Nevertheless, a POSA would have been motivated to select compound 6 identified in Figure 2 of the '049 Patent for the reasons provided above, including that the '049 Patent discloses a detailed synthesis for this compound and states that its compounds “are useful in the synthesis of Oligomers.” (Ex. 1045 at 6:6-7, 10:59-11:2.)

2. The '049 Patent and Pitsch

118. 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.

119. As described above, the '049 Patent discloses the compound of Substitute Claim 6 where B is 5-methyl cytosine-N-isobutyryl (*i.e.*, the isobutyryl-protected compound in Figure 2 of the '049 Patent where R is methyl).

120. 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.

121. 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.) Pitsch’s disclosure also includes acetyl-protected cytosine. (*Id.* at 3775.)

122. Thus, for the same reasons described above, 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.

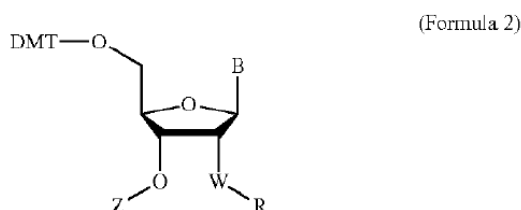
V. SUBSTITUTE CLAIM 7 WOULD HAVE BEEN OBVIOUS IN LIGHT OF THE PRIOR ART

123. In my opinion, Substitute Claim 7 is obvious in view of each of the following five combinations of references:

- The '719 Patent (Ex. 1043) and Scaringe (Ex. 1022)
- The '719 Patent (Ex. 1043), Pitsch (Ex. 1018), and Scaringe (Ex. 1022)
- The '049 Patent (Ex. 1045) and Scaringe (Ex. 1022)
- The '049 Patent (Ex. 1045), Pitsch (Ex. 1018), and Scaringe (Ex. 1022)
- The Glen Report (Ex. 1046) and Scaringe (Ex. 1022)

124. Substitute Claim 7, which is a proposed substitute for claim 1 of the '885 Patent, recites:

Derivatized nucleosides, succinates and solid supports of general formula 2,



wherein B is selected from the group consisting of Guanine-N-acetyl, adenine-N-acetyl, ~~cytosine-N-acetyl~~, ~~cytosine-N-isobutyryl~~, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl;

W is Oxygen and R is methyl; and

Z is C(O)-M-C(O)-NH, where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1-C20 alkyl, ethyloxyglycol,

and a combination of alkyl and ethyleneglycoxy.

(Motion to Amend at Appx. A.)

125. Substitute Claim 7 is identical to Claim 5 of the '885 Patent, except that it (1) omits the “cytosine-N-acetyl” and “cytosine-N-isobutyryl” species of B as reflected in strikethrough text above, (2) adds “[d]erivatized nucleosides, succinates and solid supports of general formula 2,” and (3) adds “NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1-C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy.”

126. With respect to (3) above, the added language is consistent with how I previously stated a POSA would understand Claim 5 of the '885 patent (for which Claim 7 is a substitute). As I explained in my opening declaration, a POSA would have understood that Claim 5 of the '885 patent should include the same language found in the respective last phrases of Claims 3-4, and should read “NH is [capable of being attached to a solid support with a spacer selected from the group consisting] of C1-C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy.” (Ex. 1003 at ¶ 162.) Thus, the addition of the language in (3) is consistent with and does not change my opinions.

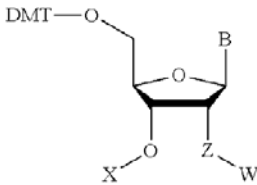
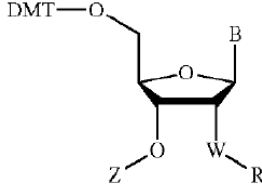
127. Similarly, with respect to (2) above, the addition of “solid” to “solid supports” is consistent with how a POSA would have understood Claim 5 (for

which Claim 7 is a substitute). The addition of (3) includes language that NH “capable of being attached to a solid support,” which already describes a solid support. Thus, the addition of the language in (2) is consistent with and does not change my opinions.

128. The “B” group in Substitute Claim 7 contains four members: guanine-N-acetyl; adenine-N-acetyl; 5-methyl cytosine-N-acetyl; and 5-methyl cytosine-N-isobutyryl. These are four of the same members as in Substitute Claim 6, described above.

129. The remainder of Substitute Claim 7 is identical to Claim 5 of the ’885 Patent, which I discussed in my opening declaration. (Ex. 1003 at ¶¶ 158, 164.)

