

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

PETITION FOR *INTER PARTES* REVIEW OF

U.S. PATENT NO. 9,884,885

CLAIMS 1-5

UNDER 35 U.S.C. §§ 311-319 & 37 C.F.R. §§ 42.1-42.80, 42.100-42.123

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EXHIBIT LIST

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

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

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

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

1026	H. Inoue et al., <u>Synthesis and hybridization studies on two complementary nona(2'-O-methyl)ribonucleotides</u> , Nucleic Acids Research (1987) Vol. 15, No. 15, 6131-6148	Inoue (1987)
1027	H.A. White, <u>Manual Oligonucleotide Synthesis Using the Phosphoramidite Method</u> , Methods in Molecular Biology Vol. 4 (1988), Ch. 14, 193-213	White (1988)
1028	G.G. Sivets et al., <u>Synthesis and Conformational Analysis of 1'- and 3'-Substituted 2-Deoxy-2-fluoro-D-ribofuranosyl Nucleosides</u> , Helvetica Chimica Acta – Vol. 90 (2007), 1818-1836	Sivets (2007)
1029	R.A. Donga et al., <u>Ion-tagged synthesis of an oligoribonucleotide pentamer — The continuing versatility of TBDMS chemistry</u> , Can. J. Chem. (2007) Vol. 85, 274-282	Donga (2007)
1030	N. Usman et al., U.S. Patent 6,528,639 B2	Usman (2003)

37 C.F.R. § 42.8 MANDATORY NOTICES

Pursuant to 37 C.F.R. § 42.8(b), Petitioner states as follows:

1. **Real Party-in-Interest (37 C.F.R. § 42.8(b)(1)).** There is no real party-in-interest for Petitioner Shanghai Hongene Biotech Corporation. Petitioner is not barred by operation of estoppel to submit this petition for *inter partes* review.

2. **Related Matters (37 C.F.R. § 42.8(b)(2)).** On February 18, 2022, Patent Owner ChemGenes Corporation (“ChemGenes”) filed a complaint asserting infringement of U.S. Patent No. 9,884,885 against “Hongene Biotechnology Ltd.” in the U.S. District Court for the District of Massachusetts, case no. 1:22-cv-10290-PBS. On March 30, 2022, ChemGenes filed a first amended complaint against “Hongene Biotechnology Ltd.” Neither complaint were served on Petitioner. On May 27, 2022, ChemGenes filed a second amended complaint against “Hongene Biotech Corporation (of Shanghai, China),” and service of the second amended complaint was accepted on behalf of Petitioner. On July 7, 2022, ChemGenes filed a notice of voluntary dismissal to dismiss the district court case.

3. Lead and Back-Up Counsel, and Service Information (37 C.F.R.

§§ 42.8(b)(3)-(4)). Petitioner identifies its counsel as follows:

Lead Counsel	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
Back-Up Counsel	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

INDEX OF ABBREVIATIONS

Ac	acetyl
ALE	acetal levuliny l ester
DMT	dimethoxytrityl
DMTO / DMT–O	dimethoxytrityl oxygen
DNA	deoxyribonucleic acid
Exh.	Exhibit
Ibu / iBu	isobutyryl
iPr	isopropyl
LCAA-CPG	long chain alkylamine controlled pore glass
Me	methyl
POSA	person of ordinary skill in the art (at the time of the purported inventions claimed in the patent)
RNA	ribonucleic acid
SPOS	solid phase oligonucleotide synthesis
TBDMS	tButyldimethylsilyl, t-Butyldimethylsilyl, tert-Butyldimethylsilyl

I. INTRODUCTION

Petitioner Shanghai Hongene Biotech Corporation (“Petitioner”) requests *inter partes* review of Claims 1-5 of U.S. Patent No. 9,884,885 (“the ’885 Patent”), which claims an earliest priority date of May 18, 2009.

The claims of the ’885 Patent are directed to basic building blocks used in solid phase oligonucleotide synthesis (“SPOS”). Claims 1-2 are directed to certain nucleoside phosphoramidites, whereas Claims 3-5 are directed to certain nucleoside succinates. SPOS involves a multi-cycle process in which an oligonucleotide is synthesized by adding one nucleotide per cycle to a growing nucleotide chain. Since the advent of phosphoramidite chemistry in the 1980s, SPOS has been carried out using the phosphoramidite method, in which: (a) the first nucleotide of the desired oligonucleotide is introduced as its corresponding nucleoside succinate linked to a solid support via an amino spacer, and (b) subsequent nucleotides are added one-by-one via multiple cycles of coupling reactions with their respective corresponding nucleoside phosphoramidites. In other words, Claims 3-5 are directed to starter building blocks used in the first cycle of the SPOS process, while Claims 1-2 are directed to building blocks used in subsequent cycles.

Nucleotides and nucleosides have reactive hydroxyl (-OH) and amine (-NH₂) functional groups. These groups tend to engage in undesirable side reactions during oligonucleotide synthesis, leading to branching, truncation, and/or poorly-controlled

sequencing rather than the synthesis of the desired product oligonucleotide. Thus, hydroxyl and amine groups are shielded with “protecting groups” during synthesis, and then “deprotected” (*i.e.*, converted back into -OH or -NH₂) when appropriate, for example, after the desired oligonucleotide sequence has been formed. One such reactive functional group is the exocyclic amine group of the adenine (“A”), cytosine (“C”), and guanine (“G”) nucleobases of nucleotides and nucleosides.

The inventors of the '885 Patent apparently believed that they had discovered that by using an acetyl instead of an isobutyryl protecting group for this exocyclic amine group — particularly for guanine — they could reduce deprotection time and obtain better oligonucleotide purity. However, this purported discovery was known long before the earliest priority date of the '885 Patent. Pitsch (2001) extols the suitability of the acetyl protecting group for adenine (“A”), cytosine (“C”), and guanine (“G”) nucleobases, and explains that the acetyl protecting group was chosen for its fast deprotection speed. (Exh. 1018 at 3775 & 3778.) Fan (2004) discloses a direct comparison of the respective deprotection rates of isobutyryl-N-guanosine and acetyl-N-guanosine derivatives, reporting that it took the former four times as long as the latter to reach 50% deprotection. (Exh. 1019 at 2556-57; Table 1.) Thus, the use of an acetyl protecting group for the exocyclic amine of nucleobases would have been obvious to a person of ordinary skill in the art.

II. GROUNDS FOR STANDING

Pursuant to 37 C.F.R. § 42.104(a), Petitioner certifies that the '885 Patent is available *for inter partes* review, and that Petitioner is not barred or estopped from requesting an *inter partes* review to challenge the patent claims on the grounds identified below. The Office is authorized to charge all fees due in connection with this proceeding to Deposit Account No. 50-2075.

III. IDENTIFICATION OF CHALLENGE

Pursuant to 37 C.F.R. § 42.104(b), Petitioner requests review and cancellation of Claims 1-5 of the '885 Patent pursuant to the following statement of precise relief requested:

Ground	Claim	Basis	Prior Art Reference(s)
I	1	§ 102(b)	U.S. Patent No. 5,808,039 (Exh. 1016)
II	2	§ 103	U.S. Patent No. 5,898,031 (Exh. 1017) Pitsch (2001) (Exh. 1018) Fan (2004) (Exh. 1019)
III	2	§ 103	U.S. Patent No. 7,879,991 (Exh. 1020) Pitsch (2001) (Exh. 1018)
IV	3	§ 103	U.S. Patent No. 5,898,031 (Exh. 1017) Pitsch (2001) (Exh. 1018) Fan (2004) (Exh. 1019) Scaringe (1990) (Exh. 1022)
V	4	§ 103	Scaringe (1990) (Exh. 1022) Pitsch (2001) (Exh. 1018) Fan (2004) (Exh. 1019)
VI	5	§ 102(b)	Gaur (1992) (Exh. 1024)

* Full titles of scientific papers in Exhibit List.

IV. SCOPE AND CONTENT OF THE PRIOR ART

A. Nucleotide Chemistry

Nucleotides are the molecular building blocks of deoxyribonucleic acid (“DNA”) and ribonucleic acid (“RNA”). DNA and RNA are nucleic acids, which are macromolecules that store genetic information and enable protein production. DNA and RNA are typically made up of millions of nucleotides bound together in a long chain. (Exh. 1003, ¶ 40.)

DNA is made up of a complementary pair of nucleotide chains that coil around each other in the famous “double helix” three-dimensional configuration. The two chains of a DNA macromolecule are connected to one another by bonds between complementary subunits called “nucleobases,” or more simply “bases.” Below is **Figure 1**, which is a general depiction of the basic structure of DNA:

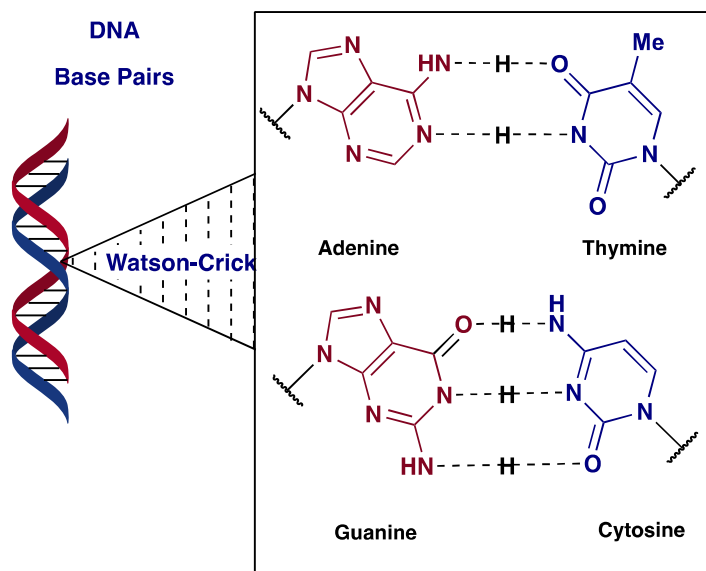


Figure 1: Basic Structure of DNA

(*Id.* at ¶ 41.) RNA is a single chain of nucleotides, as opposed to a complementary pair of chains. (*Id.* at ¶ 42.)

Nucleotides, in turn, have identifiable substructures. **Figure 2** below depicts the substructures of a generalized nucleotide, and identifying the chemical bonds between those substructures:

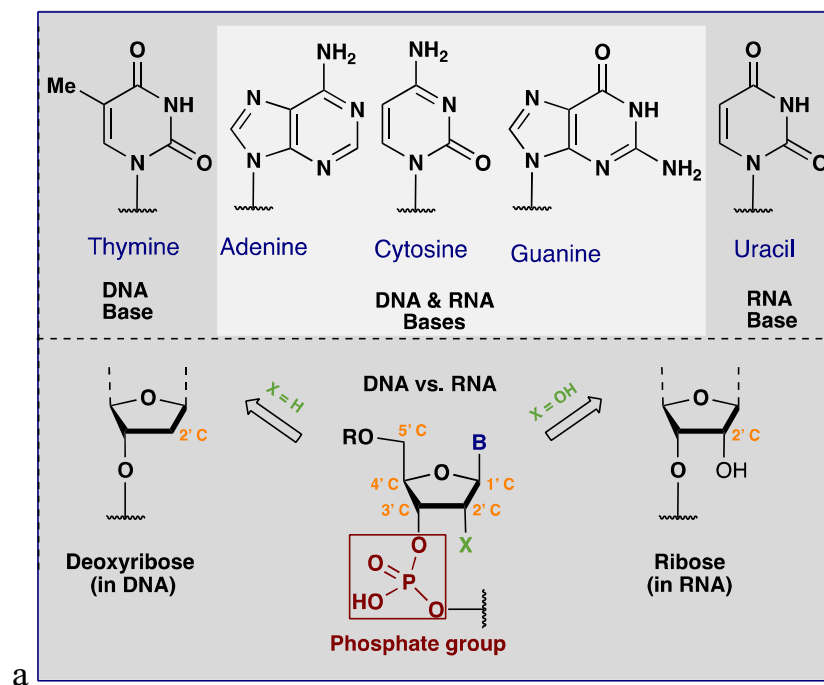


Figure 2: Nucleotide Substructure

(*Id.* at ¶ 43.) As shown above, nucleotides are made up of three substructures: (1) a five-carbon sugar ring, *i.e.*, “deoxyribose” in DNA and “ribose” in RNA; (2) a “phosphate group,” and (3) one of four major “nucleobases.” The bond between the nucleobase (**B** in the above diagram) and the deoxyribose (in DNA) or ribose (in RNA) is called a “glycosidic” bond. (*Id.* at ¶ 44.)

There are four major species of nucleobases in DNA: adenine (“A”), thymine (“T”), cytosine (“C”), and guanine (“G”). RNA contains uracil (“U”) instead of thymine, so the four major nucleobases in RNA are A, C, G, and U. **Figure 2** above depicts the chemical structure of each nucleobase; adenine and guanine are “purines” with a double ring structure, while cytosine, thymine, and uracil are “pyrimidines” which each has a single ring structure. (*Id.* at ¶ 45.)

