

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SHANGHAI HONGENE BIOTECH CORPORATION,

Petitioner,

v.

CHEMGENES CORPORATION,

Patent Owner.

IPR2023-00490

U.S. Patent No. 9,884,885 B2

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

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I. INTRODUCTION

The claims of U.S. Patent No. 9,884,885 (“the ’885 Patent”) are directed to derivatized phosphoramidites according to independent Claims 1 and 2 and derivatized nucleosides, succinates and solid supports according to independent Claims 3-5. Each independent claim encompasses a genus of compounds. This Motion to Amend proposes to narrow the scope of Claims 1, 4, and 5 to delete species from the recited genera and to insert inadvertently omitted language into Claim 5. Such narrowing amendments are fully supported by the ’885 Patent and its priority application and are not anticipated by or rendered obvious by Petitioner’s cited prior art or any other prior art known to Patent Owner.

II. STATEMENT OF RELIEF REQUESTED

Patent Owner respectfully requests that the Board grant this Motion to Amend and substitute challenged Claims 1 and 5 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” 6 and 7 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 claims (Claims 1 and 5) 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 (originally-filed patent application) 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 1-5 in the '885 patent. Substitute Claims 6 and 7 correspond to issued Claims 1 and 5, 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 '885 patent claims. As shown in Appendix A, Substitute Claim 6 retains all limitations of original independent Claim 1, but further narrows the element of “B is selected from the group consisting of” by removing the species “cytosine-N-acetyl.”

Substitute Claim 7 retains all limitations of original independent Claim 5, but has been amended to add the following narrowing limitations: (1) removing the species “cytosine-N-acetyl, cytosine-N-isobutyryl,” (2) specifying “Derivatized nucleosides, succinates and solid supports of general formula 2,” and (3) specifying that “NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1-C20 alkyl.”

In view of these added limitations, each of Substitute Claims 6 and 7 is narrower in scope than the original claims. *See* 37 C.F.R. § 42.121 (a)(2)(ii).

C. The Substitute Claims Are Fully Supported by the '885 Patent and the International Priority Application.

The '885 patent issued from U.S. Application No. 13/261,029 (“the '029 application”) (Ex. 1002 at 1-64), and claims priority to International Application

PCT/US2010/001494 (“PCT ’494 application”)¹ (*Id.* at 13-64), and U.S. provisional Appl. No. 61/216,491 (“the ’491 provisional”) (*Id.* at 65-124)². Patent Owner identifies the following portions of the ’029 application, and PCT ’494 application (collectively “the supporting applications”), 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 supporting applications, and the inventors were in possession of the Substitute Claims at the time of the invention. *See* 37 C.F.R. §§ 42.121(a)(2)(ii), 42.121(b).

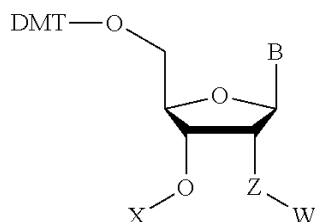
1. Substitute Claim 6 is Fully Supported

Substitute Claim 6 recites a derivatized nucleoside and phosphoramidite of general formula 1 below:

¹ The ’029 application is a National Stage filing under 35 U.S.C. § 371 of International Application PCT/US2010/001494, filed May 19, 2010.

² Because Patent Owner does not currently seek the benefit of the filing date of the disclosure set forth in the earlier-filed provisional application, 61/216,491, this Motion is not required to set forth support in the provisional application for the proposed Substitute Claims.

Formula 1

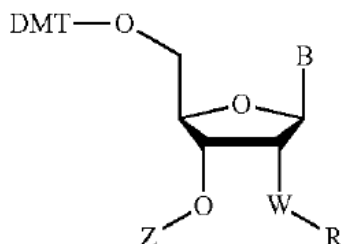


where the B substituent is selected from a group consisting of guanine-N-acetyl, adenine-N-acetyl, cytosine-N-isobutyryl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl. The Z substituent is oxygen, the W substituent is methyl and the X substituent is cyanoethyldialkyl phosphoramidite. Each of these elements is recited in original Claim 1 of the '885 patent, and is supported by pages 30-31 (Claim 3) of each of the supporting applications. *See* the '029 Application at pp. 30-31 (Ex. 1002 at 44-45), original Claim 3, which is also the PCT '494 application at p. 30-31 (*Id.*), Claim 3.