130. Similar to the differences between Claims 2 and 3 of the ’885 Patent discussed in my opening declaration, (Ex. 1003 at ¶ 142), Substitute Claims 6 and 7 claim nearly identical chemical structures, as shown by the following table:

Substitute Claim 6	Substitute Claim 7
Derivatized nucleoside and phosphoramidite of general formula 1,	Derivatized nucleosides, succinates and solid supports of general formula 2,
Formula 1 	(Formula 2) 
where B is selected from the group consisting of	wherein 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;	Guanine-N-acetyl, adenine-N-acetyl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl;
Z is Oxygen and W is methyl; and	W is Oxygen and R is methyl; and
X is cyanoethyl dialkyl phosphoramidite.	Z is C(O)-M-C(O)-NH, where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1-C20 alkyl, ethoxyglycol, and a combination of alkyl and ethyleneglycoxy.

131. Thus, 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. In Substitute Claim 6, "X" is cyanoethyl dialkyl phosphoramidite, whereas in Substitute Claim 7, "Z" can be a succinyl-NH (-COCH₂CH₂CO-NH) group, which is capable of being attached to a solid support with a one of the enumerated spacers.

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

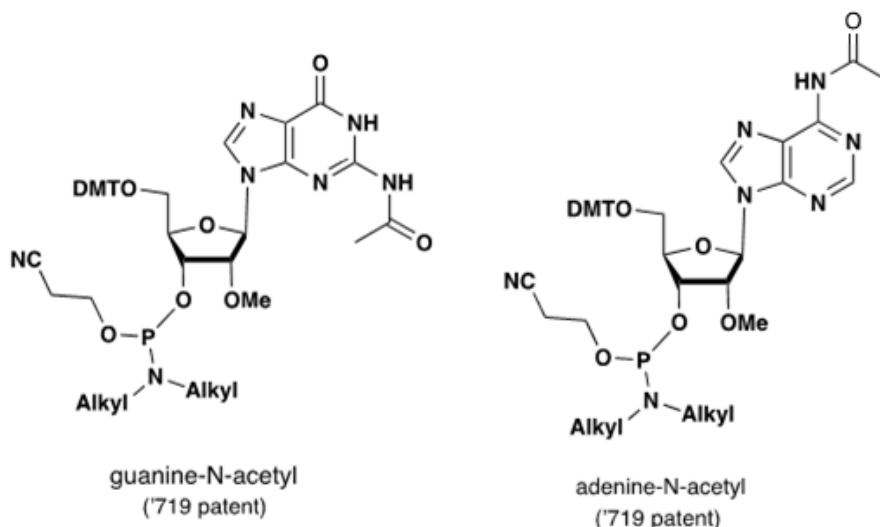
132. As I explained above, the '719 Patent anticipates Substitute Claim 6 and renders this claim obvious over the '719 Patent alone or with Pitsch. For those

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

133. 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.

134. 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.



135. 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. 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.

136. 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.

137. It was well known basic textbook knowledge to a POSA that in solid phase oligonucleotide synthesis using phosphoramidite chemistry (as shown in Figures 5 and 6 of my opening declaration, Ex. 1003 at ¶¶ 58-59), 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).

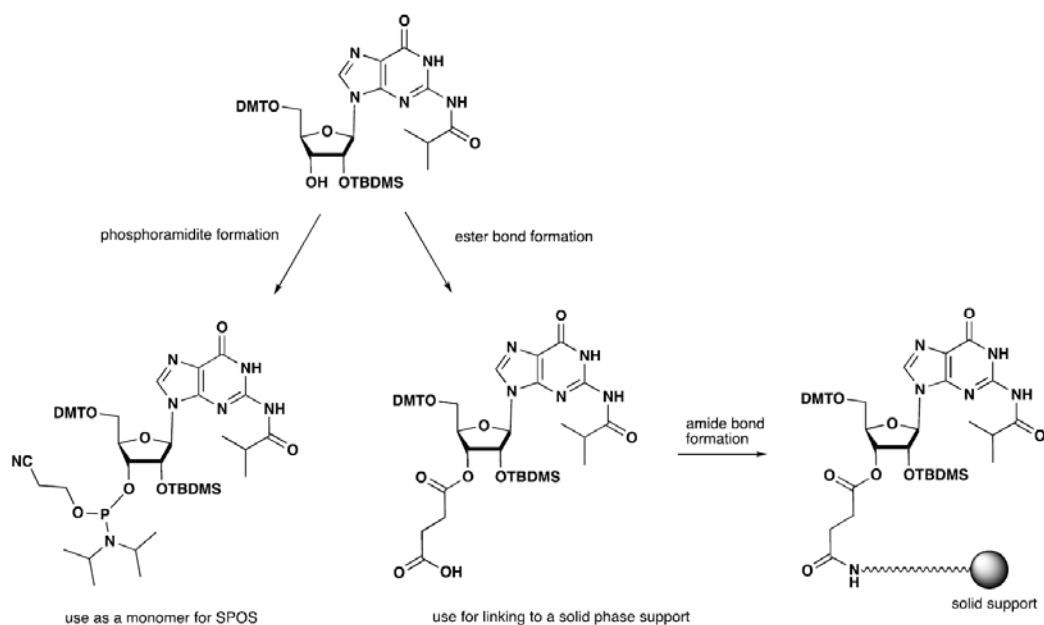
138. It was also well known to a POSA that the choice between these options (*i.e.*, phosphoramidite or succinate) depended on the desired location of the nucleoside during synthesis. A POSA would have understood that, in general, a nucleoside attached to a phosphoramidite could be added at any position during oligonucleotide synthesis except as the 3'-terminal nucleoside residue, while a nucleoside attached to a succinate could be added at this position. 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. (See, e.g., Reese 2005 (Ex. 1009) at 3861 (“The 3’-terminal nucleoside residue is commonly attached to these solid supports via a succinoyl group[.]”); Pon 2000 (Ex. 2031) at 6 (disclosing that the “two most commonly used solid-phase supports for oligonucleotide synthesis” use succinyl linkers); *id.* at 11 (succinyl, in use since the 1970s, is the “most commonly used linker arm” and has “remained very popular because of low cost and ease of incorporation”).)