Chemists use standard numbering to identify positions of each carbon atom (“C”) in the five-carbon sugar ring of a nucleotide. As shown in **Figure 3** below, these numbered positions are given prime (“’”) designations to distinguish them from the numbered positions on the ring(s) of the attached nucleobase. This numbering is employed in standard chemical nomenclature to identify the locations of bonds between the component parts of the molecule being named. (*Id.* at ¶ 46.)

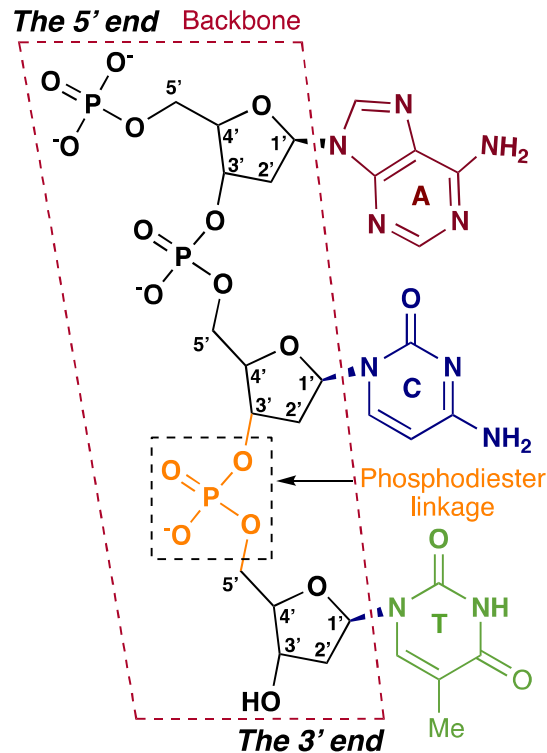


Figure 3: Exemplary Oligonucleotide Structure

As shown above in **Figure 3**, in a single strand of DNA or RNA, nucleotides are connected by covalent bonds between the sugar of one nucleotide and the phosphate of the next nucleotide. This covalent bond is known as a “phosphodiester linkage” or “phosphodiester bond.” Thus, DNA has a “phosphate-deoxyribose backbone,” while RNA has a “phosphate-ribose” backbone; both of which are “phosphate-sugar backbones.” The phosphodiester bond forms between the 3' and 5' carbons of adjacent nucleotides. Consequently, nucleotide chains have a “3' end” and a “5' end.” This directionality of DNA and RNA strands is illustrated in **Figure 3** above. As explained below, oligonucleotide synthesis takes advantage of this directionality.

(*Id.* at ¶ 47.)

B. Oligonucleotides: Uses, Chemistry, and Synthesis

Oligonucleotides are relatively short nucleotide chains, generally a few hundred or fewer nucleotides. They have the same general structural features as DNA and RNA discussed above. (Exh. 1003, ¶ 48.) Oligonucleotides have many important uses in research, genetic testing, forensics, diagnostics, and therapeutics. They are often used as probes that will bind to, and therefore detect the presence of, complementary sections of DNA or RNA in a sample. Small interfering RNA are used to reduce the expression of (or “silence”) a target gene, which prevents cells from producing an offending protein. (*Id.* at ¶ 49.)

The sugar rings and nucleobase rings of nucleotides have reactive hydroxyl (-OH) and amine (-NH₂) functional groups, which tend to engage in undesirable side reactions during oligonucleotide synthesis. (*Id.* at ¶ 50.) These side reactions cause branching, truncation, and/or poorly-controlled sequencing. (*Id.* at ¶ 51.) Thus, chemists have long found it useful to modify nucleotides by shielding these groups with “protecting groups” during synthesis, and then “deprotecting” them (*i.e.*, converting them back into -OH or -NH₂) when appropriate, for example, after the formation of the desired oligonucleotide sequence. (*Id.* at ¶ 50.)

Todd synthesized the first oligonucleotide using P(V) phosphorochloridates in 1955. This breakthrough set the stage for Khorana’s seminal contributions, including “on/off” protecting groups, which allowed for the synthesis of the first

oligonucleotides of significant length, a 72mer tRNA. From 1965 through 1975, Letsinger introduced Solid Phase Oligonucleotide Synthesis (“SPOS”), and increased coupling reactivity through the use of P(III) phosphite-triesters. These developments laid the groundwork for a revolution in SPOS in the early 1980s by Caruthers and his colleagues Beaucage,² Matteuci,³ and McBride,⁴ who pioneered the use of P(III) phosphoramidite reagents and inorganic, non-swelling supports for oligonucleotide synthesis.⁵ Their contributions formed the basis for the modern phosphoramidite method, and with the concurrent development of automated SPOS

² S.L. Beaucage & M.H. Caruthers, Deoxynucleoside Phosphoramidites – A New Class of Key Intermediates for Deoxypolynucleotide Synthesis, Tetrahedron Letters (1981) Vol. 22, No. 20, 1859-1862 (Exh. 1004.)

³ M.D. Matteuci & M.H. Caruthers, Synthesis of Deoxyoligonucleotides on a Polymer Support, J. Am. Chem. Soc. (1981) 103, 3185-3191 (Exh. 1005.)

⁴ L.J. McBride & M.H. Caruthers, An Investigation of Several Deoxynucleoside Phosphoramidites Useful for Synthesizing Deoxyoligonucleotides, Tetrahedron Letters (1983) Vol. 24, No. 3, 245-248 (Exh. 1006.)

⁵ S.L. Beaucage & R.P. Iyer, Advances in the Synthesis of Oligonucleotides by the Phosphoramidite Approach, Tetrahedron (1992) Vol. 48, No. 12, 2223-2311 (Exh. 1007.)

instruments, gave rise to modern SPOS. (*Id.* at ¶ 54.) A brief historical perspective through the development of the modern SPOS via phosphoramidite chemistry is outlined in **Figure 4** below. (*Id.* at ¶ 55.)

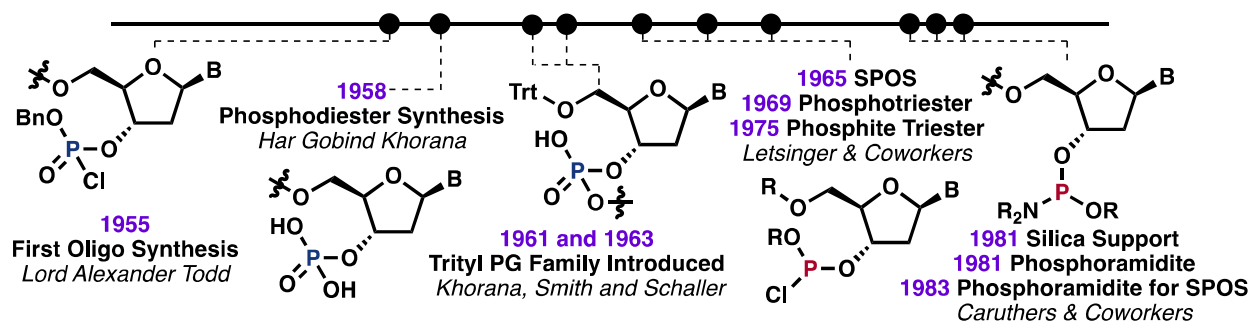


Figure 4: Brief Historical Perspective

Modern oligonucleotide synthesis employs molecules called nucleoside phosphoramidites (also called nucleoside amidites or simply “phosphoramidites”) to provide longer and better controlled oligonucleotide sequences with higher yields and greater purity. (A nucleoside is just a nucleotide without its phosphate group.) (*Id.* at ¶ 52.) A phosphoramidite is characterized as a phosphorus atom in its P(III)-oxidation state having three substituents: one substituted amine group and two oxygen-containing functional groups. Of the two oxygen-containing functional groups, one is usually a protecting group and the other is attached to a nucleoside. Phosphoramidites are highly reactive. Since their discovery, this high reactivity has led to their widespread adoption and optimization as key reagents in oligonucleotide synthesis. (*Id.* at ¶ 53.)

The impact of the phosphoramidite method on research in biochemistry and medicine cannot be overstated. As synthetic oligonucleotides increase in length, small inefficiencies during the synthesis propagate, often posing significant purification issues and drastically reducing overall yield. The phosphoramidite method improved purity, yield, and reaction rate, enabling the synthesis of oligonucleotides with greater lengths and with higher fidelity. The ability to synthesize long (and short) oligonucleotides in high purity and yield has enabled numerous technologies, such as oligonucleotide therapeutics, high-throughput sequencing, and hybridization probes, which have immensely impacted human health and basic science. (*Id.* at ¶ 56.)

Phosphoramidite chemistry — encompassing not only the P(III)-reactive center but also the accompanying protecting groups, activating agents, and adaptations for automated oligonucleotide synthesis — “is the gold standard method for DNA synthesis that has been used in the industry for almost 35 years.”⁶ Phosphoramidite chemistry is also highly flexible and can be used to produce oligonucleotides, and their conjugates, with diverse chemical modifications. In light

⁶ A Simple Guide to Phosphoramidite Chemistry and How It Fits in Twist Bioscience’s Commercial Engine (9/13/2018) (Exh. 1008 at 1.)

of these benefits, considerable effort has been made to modernize this approach to make it more suitable for large scale applications. (*Id.* at ¶ 57.)

The canonical cycle for the phosphoramidite method of oligonucleotide synthesis is depicted below in **Figure 5**. The cycle starts with an initial deprotection step, where the 5'-Dimethoxytrityl (“DMT”) protecting group of the solid-support-linked nucleoside is removed. In Step 1, the resulting 5'-hydroxyl group (“-OH”) reacts with the phosphorus (“P”) in the phosphoramidite group of the incoming nucleoside, thereby displacing its pendant amine (usually diisopropylamino) and coupling the incoming nucleoside to the one linked to the solid support. Step 2 involves oxidation of the phosphorus from a P(III) to a native P(V) oxidation state (usually by adding I_2/H_2O) to convert the bond between the two nucleosides into a stable phosphate-triester linkage. In Step 3, a “capping” process is performed to protect any unreacted 5'-OH groups (as acetates) to prevent undesired elongation of incomplete oligonucleotide sequences. Capping is performed after the oxidation step to minimize water content that can inhibit the next cycle, as phosphoramidites are water sensitive. In Step 4, the DMT protecting group at the 5' end of the forming oligonucleotide is removed (*i.e.*, deprotected) to expose a hydroxyl group (“-OH”), setting the stage for the next cycle to start again with Step 1, where the exposed -OH reacts with the phosphoramidite group of the next incoming nucleoside. (*Id.* at ¶ 58.)