2. Substitute Claim 7 is Fully Supported

Substitute Claim 7 recites a derivatized nucleoside, succinates and solid supports of general formula 2 below:

(Formula 2)



where the B substituent is selected from a group consisting of guanine-N-acetyl, adenine-N-acetyl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl. The W substituent is oxygen and R is methyl. The Z substituent 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. Each of these elements is recited in Claim 5 of the '885 patent.

These elements are also disclosed in the '029 Application at page 32-33 (Ex. 1002 at 46-47) (Claim 7), at page 15 (compound 24) (*Id.* at 29), and at page 24 (*Id.* at 38), disclosing long chain alkyl amine (lcaa) spacers and the PCT '494 application at page 32-33 (Ex. 1002 at 46-47) (Claim 7), at page 15 (compound 24) (*Id.* at 29), and at page 24 (*Id.* at 38), disclosing long chain alkyl amine (lcaa) spacers. A POSA would have understood that “long chain spacers” and “lcaa” or “LCAA” spacers were commonly used spacers 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 support. Ex. 1003, ¶147; *see also* Ex. 2008, ¶ 81. As explained by Dr. Baran and Dr. Hrdlicka, long chain spacers of various lengths were commonly used spacers used in solid phase oligonucleotide synthesis including the ones illustrated in Ex. 1005 at 3186 in Fig. 1 (C3 alkyl spacer); Ex. 1007 at 2228 (compound 35 showing

C3 alkyl spacer), Ex. 1014 at 892 (compound 1a has R3 with a LCAA spacer), Ex. 1022 at 5435 and 5440 (using LCAA-CPG from CPG Inc., NJ), Ex. 2031 at p. 3.1.5 (“This spacer can be as simple as a single methylene group (e.g., aminomethyl polystyrene) or it can be a lengthy alkyl or alkyloxy chain (e.g., long-chain alkylamine CPG”), and at p. 3.1.6 in Fig. 3.1.3 (showing LCAA spacer), and at Fig. 3.1.9 (showing a polyethylene glycol linker (H), and a combination of alkyl and ethyleneglycoxy (L)). Ex. 1003, ¶147; *see also* Ex. 2008, ¶ 81.

Thus, “the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc).

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 6 deletes the species in Claim 1 that Petitioner alleged was anticipated in Ground I, and proposed Substitute Claim 7 deletes the species in Claim 5 that Petitioner alleged was anticipated in Ground VI. For this reason, 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).

IV. THE SUBSTITUTE CLAIMS ARE PATENTABLE OVER THE INSTITUTED GROUNDS

A. Level of Ordinary Skill in the Art

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

a person of ordinary skill in the art 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 those fields, and who had gained a thorough understanding of the development of nucleic acid-based materials, would also have qualified as a person of ordinary skill in the art.

Paper 7, at 7-8.

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

As of May 18, 2009, a person of ordinary skill in the art ("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 synthesis of nucleosides, nucleotides, and nucleic acids, including, but not limited to, the synthesis 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 synthesis of nucleosides, nucleotides, and nucleic acids, including, but not limited to, the synthesis 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 synthesis of nucleic acid-based materials pursuant to P(III) chemistry, would also have qualified as a POSA.

Ex. 2008, ¶ 90. This definition would not exclude medicinal chemists so long as the medicinal chemist in question met the above requirements.

Patent Owner contends that the amended claims are patentable over the instituted grounds under either definition of a POSA.

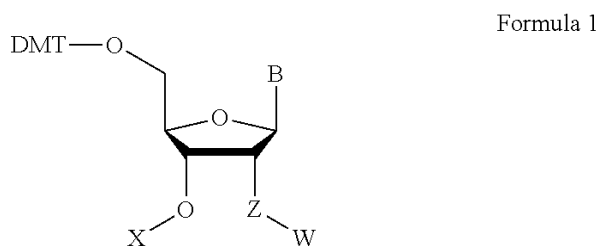
B. Claim Construction

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” and the constructions discussed in the Patent Owner’s Response to correct clear errors in Claim 5. 37 C.F.R. § 42.100. Specifically, for the reasons stated in the Petition,

Patent Owner agrees that a POSA would have understood “M” should be “ethyl” in Claim 5 and Substitute Claim 7 and that the last clause in Claim 5 and Substitute Claim 7 should be “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.” Paper No. 1, 17-20; Ex. 2008, ¶ 242.