139. Thus, a POSA seeking to use the phosphoramidite compounds disclosed in the ’719 Patent at the 3’-terminal end of an oligonucleotide would have been motivated to substitute the phosphoramidite with a succinate group, which was the most commonly used linker for oligonucleotide synthesis.

140. 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. A POSA would have known that succinate was “very popular because of low cost and ease of incorporation,” and would have reasonably expected the same ease here. (Pon (2000) (Ex. 2031) at 11.) A POSA also would have known how to switch between a phosphoramidite group and a succinate group based on the prior art.

141. 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.) The similarities between the two molecules are illustrated below.



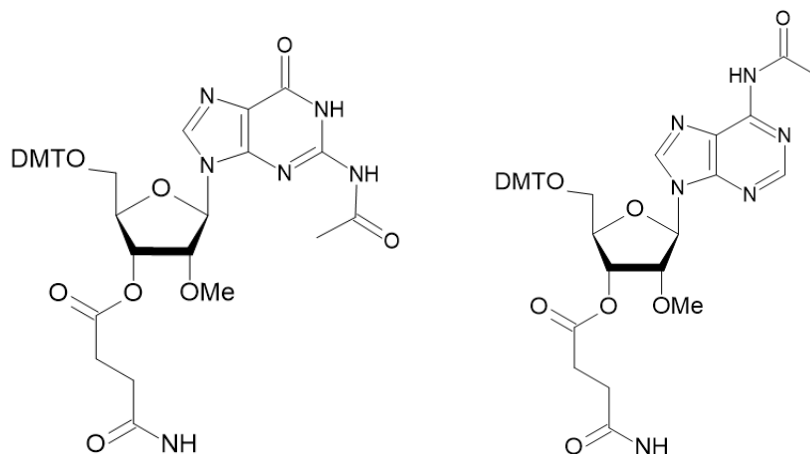
142. Scaringe further explains that the succinylated derivatives, *i.e.*, 5'-O-(dimethoxytrityl)-2'-O-(*t*-butyldimethylsilyl) ribonucleoside 3'-O-succinates, are coupled to LCAA-CPG to prepare the solid supports for SPOS.

All solid phase syntheses were performed on commercially available DNA synthesizers ... on a 0.5 μmol scale using derivatized 1000 Å CPG [] solid supports. These supports were prepared by the coupling of compounds 5a-d to LCAA-CPG.

(*Id.* at 5435; *see also id.* at 5440 (identifying compounds 5a-d as 5'-O-(dimethoxytrityl)-2'-O-(t-butyldimethylsilyl) ribonucleoside 3'-O-succinates).)

143. 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. (*See, e.g.*, Scheuer-Larsen (1997) (Ex. 1023) at 74.) A POSA would also have regarded a C6 alkyl as a suitable long chain alkyl spacer. (*See, e.g.*, Ex. 1007 at 2229, molecule #40.) A C6 alkyl falls within the claimed “C1-C20 alkyl” recited in Substitute Claim 6. 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.”

144. The succinylated derivatives of the '719 Patent compounds described above would result in the guanine-N-acetyl and adenine-N-acetyl compounds within the scope of Substitute Claim 7 depicted below.



145. Finally, to the extent Chemgenes or Dr. Hrdlicka contend that the “lead compound” framework is required for Substitute Claim 7, I disagree for the same reasons provided above with respect to Substitute Claim 6.

2. The '719 Patent, Pitsch, and Scaringe

146. 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.

147. 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. For the same reasons explained above 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.