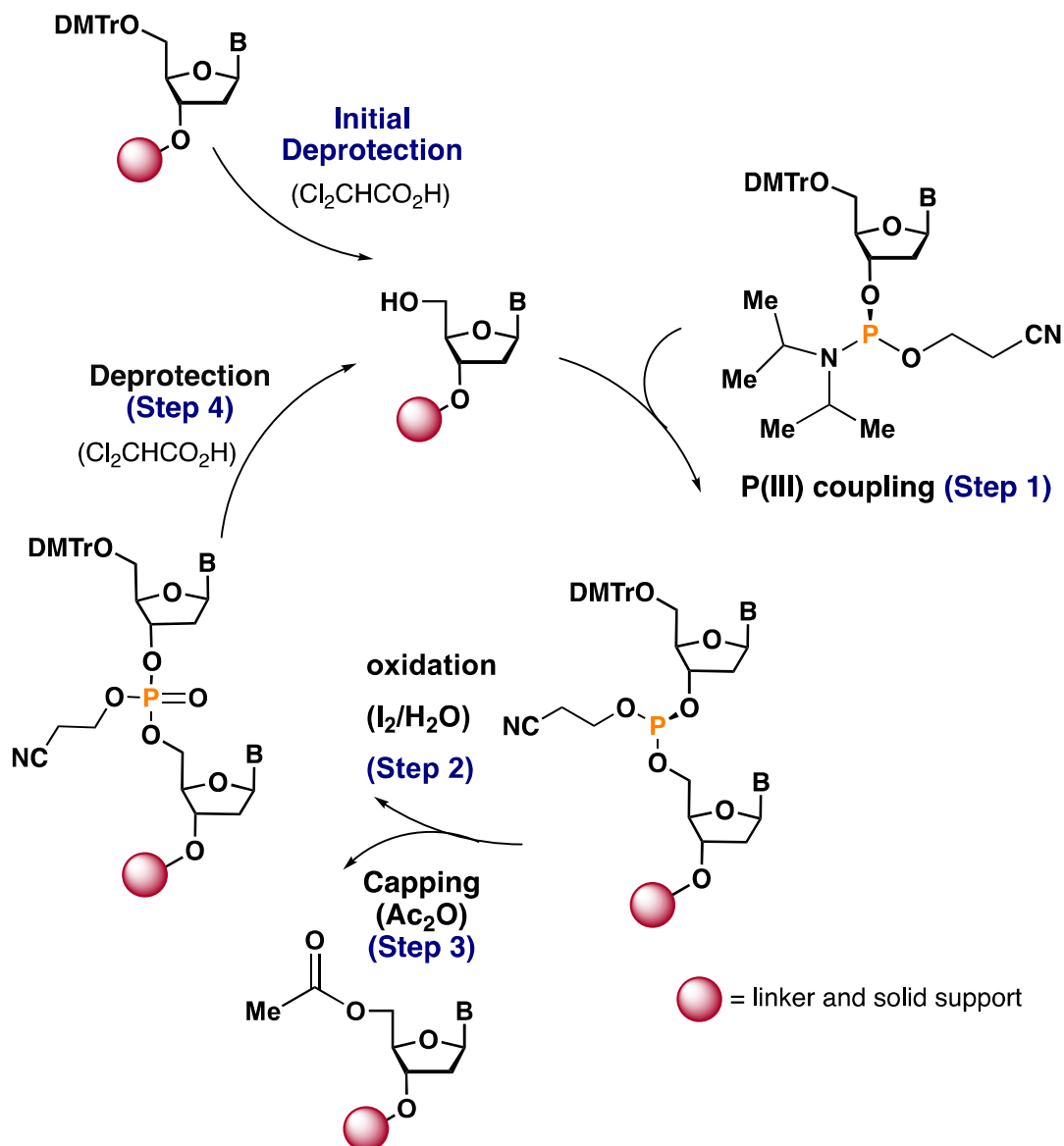


Figure 5: Phosphoramidite Method Canonical Cycle⁷

⁷ H.A. White, Manual Oligonucleotide Synthesis Using the Phosphoramidite Method, Methods in Molecular Biology Vol. 4 (1988), Ch. 14, 193-213 (Exh. 1027 at 196.)

Figure 6 is a simplified schematic of the canonical cycle. (*Id.* at ¶ 59.)

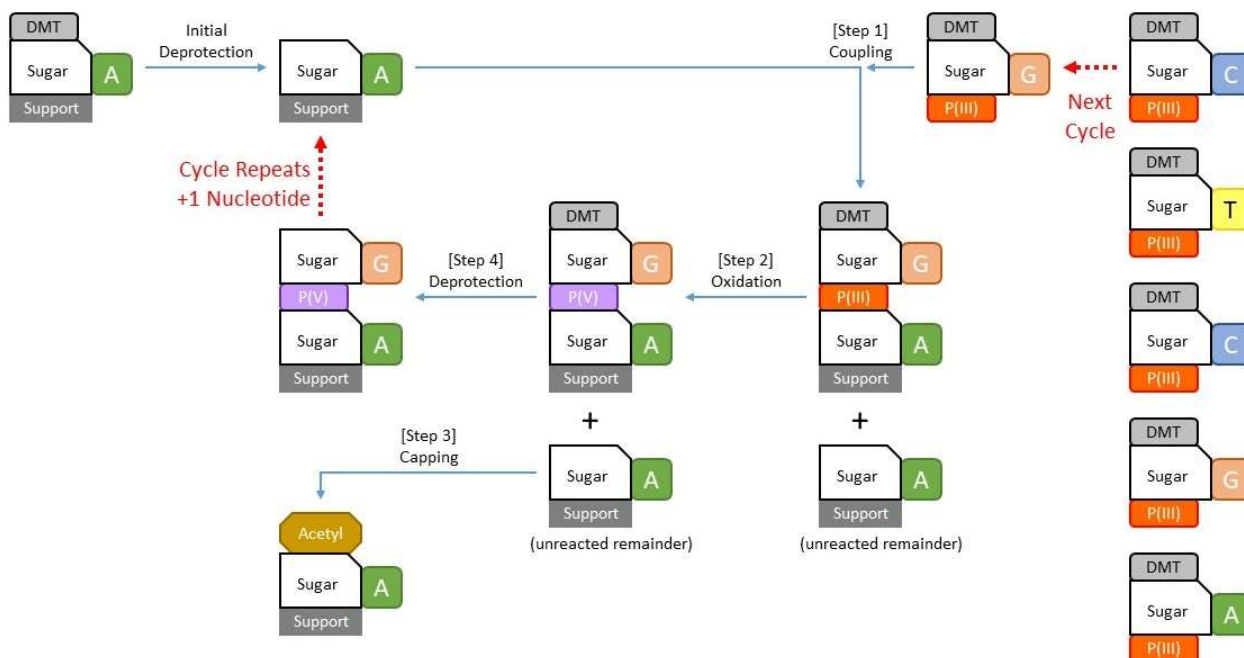


Figure 6: Phosphoramidite Method Canonical Cycle (Simplified Schematic)

The exocyclic nucleophilic NH_2 groups of the adenine, cytosine, and guanine nucleosides are typically protected through acylation, as shown below.

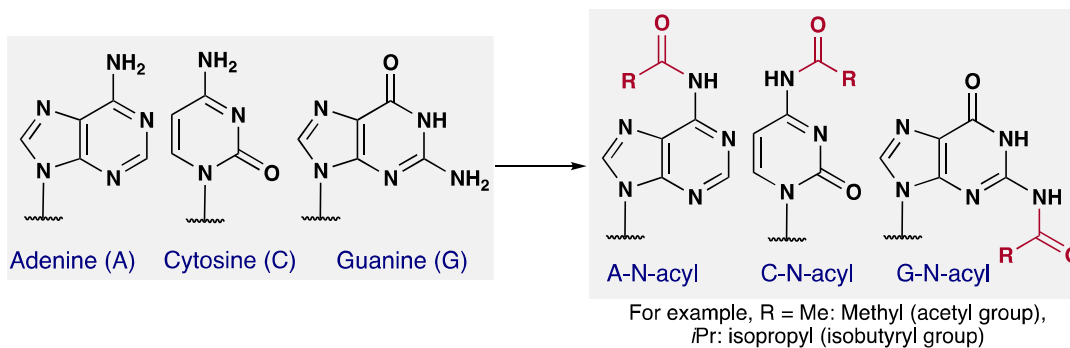


Figure 7: Protection of Exocyclic Amine Groups ($-\text{NH}_2$) of A, C, and G

(*Id.* at ¶ 60; Exh. 1007 at 2251-52.) The acyl protection groups are subsequently removed at the end of the sequence along with the 2-cyanoethyl groups with concomitant detachment from the solid support. (*Id.* at ¶ 60; Exh. 1027 at 196.)

As mentioned above, the chemical synthesis of oligonucleotides is routinely automated and is carried out on a solid phase by the cycle outlined above of appropriately activated and protected nucleotide building blocks until the desired sequence has been obtained. At the end of the process, all of the protecting groups required during the synthesis are discarded and the product is cleaved from the solid support. The length, uniformity, and purity of the product are limited by the coupling and deprotection efficiencies. It is thus vital in each cycle to maximize coupling yield (approaching 99%) and to improve the respective speeds of the coupling and deprotection reactions while maintaining near-quantitative yield. (*Id.* at ¶ 61.) The phosphoramidite “used virtually exclusively” in phosphoramidite-based SPOS has a diisopropylamino group on the phosphorus and a cyanoethyl protecting group on the oxygen (as shown above in Figure 5, Step 1).⁸ (*Id.* at ¶ 62.)

Historically, improvements in this area have focused on improving coupling efficiencies, fidelity of final deprotection and cleavage from the solid support, and overall purity profile of final product to avoid, for example, truncated sequences. (*Id.* at ¶ 63; Exh. 1007 at 2293.) Overall, such improvements reduce the amount of reagents needed and the cost and time associated with its preparation. (*Id.*)

⁸ See, e.g., C.B. Reese, Oligo- and poly-nucleotides: 50 years of chemical synthesis, Org. Biomol. Chem. (2005) Vol. 3, 3851-68 (Exh. 1009 at 3857.)

V. CLAIM CONSTRUCTION

A. Standard

In an *inter partes* review, a patent claim “shall be construed ... in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” (37 C.F.R. § 42.100.)

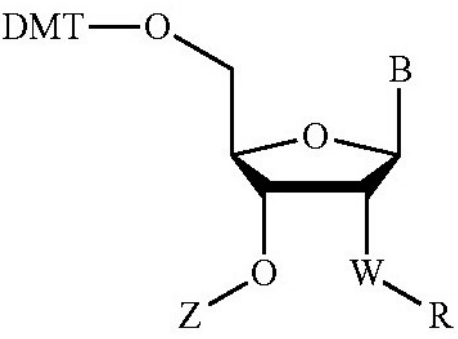
B. Person of Ordinary Skill in the Art

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 or medicinal chemistry, and 2 to 3 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. (Declaration of Phil S. Baran, Ph.D. (“Baran Decl.”) (Exh. 1003), ¶ 24.)

Alternatively, someone 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 a POSA with a Bachelor’s or Master’s degree in organic chemistry or medicinal chemistry. (*Id.*)

C. Clear Errors in Claims 3-5 of the ’885 Patent

Claims 3-5 of the ’885 Patent are directed to certain nucleoside succinates and recite, in relevant part:

Claims 3-4	Claim 5
Derivatized nucleosides, succinates and solid supports of general formula 2,	
(Formula 2) 	
...	
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.	and NH is C1-C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy.

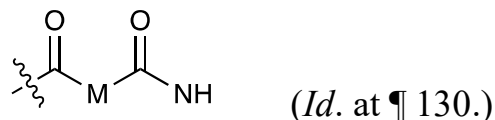
(See the '885 Patent (Exh. 1001), 25:66-26:65 (color added).)

1. “M” is ~~Succinyl~~ Ethyl / Oxalyl / Hydroquinolynyl

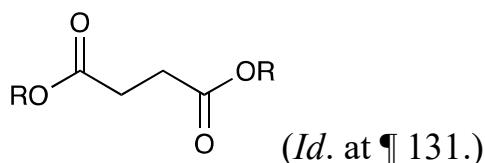
A POSA would have readily recognized the clear error in the definition of substituent “M” in Claims 3-5. (Exh. 1003, ¶¶ 129; 147; 155.) As explained below, a POSA would have readily recognized that, in the context of the claimed invention,

it was “Z”, rather than “M”, that should have been defined as a succinyl group, such that “M” should correspondingly have been an ethyl group (*i.e.*, -CH₂CH₂-).

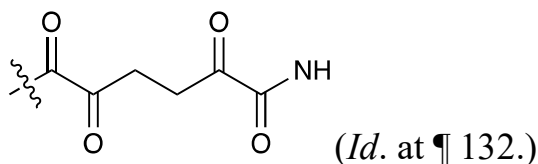
In Claims 3-5 of the '885 Patent, “Z” is defined as C(O)-M-C(O)—NH, which has the following structure:



A succinyl group has the following structure:



Therefore, if “M” itself was a succinyl group, then “Z” would have this structure:



However, the above resulting structure is dysfunctional for the purpose of serving as a linkage to a solid support in SPOS. A POSA would have recognized that this structure would be inherently unstable, because it could rapidly undergo, for example, dehydration to produce a furan, hydration to form delicate hydrates (as 1,2-dicarbonyl compounds often do), or intramolecular condensation to prematurely release the nucleoside from the solid support. Generally, a POSA would have known that a linkage was supposed to be inert and stable, and would have never chosen

such a structure, which has an inherent ability to react with itself or with water in a myriad of ways. (*Id.* at ¶ 133.)

Thus, a POSA would have understood that it was “Z”, rather than “M”, which should have been a succinyl group bound to “—NH,” such that “M” itself should correspondingly have been an ethyl group (*i.e.*, -CH₂CH₂-). In other words, a POSA would have understood the two relevant limitations of Claims 3-5 as follows:

Z is C(O)-M-C(O)—NH,
where M is selected from the group consisting of ethyl , oxalyl, and hydroquinolynyl,

(*Id.* at ¶ 134.) This interpretation is confirmed by the '885 Patent, which includes “5'-DMT-**3'-succinyl**-lcaa CPG-N-acetyl guanine protected nucleoside” among “[t]he nucleic bases in our invention protected with N-2 acetyl guanine and sugar moiety in the nucleosides.” (Exh. 1001, 21:47-66 (emphasis added).⁹) “3'-succinyl” clearly identifies the side group bound to the O on the 3' C of the sugar ring — *i.e.*, the “Z” in Formula 2 of Claims 3-5 — as a “succinyl” group. (Exh. 1003, ¶ 135.)

⁹ The '885 Patent contains two instances of the same typo, “lcaa CPG.” However, a POSA would have recognized that the authors meant “lcaa CPG,” *i.e.*, long chain alkyl amine Controlled Pore Glass, a commonly used solid support for solid phase oligonucleotide synthesis.