C. Petitioner’s References Do Not Anticipate or Render Substitute Claim 6 Obvious.

Substitute Claim 6 is directed to a derivatized nucleoside and phosphoramidite of general formula 1,



where B is selected from the group consisting of Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-isobutyryl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl; Z is Oxygen and W is methyl; and X is cyanoethyl dialkyl phosphoramidite. Petitioner’s cited references do not disclose these limitations.³

³ Patent Owner has sought reissue of unamended Claim 1 in U.S. Reissue Application No. 18/130,902 to remove a compound from Claim 1’s Markush Group (where B is cytosine-N-acetyl) based on a prior sale of that compound.

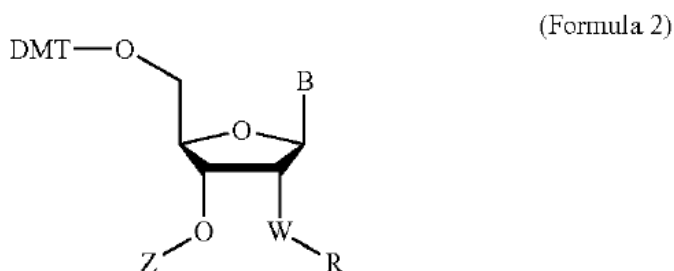
Petitioner cites U.S. Patent No. 5,808,039 (“Reddy”) (Ex. 1016) as anticipating Claim 1 because Reddy discloses a phosphoramidite molecule where the substituent group at the 1’ position (“B”) is cytosine-N-acetyl. The Institution Decision stated that “Reddy expressly discloses and depicts the identical compound recited by challenged Claim 1 in which ‘B’ is cytosine-N-acetyl and ‘X’ is 2-cyanoethyl N,N-diisopropyl phosphoramidite.” Paper 7, at 17. Substitute Claim 6 limits “B” such that it excludes “cytosine-N-acetyl” 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.” Reddy does not disclose a phosphoramidite group with any of the “B” species recited in Substitute Claim 6 and therefore does not anticipate Substitute Claim 6. Ex. 2008, ¶ 96.

Reddy does not disclose or suggest any phosphoramidites having a group at the “B” position other than cytosine-N-acetyl. All of the compounds disclosed in Reddy have cytosine-N-acetyl at the “B” position (or a cytosine as in the starting material in Scheme I). *Id.*, ¶ 97. Reddy does not disclose or suggest modifying the group at the “B” position at all. Nothing in Reddy alone or in combination with any of the other references of record or references known to Patent Owner would have provided a POSA with a reason or motivation to modify the “B” group of Reddy with a reasonable expectation of success. *Id.*, ¶ 98.

Thus, the record does not establish a reasonable likelihood that Substitute Claim 6 is unpatentable.

D. Petitioner's References Do Not Anticipate or Render Substitute Claim 7 Obvious.

Substitute Claim 7 is directed to derivatized nucleosides, succinates and solid supports of general formula 2,



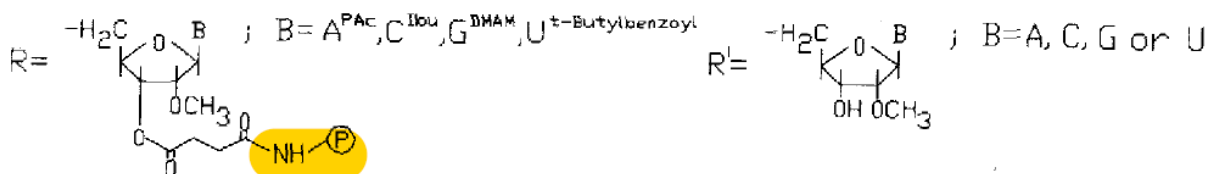
wherein B is selected from the group consisting of Guanine-N-acetyl, adenine-N-acetyl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl; W is Oxygen and R is methyl; and Z is C(O)-M-C(O)-NH, where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl, and NH is 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. Petitioner's cited references do not disclose these limitations.⁴

Petitioner cites references Gaur (1992) (Ex. 1024), as anticipating Claim 5 because Gaur discloses a succinate molecule where the substituent group at the 1' position (corresponding to "B" in Substitute Claim 7) is cytosine-N-isobutyryl. Substitute Claim 7 limits "B" such that it excludes cytosine-N-isobutyryl group from the group "consisting of Guanine-N-acetyl, adenine-N-acetyl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl." Gaur does not disclose a succinate group with any of the "B" species recited in Substitute Claim 7 and therefore does not anticipate Substitute Claim 7. Ex. 2008, ¶ 245.