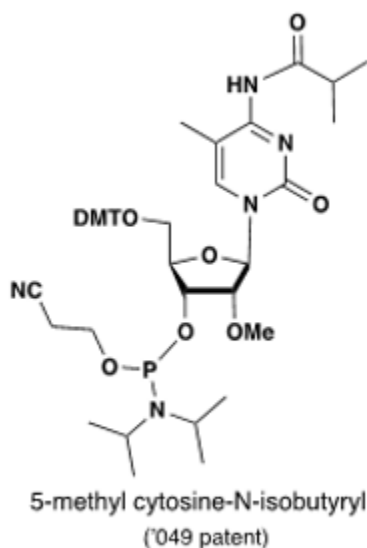
B. Substitute Claim 7 Would Have Been Obvious in View of (1) the '049 Patent and Scaringe or (2) the '049 Patent, Pitsch, and Scaringe

148. As I explained above, the '049 Patent anticipates Substitute Claim 6 and renders this claim obvious over the '049 Patent alone or with Pitsch. 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

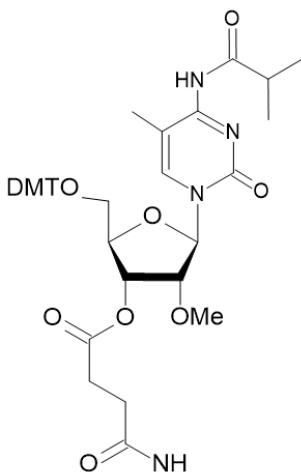
149. Substitute Claim 7 of the '885 Patent (where B is **5-methyl cytosine-N-isobutyryl**) would have been obvious in view of the '049 Patent and Scaringe.

150. 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.



151. 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.

152. For the same reasons discussed above 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 group on this compound of the '049 patent to a succinyl group with a reasonable expectation of success, which would result in a compound within the scope of Substitute Claim 7.



153. Finally, to the extent Chemgenes or Dr. Hrdlicka contend that the “lead compound” framework is required for Substitute Claim 7, I disagree for the same reasons provided above with respect to Substitute Claim 6.

2. The '049 Patent, Pitsch, and Scaringe

154. 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.

155. 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. For the same reasons explained above that Substitute Claim 7 of the '885 Patent would have been obvious in view of the '049 Patent and Scaringe, this claim would have been obvious in view of the '049 Patent, Pitsch, and Scaringe as well.

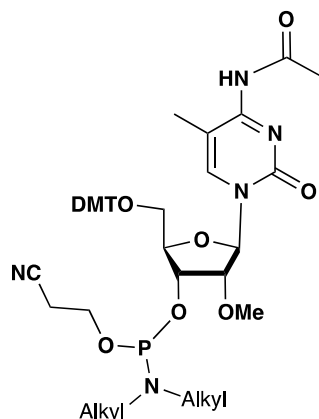
C. Substitute Claim 7 Would Have Been Obvious in View of the Glen Report and Scaringe

156. As I explained above, Glen Report anticipates Substitute Claim 6. 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 the Glen Report and Scaringe.

1. The Glen Report and Scaringe

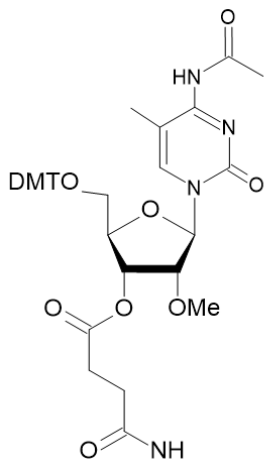
157. Substitute Claim 7 of the '885 Patent (where B is **5-methyl cytosine-N-acetyl**) would have been obvious in view of the Glen Report and Scaringe.

158. 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.



159. 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.

160. For the same reasons discussed above 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 group on this compound of the Glen Report to a succinyl group with a reasonable expectation of success, which would result in a compound within the scope of Substitute Claim 7.



161. Finally, to the extent Chemgenes or Dr. Hrdlicka contend that the “lead compound” framework is required for Substitute Claim 7, I disagree. As I explained further in my reply declaration submitted with this declaration, that framework is not consistent with how a POSA would have approached the selection of building blocks for oligonucleotide synthesis. (Ex. 1033.) Nevertheless, a POSA would have been motivated to select 2’-OMe-5-Me-C from the Glen Report for the reasons provided above, including that the Glen Report discloses that this compound “would be of interest to researchers involved in triplex and antisense studies using 2’-OMe-RNA.” (Ex. 1046 at 6.)

VI. CONCLUSION

162. For the reasons set forth above, it is my opinion that Substitute Claims 6 and 7 of the ’885 Patent are invalid.

I declare under the penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Dated: January 19, 2024



Phil S. Baran, Ph.D.