2. NH is Capable of Being Attached to a Solid Support

A POSA would also have readily recognized a clear error in the last phrase of Claim 5, which reads: “and NH is C1-C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy.” (Exh. 1001, 26:64-65.) As written, this phrase is nonsensical. (Exh. 1003, ¶ 156.) “NH” is an amine group. A POSA (and anyone with a modicum of organic chemistry knowledge) would have readily understood that an “NH” cannot be a “C1-C20 alkyl,” an “ethyloxyglycol,” or “a combination of alkyl and ethyleneglycoxy.” All three are spacers with carbon atoms, none of which are found in an amine group. (*Id.* at ¶ 157.)

Rather, in the context of Claim 5 (and the similar Claims 3-4), “NH” must be part of the structure of “Z”, which is defined as C(O)-M-C(O)—NH in Claims 3-5. A POSA would have also understood that “NH” is the amine group in a long chain alkyl amine controlled pore glass, a commonly used solid support for solid phase oligonucleotide synthesis. (*Id.* at ¶ 158.) This is confirmed by the '885 Patent, which explains that, in Formula 2, “Z = succinimido long chain attached to a solid support, hydroquinone succinimido long chain spacer attached to solid support, or oxalyl amido long chain spacer attached to solid support.” (Exh. 1001, 18:6-23.) Thus, a POSA would have readily appreciated that last phrase in Claim 5 should include the additional 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.” (Exh. 1003, ¶ 158.)

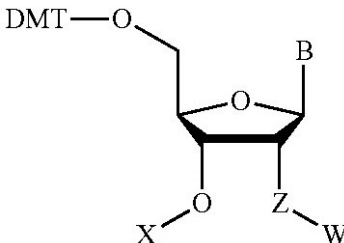
The file history of the '885 Patent shows that the additional language (in brackets above) was inadvertently omitted during prosecution. Original Claims 5-7 — which eventually issued respectively as Claims 3-5 of the '885 Patent — were rejected under § 112 as indefinite because the term “long chain” in the definition of “Z” was a relative term from which the scope of the claims could not be reasonably ascertained. (Exh. 1002, 0153-54.) In response, the definition of “Z” in Original Claims 5-7 were all amended as reflected in Claims 3-4 of the '885 Patent. (*Id.* at 0202-05.) After this amendment, the Examiner allowed Original Claims 6-7. (*Id.* at 0217 & 0223.) However, in the next amendment (to address a different rejection of Original Claim 5), the additional language (in brackets above) was inexplicably omitted from Original Claim 7. (*Id.* at 0244-45.) However, the remarks submitted with the amendment do not reflect any intent to omit the omitted language from Original Claim 7. (*Id.* at 0248.)

VI. THE CHALLENGED CLAIMS ARE UNPATENTABLE

A. Ground I: Claim 1 of the '885 Patent is Anticipated Under § 102(b) by U.S. Patent No. 5,808,039

1. Claim 1 where “B” is cytosine-N-acetyl

Claim 1 of the '885 Patent is anticipated by U.S. Patent No. 5,808,039 (“the '039 Patent”) (Exh. 1016). (Exh. 1003, ¶ 87.) Claim 1 recites:

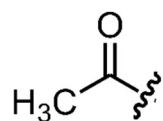
Derivatized nucleoside and phosphoramidite of general formula 1,	
(Formula 1)	
	
where B is selected from the group consisting of Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N-isobutyryl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl;	
Z is Oxygen and W is methyl; and	
X is cyanoethyl dialkyl phosphoramidite.	

(Exh. 1001, 25:25-45.)

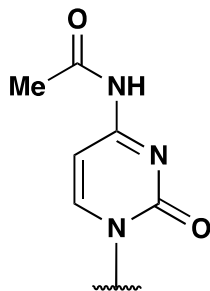
In Formula 1, “B” is used to denote a nucleobase or modified nucleobase, as its customary use in the field of nucleic acid chemistry. (Exh. 1003, ¶ 89.) “B” is a member of a Markush group. When a claim element recites a Markush group, the entire element is disclosed by the prior art if one member of the Markush group is in the prior art. (*Fresenius USA, Inc. v. Baxter International, Inc.*, 582 F.3d 1288, 1298

(Fed. Cir. 2009).) As explained below, the '039 Patent discloses the molecule of Claim 1 where B is cytosine-N-acetyl.

Cytosine-N-acetyl refers to a cytosine nucleobase with an acetyl protecting group (“Ac”) bound to the nitrogen (“N”) of its exocyclic amine group (“-NH₂”).



The acetyl group has a chemical structure (left) which in turn has a -CH₃, commonly called a methyl group, abbreviated as “Me.” Thus, cytosine-N-acetyl has the structure below. (Exh. 1003, ¶ 90.)

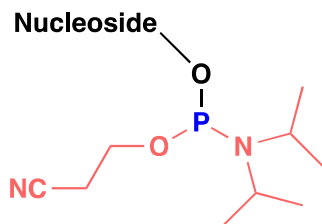


“Z” is oxygen, represented by an “O.” (*Id.* at ¶ 91.)

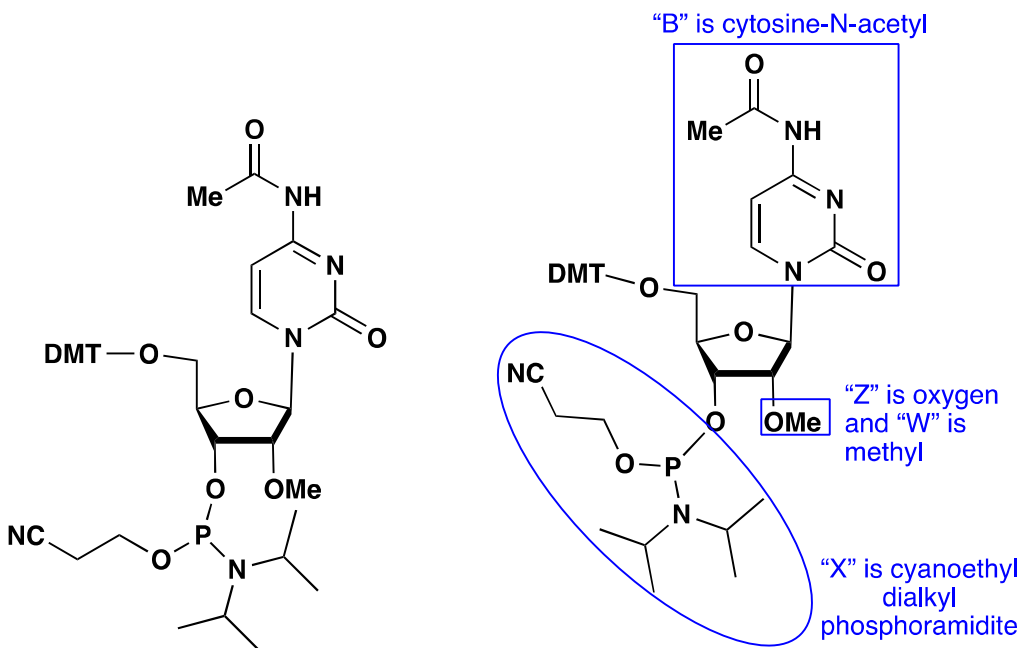
“W” is methyl (*i.e.*, -CH₃), abbreviated as “Me.” (*Id.* at ¶ 92.)

“X” is cyanoethyl dialkyl phosphoramidite. It is a phosphorus (“P”) atom in a P(III)-oxidation state with three substituents: one substituted amine group and two oxygen-containing functional groups. (*Id.* at ¶ 93.) Of the two oxygen-containing functional groups, one is attached to the nucleoside, and the other has a cyanoethyl protecting group. (*Id.* at ¶¶ 93-94.) The substituted amine is a dialkyl amine, which has two “alkyl” groups. (An “alkyl” group is simply an alkane minus a hydrogen (“H”) atom; one example of an alkyl group is an “isopropyl” group.) (*Id.* at ¶ 94.)

The most well-known “cyanoethyl dialkyl phosphoramidite” is 2-cyanoethyl N,N-diisopropyl phosphoramidite, which has “been used virtually exclusively in phosphoramidite-based solid phase nucleotide synthesis.” (*Id.*; Exh. 1009 at 3857.) It has the following structure (Exh. 1003, ¶ 94):

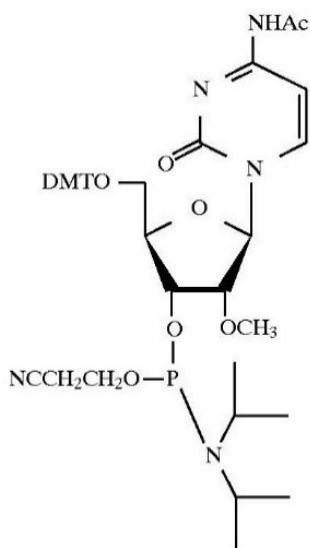


Thus, where “B” is cytosine-N-acetyl, Claim 1 claims the molecule on the left below. (*Id.* at ¶ 95.) It is annotated on the right below to indicate the respective portions corresponding to “B,” “Z,” “W,” and “X” in Formula 1. (*Id.* at ¶ 97.)

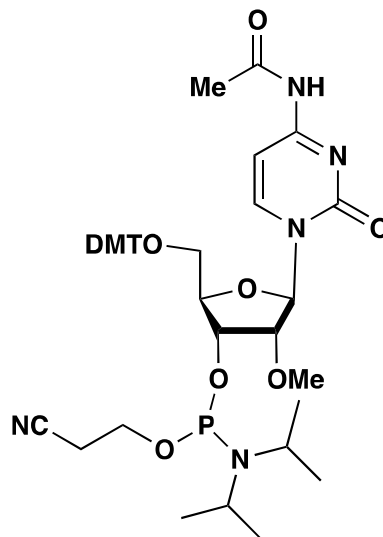


2. The '039 Patent Discloses the Identical Molecule as Claim 1 of the '885 Patent where “B” is cytosine-N-acetyl

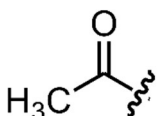
The '039 Patent discloses the identical molecule as Claim 1 of the '885 Patent where “B” is cytosine-N-acetyl, and a detailed scheme for its synthesis. It is identified as “DMT C^{Ac}-2'-OMe-3'-cyanoethylphosphoramidite,” or simply as “C^{Ac}-2'-OMe phosphoramidite,” and discloses its chemical structure on the left below. (Exh. 1003, ¶ 98; Exh. 1016, 3:5-25.)



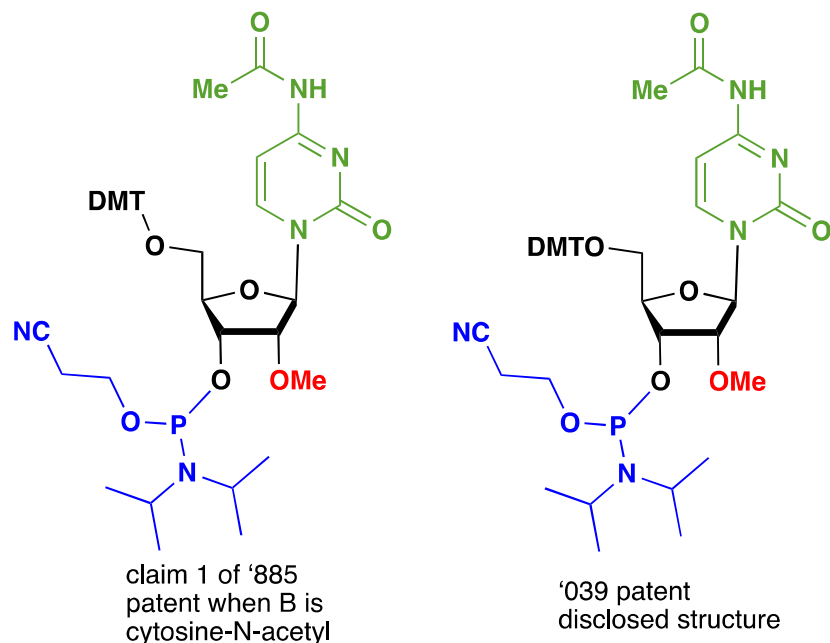
The '039 Patent, 3:8-25



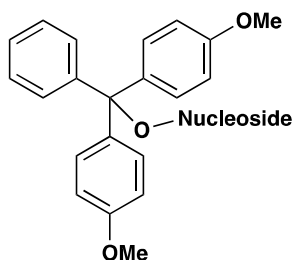
Using abbreviation “Me”

(Exh. 1003, ¶ 98.) The “NHAc” at the top end of the above left molecule indicates that an acetyl group (“Ac”) is bound to the exocyclic amine group (“-NH₂”) of the cytosine base. As discussed above, an acetyl group has a structure with  a -CH₃ portion, *i.e.*, a methyl group, abbreviated as “Me.” Thus, the phosphoramidite molecule disclosed in the '039 Patent can also be depicted as shown on the right above. (*Id.* at ¶ 99.)