Also, Gaur discloses NH linked to a polymer support and does not disclose or suggest the spacer recited in Substitute Claim 7:

⁴ Patent Owner has sought reissue of unamended Claim 5 in U.S. Reissue Application No. 18/130,902 to remove a compound from Claim 5's Markush Group (where B is cytosine-N-acetyl) based on a prior sale of that compound.



Scheme 1. Reagents and conditions: (i), 3% TCA in CH₂Cl₂; (ii), salicyl phosphorochloridite; (iii), 0.5 M bis-tri-n-butylammonium pyrophosphate in DMF and tri-n-butylamine; (iv), sulphur; (v), dioxan-water; (vi) & (viii), 25% aq. ammonia; (vii), Iodine-water-pyridine-THF; Pac=phenoxyacetyl; Ibu=isobutyryl; DMAM=dimethylaminomethylidene, P=polymer support, DMT=4,4'-dimethoxytrityl.

(Ex. 1024 at 3303).

Gaur does not disclose or suggest any succinates having a group at the “B” position other than Adenine-phenoxyacetyl (“A^{Pac}”), cytosine-N-isobutyryl (“C^{Ibu}”), guanine-dimethylaminomethylidene (“G^{DMAM}”), and uridine-tert-butylbenzoyl (“U^{t-Butylbenzoyl}”). Ex. 1024 at 3303; Ex. 2008, ¶ 247. Nothing in Gaur alone or in combination with any of the other references of record or references known to Patent Owner would have provided a POSA with a reason or motivation to modify the “B” group of Gaur to replace the specifically disclosed substituents at position B and to further modify the compound of Scheme 1 to arrive at the derivatized nucleosides, succinates and solid supports of Substitute Claim 7 with a reasonable expectation of success. *Id.*

Thus, the record does not establish a reasonable likelihood that Substitute Claim 7 is unpatentable.

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 and catalogs that may be material to patentability of certain claims of the '885 Patent.

VI. CONCLUSION

For all the above and foregoing reasons, Patent Owner respectfully submits that Substitute Claims 6 and 7 are patentable, and respectfully requests a Final Written Decision confirming the patentability of these claims.

Dated: October 17, 2023

Respectfully submitted,

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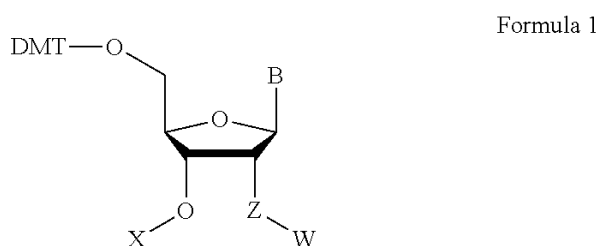
**Counsel for Patent Owner,
ChemGenes Corporation**

APPENDIX A

CLAIM LISTING

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

Claim 6 (proposed substitute for Claim 1). Derivatized nucleoside
and phosphoramidite of general formula 1,

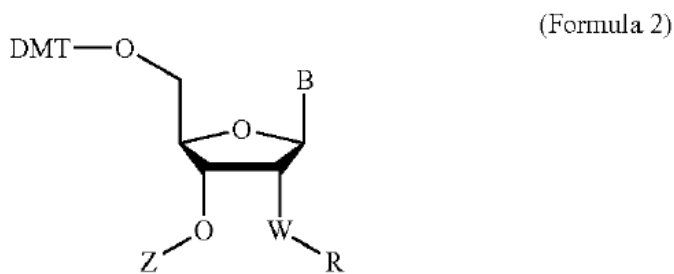


where B is selected from the group consisting of Guanine-N-acetyl, adenine-N-acetyl, ~~cytosine-N-acetyl~~, cytosine-N-isobutyryl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl;

Z is Oxygen and W is methyl; and

X is cyanoethyl dialkyl phosphoramidite.

Claim 7 (proposed substitute for Claim 5). 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.

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
2026	ChemGenes Corporation Invoice 29663 dated 11/11/2004
2027	ChemGenes Corporation Invoice 46458 dated 8/11/2008
2028	ChemGenes Corporation Invoice 36116 dated 6/6/2006
2029	ChemGenes Corporation Catalog, Bio Technology Products & Manufacturer of DNA-RNA Intermediates (1999)
2030	ChemGenes Corporation Catalog, Bio Technology Products & Manufacturer of DNA-RNA Intermediates (Feb. 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 October 17, 2023, to the following counsel for Petitioner via electronic mail at Hongene@procopio.com:

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