For comparison, both (a) the molecule claimed in Claim 1 of the '885 Patent where “B” is cytosine-N-acetyl and (b) the molecule disclosed in the '039 Patent (Exh. 1016, 3:5-25) are annotated and arranged side-by-side below. (*Id.* at ¶ 100.)



The two above molecules are identical. (*Id.* at ¶ 102.) The “DMTO–” on the 5' C of the molecule in the '039 Patent is exactly the same as the “DMT–O–” on the 5' C of Formula 1 in Claim 1 of the '885 Patent; both denote a dimethoxytrityl (“DMT”) protecting group on the oxygen (“O”) atom bound to the 5' C of the ribose ring (below), and are simply two ways of rendering the same protecting group. (*Id.* at ¶¶ 96 & 101.)



3. The '039 Patent Would Have Enabled a POSA to Make the Molecule in Claim 1 of the '885 Patent

An anticipatory prior art reference is presumed to be enabling. (*Impax Labs. v. Aventis Pharms, Inc.*, 545 F.3d 1312, 1316 (Fed. Cir. 2008).) Enablement for the purposes of anticipation under § 102 differs from the enablement standard under § 112, and requires only enablement of an embodiment that falls within the scope of the claim. (*Samsung Electronics Co., Ltd. v. Acorn Semi, LLC*, 2022 WL 136755, *15 (PTAB 2022) (citing *Chester v. Miller*, 906 F.2d 1574, 1577 (Fed. Cir. 1990)).)

Regardless of this presumption, the '039 Patent would have enabled a POSA to make and use the molecule claimed in Claim 1 of the '885 Patent (where “B” is cytosine-N-acetyl) as of its priority date without undue experimentation. (Exh. 1003, ¶ 104.) The '039 Patent provides a detailed methodology, “Scheme I,” for the synthesis of C^{Ac}-2'-OMe phosphoramidite. (*Id.* at ¶ 105; Exh. 1016, 3:5-5:20.) It includes citations to supporting scientific literature, and detailed description of the structures of the starting materials; the structures of the intermediates; the reagents, catalysts, and reaction media; the reaction conditions; the synthetic organic chemistry techniques employed; and the percent yield at each step. (*Id.*)

Based on this disclosure, and a general knowledge of synthetic organic chemistry, a POSA following the '039 Patent would not have had to engage in very much, if any, experimentation to make the molecule claimed in Claim 1 of the '885 Patent (where “B” is cytosine-N-acetyl). (*Id.* at ¶ 106.)

A POSA would have further understood that the '039 Patent taught a POSA how to use C^{Ac}-2'-OMe phosphoramidite. It discloses that this compound was “successfully utilized in the synthesis of 2'-OMe oligonucleotides on an automated DNA synthesizer using a 15 minute coupling time,” and further discloses alternate deprotection conditions. (Exh. 1016, 5:22-31.) In fact, the use of C^{Ac}-2'-OMe phosphoramidite 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 and followed the parameters set forth in the '039 Patent. (Exh. 1003, ¶ 107.)

B. Ground II: Claim 2 of the '885 Patent would have been Obvious under § 103 in View of U.S. Patent No. 5,898,031, Pitsch (2001), and Fan (2004)

1. Claim 2 where “B” is guanine-N-acetyl and “Z” is ribo fluoro

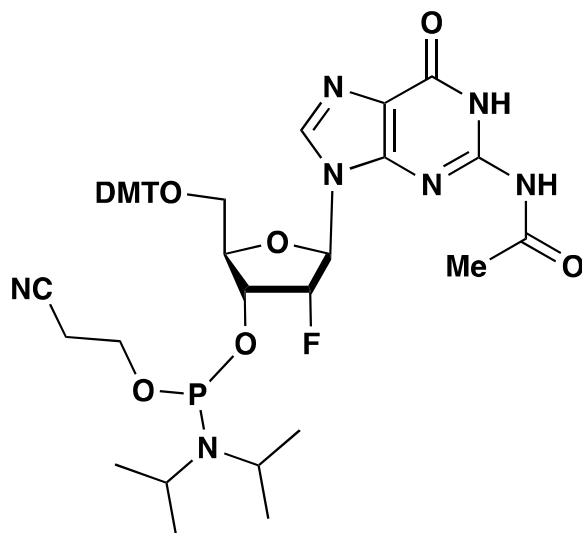
Claim 2 of the '885 Patent would have been obvious in view of U.S. Patent No. 5,898,031 (“the '031 Patent”) (Exh. 1017), Pitsch (2001) (Exh. 1018),¹⁰ and Fan (2004) (Exh. 1019).¹¹ (Exh. 1003, ¶ 110.) Claim 2 recites:

Derivatized nucleoside and phosphoramidite of general formula 1,	
(Formula 1)	
where B is Guanine-N-acetyl, or adenine-N-acetyl;	
Z = ribo Fluoro or ara fluoro, and	
W is absent; and	
X is cyanoethyl dialkyl phosphoramidite.	

¹⁰ S. Pitsch et al., Reliable Chemical Synthesis of Oligoribonucleotides (RNA) with 2'-O-[(Triisopropylsilyl)oxy]methyl(2'-O-tom)-Protected Phosphoramidites, Helvetica Chimica Acta – Vol. 84 (2001), 3773-3795

¹¹ Y. Fan et al., Transient Silylation of the Guanosine O6 and Amino Groups Facilitates N-Acylation, Organic Letters (2004) Vol. 6, No. 15, 2555-2557

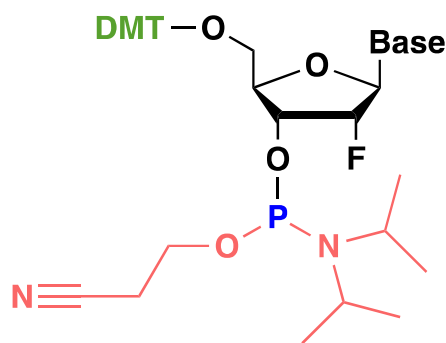
(Exh. 1001, 25:45-65.) Claim 2 where “B” is guanine-N-acetyl and “Z” is ribo fluoro claims the molecule below. (Exh. 1003, ¶ 109.)



2. The '031 Patent Discloses an Almost Identical Molecule (where “B” is guanine-N-isobutyryl)

The '031 Patent discloses several nucleoside amidites that are synthesized and used as reagents to synthesize RNA oligonucleotides. In the '031 Patent, “Examples 2 through 5 illustrate the preparation of further nucleoside amidites use[d] in preparing other illustrative oligoribonucleotide or oligoribonucleoside compounds of the invention.” (Exh. 1017, 16:35-38.)

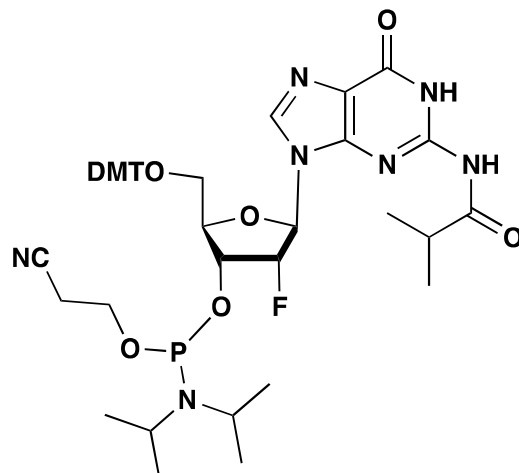
Example 4 of the '031 Patent describes 2'-fluoro nucleoside amidites, which refer to a class of nucleosides in which a fluorine (“F”) atom is bound to the 2' C of the ribose and a phosphoramidite group is bound to the oxygen (“O”) atom that is bound to the 3' C of the ribose. A general structure of a 2'-fluoro nucleoside amidite is illustrated below.



(Exh. 1003, ¶ 113.) Example 4 has four subparts: “4-a” through “4-d”, each of which describes a process for preparing a different 2'-fluoro phosphoramidite respectively corresponding to the four canonical nucleobases. Example 4-a relates to an adenosine phosphoramidite, Example 4-b relates to a uridine phosphoramidite, Example 4-c relates to a cytidine phosphoramidite, and Example 4-d relates to a guanosine phosphoramidite.¹² (*Id.* at ¶ 114.)

Example 4-d describes the synthesis of the guanosine phosphoramidite in ten steps, starting with the preparation of 9-(3',5'-[1,1,3,3-Tetraisopropylidisiloxy-1,3-diyl]-β-D-arabinofuranosyl)guanine in step “i” and culminating in the synthesis of N²-isobutyryl-9-(2'-deoxy-2'-fluoro-5'-O-[4,4'-dimethoxytrityl]-guanosine-3'-O-N,N-diisopropyl-β-D-cyanoethyl phosphoramidite in step “x”. (Exh. 1017, 25:32-28:19.) This guanosine phosphoramidite has the structure below.

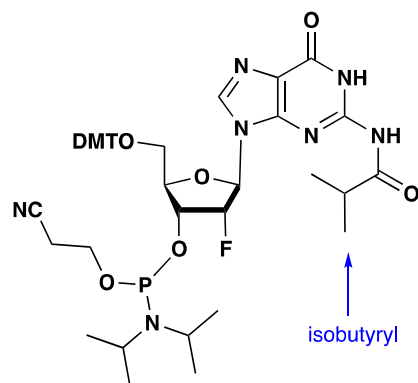
¹² Adenosine, uridine, cytidine, and guanosine are the names of the nucleosides that respectively have adenine, uracil, cytosine, and guanine nucleobases.



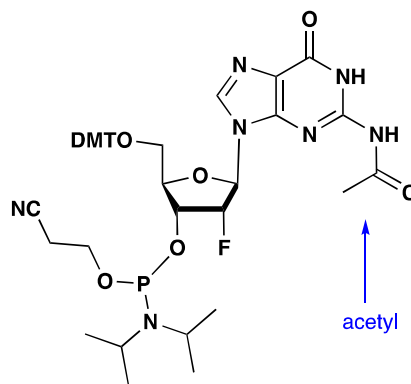
(Exh. 1003, ¶ 115.)

Since the advent of phosphoramidite chemistry in oligonucleotide synthesis in the 1980s, a POSA would have recognized that the purpose of the above phosphoramidite was to serve as a building block for incorporating a guanine base into a growing oligonucleotide chain through automated SPOS, as illustrated above in Figures 5 and 6. This use is specifically contemplated in the '031 Patent. (*Id.* at ¶ 116; Exh. 1017, 13:45-14:14; 39:1-9; 39:35-38.)

The only difference between the molecule synthesized in step “x” of Example 4-d in the '031 Patent (below left) and the molecule in Claim 2 of the '885 Patent where “B” is guanine-N-acetyl and “Z” is ribo Fluoro (below right) is the identity of the protecting group on the exocyclic NH₂ group of the guanine base: the former has an isobutyryl group, while the latter has an acetyl group. (Exh. 1003, ¶ 117.)



compound "x": '031 patent



claim 2: '885 patent

3. Pitsch (2001) and Fan (2004) Would Have Motivated a POSA to Install an Acetyl Protection Group

However, using an acetyl protecting group to shield the exocyclic NH_2 group of a nucleobase was not a novel concept by the time of the alleged inventions claimed in the '885 Patent, and a POSA would also have understood the advantage of an acetyl protecting group. (Exh. 1003, ¶ 118.)

In Pitsch (2001), the installation of an acetyl protecting group to protect the exocyclic NH_2 group of a nucleobase was the first step in “[t]he preparation of the phosphoramidite building blocks from the four ribonucleosides [which] was carried out by stepwise introduction of the base-protecting acetyl group, ..., and finally the 3'-(2-cyanoethyl diisopropylphosphoramidite) moiety.” (*Id.* at ¶ 119; Exh. 1018, 3774-75; Scheme 1, steps “a)”, “b)”, “c”). Pitsch (2001) also outlines the specific steps for synthesizing a nucleobase-protected N^2 -acetylguanosine. (Exh. 1018 at 3775.) Pitsch (2001) further explains that the acetyl protecting group (“Ac group”) was chosen for its fast deprotection speed:

... we established the conditions required for the removal of the base-protecting Ac groups with MeNH₂ [and] determined half-lives of < 2 min for the 2'-O-tom-protected N-acetylcytidine and N-acetyladenosine derivatives, and a half-life of 4 min for the 2'-O-tom-protected N-acetylguanosine, respectively (Scheme 3). These values indicated that complete base-deprotection of oligonucleotide sequences can be achieved within 1 h (equal to 15 half-lives for the acetylated guanosine residues) and demonstrated that the Ac group, in combination with MeNH₂, is indeed suited for a labile universal nucleobase protection.

(*Id.* at 3778.) This compares favorably against the 24 hour deprotection period for the removal of the isobutyryl protecting group from 2'-O-methyl G in Example 8 of the '031 Patent. (Exh. 1003, ¶ 119; Exh. 1017, 40:41-52.)

Fan (2004) discloses a direct comparison of the respective deprotection rates of N-acylguanosine derivatives with N-isobutyryl, acetyl, and phenoxyacetyl protecting groups, and reports that the “time required for 50% deprotection” for N-acetyl (4.5 h) was only 25% of that for N-isobutyryl (18 h). (Exh. 1003, ¶ 120; Exh. 1019 at 2556-57; Table 1.)

As discussed above, a POSA would have recognized that the guanosine phosphoramidite synthesized in step “x” of Example 4-d in the '031 Patent serves as a building block for incorporating a guanine base into a growing oligonucleotide

chain via automated SPOS. A POSA would have also known that automated SPOS involved a cyclical series of reactions (illustrated above in Figures 5 and 6), one of which was the deprotection step. Thus, a POSA would have been motivated by the respective teachings of Pitsch (2001) and Fan (2004) to synthesize a guanosine phosphoramidite similar to the one made in step “x” of Example 4-d in the '031 Patent — but with an acetyl instead of an isobutyryl protecting group on the exocyclic NH₂ group of the guanine base — to take advantage of the drastic improvement in deprotection speeds. This would have resulted in the molecule in Claim 2 of the '885 Patent where “B” is guanine-N-acetyl and “Z” is ribo Fluoro. (Exh. 1003, ¶ 121.)

4. A POSA Would Have Had Reasonable Expectation of Successfully Synthesizing the Molecule in Claim 2

A POSA would have had a reasonable expectation of successfully synthesizing the molecule in Claim 2, and would have regarded the conditions and yield for the installation of an acetyl protecting group as trivial and similar to those for an isobutyryl group. Step “ii” of Example 4-d in the '031 Patent teaches the installation of the isobutyryl protecting group through the addition of isobutyric anhydride, in a process to convert 9-(3',5'-[1,1,3,3-Tetraisopropylidisilox-1,3-diyl]-β-D-arabinofuranosyl)guanine into N²-Isobutyryl-9-(2'-O-isobutyryl-3',5'-[1,1,3,3-Tetraisopropylidisilox-1,3-diyl]-β-D-arabinofuranosyl)guanine. (Exh. 1017, 25:61-

26:10.) Pitsch (2001) analogously teaches the installation of the acetyl protecting group through the addition of acetic anhydride:

A convenient synthesis of N₂-acetylguanosine (3) was achieved by peracetylation of guanosine with Ac₂O in DMF/pyridine, followed by cleavage of the O-bound Ac groups with NaOH in THF/MeOH/H₂O.

(Exh. 1018 at 3775; Scheme 1, step “c”).) Ac₂O is the abbreviation for (CH₃CO)₂O, *i.e.*, acetic anhydride. Thus, a POSA would have simply substituted acetic anhydride (for isobutyric anhydride) in step “ii” and thereafter performed the remaining steps “iii” through “x” of Example 4-d in the '031 Patent to make the molecule in Claim 2 of the '885 Patent where “B” is guanine-N-acetyl and “Z” is ribo fluoro. A POSA would have further recognized that an acetyl group would be easier to install due to its smaller physical size and lower molecular weight than an isobutyryl group, and thus less disruptive to the bulk properties of the molecule. (Exh. 1003, ¶ 122.)

As another example, a POSA could have also synthesized the molecule claimed in Claim 2 of the '885 Patent (where “B” is guanine-N-acetyl and “Z” is ribo fluoro) by starting with 2'-fluoro-2'-deoxyguanosine, either acquired from a

commercial source or synthesized according to Sivets (2007) (Exh. 1028).¹³ (Exh. 1028 at 1821 (compound 17).) A POSA would have reasonably expected that 2'-fluoro-2'-deoxyguanosine would react similarly to a “regular” 2'-deoxyguanosine (*i.e.*, one with a 2'-H instead of the 2'-F substitution) in connection with the preparation of reagents for SPOS, and thus would have had a reasonable expectation of successfully installing protecting groups onto a 2'-fluoro-2'-deoxyguanosine pursuant to known methods in the art as outlined below. (Exh. 1003, ¶ 123.)

For example, as discussed above, Pitsch (2001) teaches the installation of an acetyl protecting group on the exocyclic amine of the guanosine. (Exh. 1018 at 3775; Scheme 1, step “c”), molecule 3.) Pitsch (2001) also teaches the installation of a DMT protecting group on the 5'-oxygen of the sugar ring. (*Id.*; Scheme 1, step “d”), molecule 6.¹⁴) And in Pitsch #2 (2001) (Exh. 1021),¹⁵ Support Protocol 2 further

¹³ G.G. Sivets et al., Synthesis and Conformational Analysis of 1'- and 3'-Substituted 2-Deoxy-2-fluoro-D-ribofuranosyl Nucleosides, Helvetica Chimica Acta – Vol. 90 (2007), 1818-1836

¹⁴ (MeO)₂TrO is dimethoxytrityl–O, *i.e.*, DMT–O.

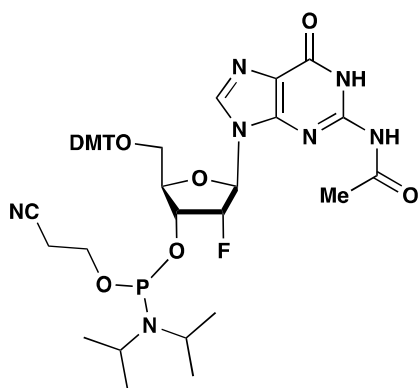
¹⁵ S. Pitsch & P. Weiss, Preparation of 2'-O-[(Triisopropylsilyl)oxy]methyl-protected Ribonucleosides, Current Protocols in Nucleic Acid Chem. (2001), 2.9.1-2.9.14

discloses a step-by-step recipe for preparing N²-acetyl-5'-O-(4,4'-dimethoxytrityl) guanosine. (Exh. 1021, 2.9.8-2.9.10.) (Exh. 1003, ¶ 124.) The installation of a phosphoramidite group on the 3'-oxygen of the sugar ring is taught, for example: in Step “f)” of Scheme 1 in Pitsch (2001) (Exh. 1018 at 3775 & 3777), Step “x” of Example 4-d in the '031 Patent (Exh. 1017, 27:62-28:19), and Figure 3 of McBride (1983) (Exh. 1006 at 246, Fig. 3). (Exh. 1003, ¶ 124.)

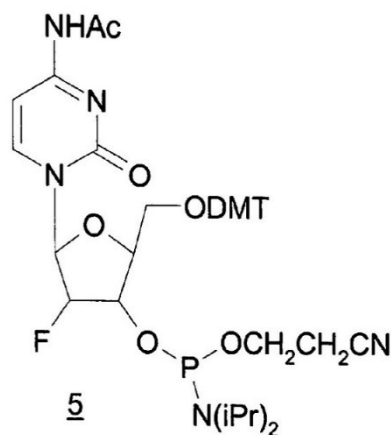
C. Ground III: Claim 2 of the '885 Patent would have been Obvious under § 103 in View of U.S. Patent No. 7,879,991 and Pitsch (2001)

1. Claim 2 where “B” is guanine-N-acetyl and “Z” is ribo fluoro

Claim 2 of the '885 Patent would have been obvious in view of U.S. Patent No. 7,879,991 (“the '991 Patent”) (Exh. 1020) and Pitsch (2001) (Exh. 1018). (Exh. 1003, ¶ 125.) Claim 2 where “B” is guanine-N-acetyl and “Z” is ribo fluoro claims the molecule shown below on the left. (*Id.* at ¶ 126.)



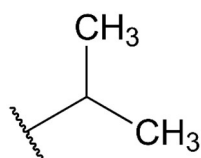
The '885 Patent, Claim 2



The '991 Patent, Fig. 16 (#5)

2. The '991 Patent Discloses an Almost Identical Molecule (where “B” is cytosine-N-acetyl)

The '991 Patent discloses the structurally similar 2'-fluoro-L-cytidine phosphoramidite shown above (in Section VI.C.1) on the right. (Exh. 1003, ¶ 127; Exh. 1020, Fig. 16, #5.) “iPr” is an abbreviation for an isopropyl group, which has the structure below. Thus, the only difference between the phosphoramidite in



Claim 2 of the '885 Patent (where “B” is Guanine-N-acetyl and “Z” is ribo Fluoro) and the 2'-fluoro-L-cytidine phosphoramidite in Fig. 16 (#5) of the '991 Patent is the nucleobase present: the former has a guanine (“G”) base while the latter has a cytosine (“C”) base. (Exh. 1003, ¶ 127.)

3. A POSA Would Have Been Motivated by the '991 Patent and Pitsch (2001) to Synthesize the Molecule in Claim 2

As discussed above, since the advent of phosphoramidite chemistry in oligonucleotide synthesis, a POSA would have recognized that the purpose of a phosphoramidite compound was to serve as a building block for incorporating the corresponding nucleobase into a growing oligonucleotide chain through automated SPOS. A POSA would also have known that the synthesis of most oligonucleotides would have required the incorporation of all four canonical nucleobases (A, C, G, T or U). Thus, the 2'-fluoro-L-cytidine phosphoramidite disclosed in Fig. 16 (#5) of the '991 Patent would have motivated a POSA to build the structurally analogous 2'-fluoro-guanosine phosphoramidite claimed in Claim 2 of the '885 Patent, especially

in view of Pitsch (2001), which (as discussed above) informed a POSA about the advantages of using an acetyl protecting group to protect the exocyclic NH₂ group of the guanine nucleobase. (Exh. 1003, ¶ 128.)

4. A POSA Would Have Had Reasonable Expectation of Successfully Synthesizing the Molecule in Claim 2

As discussed above in Section VI.B.4, a POSA would have had a reasonable expectation of successfully synthesizing the molecule in Claim 2 of the '885 Patent.

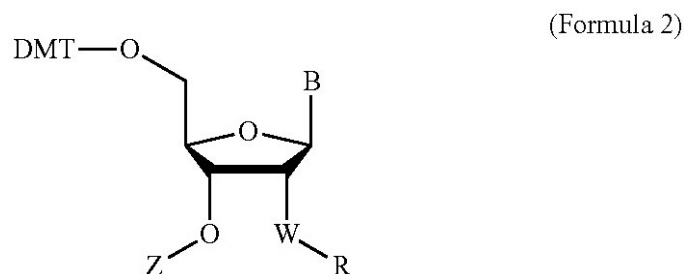
D. Ground IV: Claim 3 of the '885 Patent would have been Obvious under § 103 in View of U.S. Patent No. 5,898,031, Pitsch (2001), Fan (2004), and Scaringe (1990)

1. Claim 3 where “B” is guanine-N-acetyl and “Z” is ribofluoro

Claim 3 of the '885 Patent would have been obvious in view of the '031 Patent (Exh. 1017), Pitsch (2001) (Exh. 1018), Fan (2004) (Exh. 1019), and Scaringe (1990) (Exh. 1022).¹⁶ (Exh. 1003, ¶ 140.) Claim 3 recites:

¹⁶ S.A. Scaringe et al., Chemical synthesis of biologically active oligoribonucleotides using β -cyanoethyl protected ribonucleoside phosphoramidites, Nucleic Acids Research (1990) Vol. 18, No. 18, 5433-5441

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



where B is Guanine-N-acetyl, or adenine-N-acetyl;

W = ribo fluoro or ara fluoro,

and R is absent;

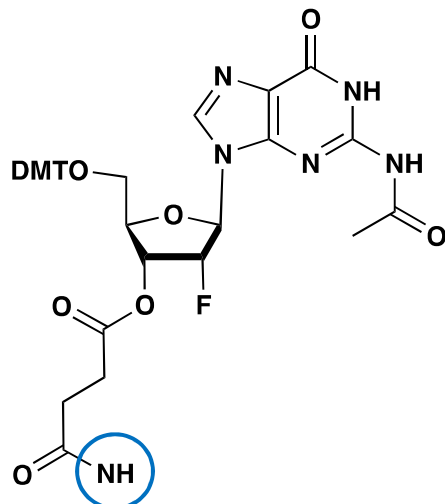
Z is C(O)-M-C(O)—NH,

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.

(Exh. 1001, 25:66-26:17.)

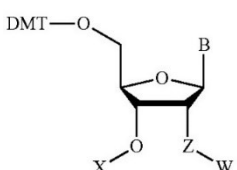
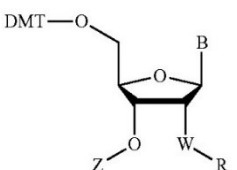
As discussed above in Section V.C.1, a POSA would have readily recognized the clear error in the definition of “M” in Claims 3-5, and would have understood that Claim 3 where “B” is Guanine-N-acetyl, “W” is ribo fluoro, and “Z” is a succinyl group bound to “—NH” (*i.e.*, such that “M” is ethyl) claims the following molecule:



(Exh. 1003, ¶ 138.) A POSA would have further understood that in this molecule, the —NH group (circled in blue) on the succinyl group is capable of being attached to a solid support with a spacer selected from the group of spacers recited in Claim 3. (*Id.* at ¶ 139.)

2. Claims 2 and 3 of the '885 Patent Claim Similar Molecules with Different 3'-O Substituents

Despite the slightly confusing use of inconsistent alphabetic characters between the respective general formulas in Claims 2 and 3 of the '885 Patent to represent side groups at the same positions relative to the sugar ring, Claims 2 and 3 claim nearly identical chemical structures, as shown by the following table:

Claim 2	Claim 3
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 Guanine-N-acetyl, or adenine-N-acetyl;	where B is Guanine-N-acetyl, or adenine-N-acetyl;
Z=ribo Fluoro or ara fluoro, and	W=ribo fluoro or ara fluoro,
W is absent; and	and R is absent;
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, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy.

(Exh. 1003, ¶ 142.) Claims 2 and 3 differ only with respect to the moiety bound to the 3'-O of the sugar ring. In Claim 2, “X” is cyanoethyl dialkyl phosphoramidite, whereas in Claim 3, “Z” can be a succinyl—NH in which the NH is capable of attachment to a solid support with one of the enumerated spacers. (*Id.* at ¶ 143.)

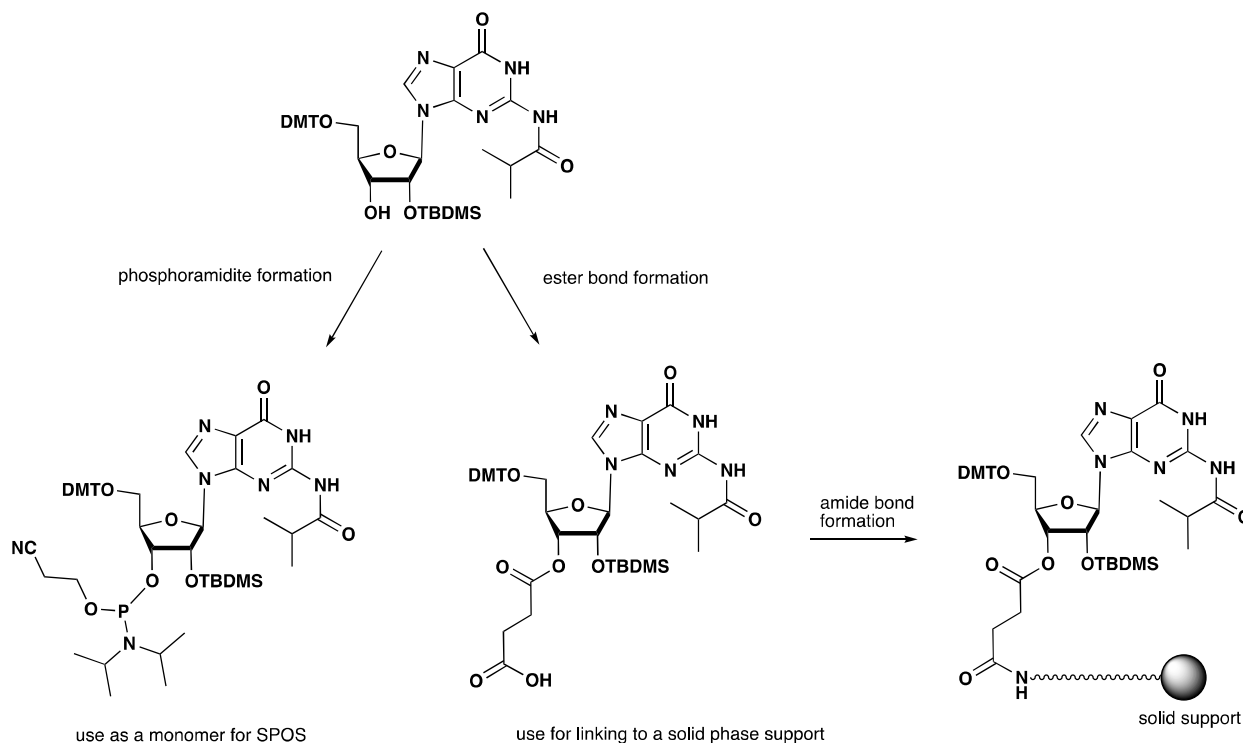
3. The Corresponding Succinate of Claim 3 Would Likewise Have Been Obvious

As discussed above in Section VI.B, (a) the guanosine phosphoramidite made in Example 4-d in the '031 Patent has an isobutyryl protecting group at the exocyclic NH₂ group of the guanine base of that molecule; (b) a POSA would have been motivated by the respective teachings of Pitsch (2001) and Fan (2004) to make and use a similar guanosine phosphoramidite, but with an acetyl instead of an isobutyryl protecting group; and (c) a POSA would have had a reasonable expectation of successfully doing so. This would have resulted in the derivatized nucleoside and phosphoramidite claimed in Claim 2 of the '885 Patent where “B” is guanine-N-acetyl and “Z” is ribo fluoro. (Exh. 1003, ¶ 141.)

The corresponding succinate in Claim 3 (where “B” is guanine-N-acetyl and “Z” is ribo fluoro) would likewise have been obvious. It was well known basic textbook knowledge to a POSA that in solid phase oligonucleotide synthesis using phosphoramidite chemistry (as shown above in Figures 5 and 6), the side group bound to the O on the 3' C of a nucleoside (*i.e.*, “X” in Claim 2 and “Z” in Claim 3) could be either a phosphoramidite (as recited in Claim 2) or a succinate (as recited in Claim 3). (*Id.* at ¶ 144.)

Scaringe (1990) 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. (Exh. 1022, 5434 & 5440.) The similarities between the two molecules are illustrated below.



(Exh. 1003, ¶ 145.) Scaringe (1990) 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.

(Exh. 1022 at 5435; *see also id.* at 5440 (identifying compounds 5a-d as 5'-*O*-(dimethoxytrityl)-2'-*O*-(*t*-butyldimethylsilyl) ribonucleoside 3'-*O*-succinates).)

(Exh. 1003, ¶ 146.) A POSA would have known that LCAA-CPG stands for “long chain alkyl amine 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. (*Id.* (citing Scheuer-Larsen (1997) (Exh. 1023)¹⁷ at 74).)

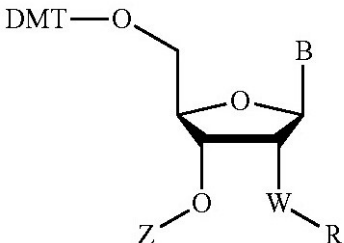
A POSA would also have regarded a C6 alkyl as a suitable long chain alkyl spacer. (Exh. 1003, ¶ 147 (citing Exh. 1007 at 2229, molecule #40).) A C6 alkyl falls within the claimed “C1-C20 alkyl” recited in Claim 3. (*Id.*) Thus, Scaringe (1990) shows that a POSA would have had a reasonable expectation of success to (a) synthesize the molecule claimed in Claim 3 of the ’885 Patent (where “B” is guanine-N-acetyl and “W” is ribo fluoro), and to (b) attach that molecule to a “long chain alkyl amine controlled pore glass.” (*Id.*)

¹⁷ C. Scheuer-Larsen et al., Introduction of a Universal Solid Support for Oligonucleotide Synthesis, Nucleosides, Nucleotides & Nucleic Acids (1997) 16:1-2, 67-80

E. Ground V: Claim 4 of the '885 Patent would have been Obvious under § 103 in View of Scaringe (1990), Pitsch (2001), and Fan (2004)

1. Claim 4 where “B” is guanine-N-acetyl and “R” is t-Butyldimethylsilyl

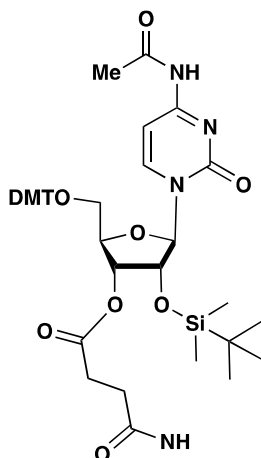
Claim 4 of the '885 Patent would have been obvious in view of Scaringe (1990) (Exh. 1022), Pitsch (2001) (Exh. 1018), and Fan (2004) (Exh. 1019). (Exh. 1003, ¶ 151.) Claim 4 recites:

Derivatized nucleosides, succinates and solid supports of general formula 2,	
 (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 selected from the group consisting of t-Butyldimethyl silyl, acetal levuliny ester (ALE), pivaloyloxy, cyanoethylmethylene (CEM), dithiomethylene (DTM)); 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.

(Exh. 1001, 26:18-43.)

As discussed above in Section V.C.1, a POSA would have readily recognized the clear error in the definition of “M” in Claims 3-5, and would have understood that Claim 4 where “B” is Guanine-N-acetyl, “R” is t-Butyldimethylsilyl,¹⁸ and “Z” is a succinyl group bound to “—NH” (*i.e.*, such that “M” is ethyl) claims the following molecule:



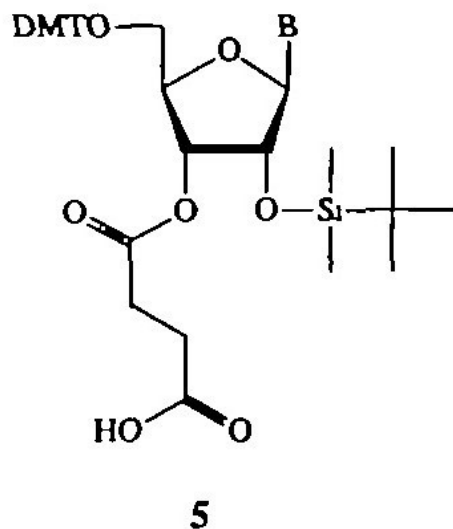
(Exh. 1003, ¶ 150.) And, as discussed above in Section VI.D.1, a POSA would have further understood that in this molecule, the —NH group on the succinyl group is capable of being attached to a solid support with a spacer selected from the group of spacers recited in Claim 4. (*Id.* at ¶ 139.)

¹⁸ Often abbreviated as “TBDMS.”

2. Scaringe (1990) Discloses an Almost Identical Molecule (where “B” is guanine-N-isobutyryl)

Scaringe (1990) discloses the following molecules:

- a) B = N⁶-Benzoyl adenine
- b) = N⁴-Benzoyl cytosine
- c) = N²-Isobutyryl guanine
- d) = Uracil



(Exh. 1022, Fig. 1, #5.) Among them, molecule 5(c) is a 5'-O-(dimethoxytrityl)-2'-O-(*t*-butyldimethylsilyl) N²-isobutyryl guanosine 3'-O-succinate. (Exh. 1003, ¶ 152 (citing *id.* at 5440).) And, as discussed above in Section VI.D.3, Scaringe (1990) also discloses the coupling of this succinate to LCAA-CPG to prepare the solid support for SPOS. (Exh. 1003, ¶ 152 (citing Exh. 1022 at 5435).)

Molecule 5(c) differs from the molecule in Claim 4 (above in Section VI.E.1) only with respect to the protecting group on the exocyclic NH₂ of the guanine base: Molecule 5(c) has an isobutyryl protecting group, whereas Claim 4 claims an acetyl-N-guanine. (*Id.* at ¶ 153.)

3. Pitsch (2001) and Fan (2004) Would Have Motivated a POSA to Install an Acetyl Protection Group

As discussed above in Section VI.B.3-4, Pitsch (2001) and Fan (2004) taught a POSA that using an acetyl group offers far superior deprotection speeds than an isobutyryl group. A POSA would have been likewise motivated by these references to make a guanosine succinate similar to molecule 5(c) of Scaringe (1990) — but with an acetyl instead of an isobutyryl protecting group on the exocyclic NH₂ group of the guanine base — to take advantage of the drastic improvement in deprotection speeds, and would have had a reasonable expectation of success. (Exh. 1003, ¶ 154.)

A POSA would have recognized that the substitution of the protecting group on the exocyclic NH₂ group of the guanine base would not be affected by the 2'-O-TBDMS protecting group, which had been commonly used to shield the 2'-OH. (*Id.* at ¶ 155.) For example, “... the use of the 2'-O-TBDMS group in conjunction with the phosphoramidite approach may be the method of choice for the synthesis of oligoribonucleotides.” (Exh. 1007 at 2270; *see also* Exh. 1017, 17:30-32, Example 1 (“... 2'-OH (blocked as 2'-t-butyldimethylsilyl derivative) nucleoside amidites are available from Glen Research, Sterling, Va.”).)

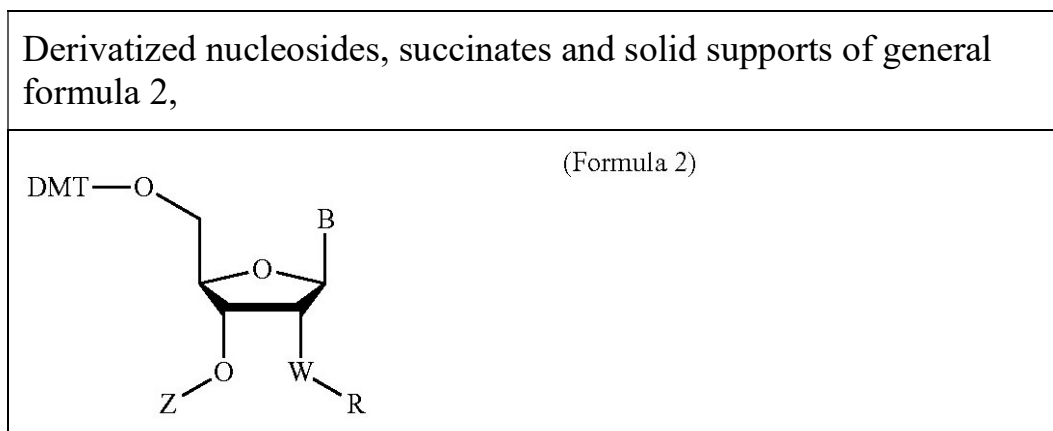
The above substitution of the protecting group on the exocyclic NH₂ group of the guanine base would have resulted in a 5'-O-DMT-2'-O-TBDMS N²-acetyl guanosine 3'-O-succinate. (Exh. 1003, ¶ 155.) As discussed above, Scaringe (1990) discloses the coupling of this succinate to LCAA-CPG to prepare the solid support

for SPOS, and a POSA would have regarded a C6 alkyl as a suitable spacer. (*Id.* at ¶ 156 (citing Exh. 1022 at 5435; Exh. 1007 at 2229 (molecule #40)).) Thus, a POSA would have had a reasonable expectation of successfully making and using the molecule in Claim 4 of the '885 Patent where (where “B” is guanine-N-acetyl, “R” is t-Butyldimethylsilyl, and “Z” is a succinyl group bound to “—NH” (*i.e.*, such that “M” is ethyl). (*Id.*)

F. Ground VI: Claim 5 of the '885 Patent is Anticipated Under § 102(b) by Gaur (1992)

1. Claim 5 where “B” is cytosine-N-isobutyrl

Claim 5 of the '885 Patent is anticipated by Gaur (1992) (Exh. 1024).¹⁹ (Exh. 1003, ¶ 165.) Claim 5 recites:



¹⁹ R.K. Gaur et al., Novel Solid Phase Synthesis of 2'-O-Methylribonucleoside 5'-Triphosphates and Their α -Thio Analogues, Tetrahedron Letters (1992) Vol. 33, No. 23, 3301-3304

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

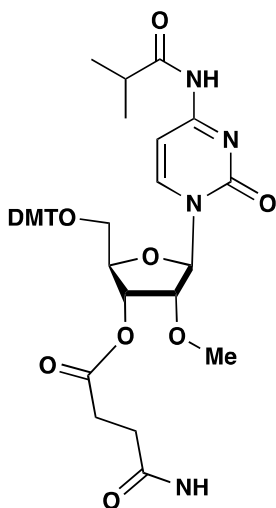
Z is C(O)-M-C(O)—NH,

where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl,

and NH is C1-C20 alkyl, ethoxyglycol, and a combination of alkyl and ethyleneglycoxy.

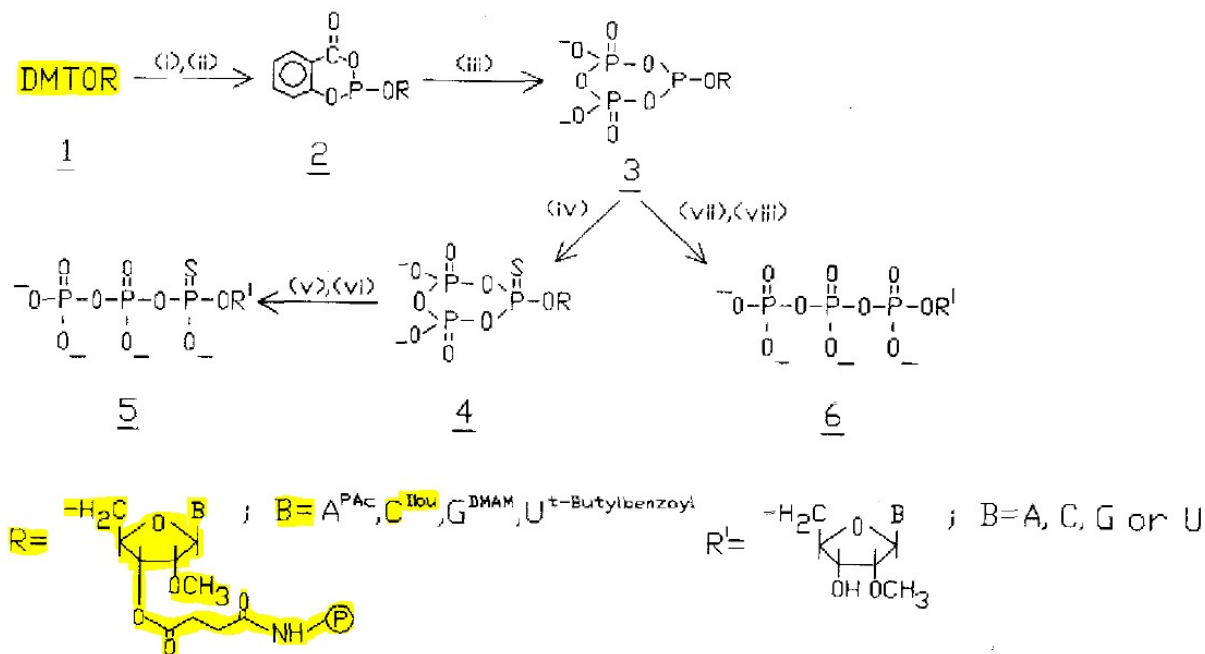
(Exh. 1001, 26:44-65)

As discussed above in Section V.C.1-2, a POSA would have recognized the clear error in the definition of “M” in Claims 3-5, and that the last phrase in Claim 5 inadvertently omits language found in Claims 3-4 regarding the attachment to a solid support. Thus, a POSA would have understood that Claim 5 where “B” is cytosine-N-isobutyryl and “Z” is a succinyl group bound to “—NH” (*i.e.*, such that “M” is ethyl) claims the molecule below. (Exh. 1002, ¶ 164.)



2. Gaur (1992) Discloses the Identical Molecule as Claim 5 of the '885 Patent where "B" is cytosine-N-isobutyryl

Gaur (1992) discloses a reaction scheme in which the starting material is identical to the molecule claimed in Claim 5 of the '885 Patent (above in Section VI.F.1) where "B" is cytosine-N-isobutyryl and "Z" is a succinyl group bound to "—NH" (*i.e.*, such that "M" is ethyl). (Exh. 1003, ¶ 166 (citing Exh. 1024 at 3303 (Scheme 1)).) The relevant portions of Scheme 1 is highlighted in yellow below. (*Id.* at ¶ 167.)



Scheme 1. Reagents and conditions: (i), 3% TCA in CH_2Cl_2 ; (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=dimethyl-aminomethylidene, P=polymer support, DMT=4,4'-dimethoxytrityl.

As shown in Scheme 1, the starting material (labeled as 1) is depicted as DMTOR ("Compound 1"), which (as discussed above) can also be depicted as

DMT-O-R. DMT is a 4,4'-dimethoxytrityl protecting group. R is a ribonucleoside having a 2'-O-CH₃ (*i.e.*, a 2'-O-Me) and a 3'-O-succinyl—NH, and the NH is also attached to a circled P (*i.e.*, a polymer support for SPOS). The nucleobase “B” on the ribonucleoside is C^{Ibu}. “Ibu” is an abbreviation for isobutyryl; therefore, “B” is isobutyryl-N-cytosine. (*Id.* at ¶ 168.)

And, as discussed above, a POSA would have regarded a C6 alkyl as a suitable spacer for attaching the NH to the polymer support. (*Id.* at ¶ 169 (citing Exh. 1007 at 2229, molecule #40).)

Thus, Compound 1 disclosed in Gaur (1992) is identical to the molecule claimed in Claim 5 of the '885 Patent where “B” is cytosine-N-isobutyryl and “Z” is a succinyl group bound to “—NH” (*i.e.*, such that “M” is ethyl). (*Id.* at ¶ 170.)

3. Gaur (1992) Would Have Enabled a POSA to Make the Molecule in Claim 5 of the '885 Patent

Regardless of the presumption that an anticipatory reference would have been enabling, Gaur (1992) would have enabled a POSA to make and use the molecule claimed in Claim 5 of the '885 Patent (where “B” is cytosine-N- isobutyryl and “Z” is a succinyl group bound to “—NH” (*i.e.*, such that “M” is ethyl)) as of its priority date without undue experimentation. (Exh. 1003, ¶ 172.)

For example, the third reference cited in Guar (1992) is an earlier paper by its co-author on the utility of 2'-O-methyloligoribonucleotides, Sproat (1991) (Exh.

1025).²⁰ (Exh. 1024 at 3301, n. 3 (citing Exh. 1025).) Sproat (1991) in turn cites Inoue (1987) (Exh. 1026).²¹ (Exh. 1025, n. 4 (citing Exh. 1026).) Inoue (1987) discusses the synthesis of N-acylated 2'-O-methyloligoribonucleotides in detail. (Exh. 1026 at 6132-35; Scheme 1.) Inoue (1987) further discusses the conversion of these compounds to their corresponding 3'-succinates. (*Id.* at 6135; Scheme 2.) The publication dates of these references demonstrate that the chemical synthesis of Compound 1 in Gaur (1992) would have been well within the technical skill of a POSA. (Exh. 1003, ¶ 173.)

VII. CONCLUSION

For the foregoing reasons, Claims 1-5 of the '885 Patent are unpatentable. Petitioner requests institution of an *inter partes* review and cancelation of these claims.

²⁰ B.S. Sproat et al., 2'-Oalkyloligoribonucleotides Synthesis and Applications in Studying RNA Splicing, Nucleosides and Nucleotides (1991) 10:1-3, 25-36

²¹ H. Inoue et al., Synthesis and hybridization studies on two complementary nona(2'-O-methyl)ribonucleotides, Nucleic Acids Research (1987) Vol. 15, No. 15, 6131-6148

Respectfully submitted,
PROCOPIO, CORY, HARGREAVES & SAVITCH LLP

Dated: January 19, 2023

By: /Jeremy J. Edwards/
Jeremy J. Edwards (Reg. No. 60,982)
Raymond K. Chan (Reg. No. 66,164)
Xiaofan Yang (Reg. No. 61,459)
Jack Shaw (Reg. No. 72,262)
Customer No. 27,189
E-mail: Hongene@procopio.com

Attorneys for Petitioner Shanghai Hongene
Biotech Corporation

CERTIFICATE OF COMPLIANCE

I, the undersigned, hereby certify that the above Petition for *Inter Partes* Review complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a)(1), this Petition, including footnotes, contains 9,441 words as counted by the word count function of Microsoft Word.

Dated: January 19, 2023

By: /Jeremy J. Edwards/
Jeremy J. Edwards (Reg. No. 60,982)
PROCOPIO, CORY, HARGREAVES
& SAVITCH LLP
E-mail: Hongene@procopio.com

Attorneys for Petitioner Shanghai Hongene
Biotech Corporation

CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that a copy of the above Petition for *Inter Partes* Review of U.S. Patent No. 9,884,885, along with all exhibits supporting and filed with the Petition, were served on January 19, 2023 via FedEx overnight courier delivery directed to counsel of record for U.S. Patent No. 9,884,885 (below left) and counsel of record for Patent Owner ChemGenes Corporation in the related district court case (below right) at the following addresses:

Indu M. Anand, Esq. (Reg. No. 52,557) 15 Green Way Chelmsford, Massachusetts 01824 Tel.: 978-250-9003	Brian T. Moriarty Lawrence P. Cogswell III, Ph.D. Samual J. Sussman HAMILTON, BROOK, SMITH & REYNOLDS, P.C. 530 Virginia Road Concord, Massachusetts 01742 Tel.: 978-341-0036
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Dated: January 19, 2023

By: /Jeremy J. Edwards/
Jeremy J. Edwards (Reg. No. 60,982)
PROCOPIO, CORY, HARGREAVES
& SAVITCH LLP
E-mail: Hongene@procopio.com

Attorneys for Petitioner Shanghai Hongene
Biotech Corporation