

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SHANGHAI HONGENE BIOTECH CORPORATION,

Petitioner,

v.

CHEMGENES CORPORATION,

Patent Owner.

IPR2023-00875
U.S. Patent No. 8,309,707 B2

PATENT OWNER RESPONSE

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EXHIBIT LIST

Ex. No.	Description
2001	Expert Declaration of Patrick Hrdlicka, Ph.D.
2002	U.S. Provisional Patent Application No. 61/191,065
2003	Deposition Transcript of Dr. Phil S. Baran (Jan. 22, 2024)
2004	U.S. Patent No. 8,541,569 (Ex. 1001 in IPR2023-00862)
2005	ChemGenes Corporation Catalog, Bio Technology Products & Manufacturer of DNA-RNA Intermediates (1999)
2006-2029	Exhibit numbers not used
2030	Knouse et. al, <i>Unlocking P(V): Reagents for chiral phosphorothioate synthesis</i> , 361 SCIENCE 1234-1238 (2018)
2031	Exhibit number not used
2032	Huang et al., <i>A P(V) platform for oligonucleotide synthesis</i> , 373 SCIENCE 1265-1270 (2021)
2033-2039	Exhibit numbers not used
2040	BioITWorld.com, New expert advisory board appointments set to drive growth and innovation at Hongene (Oct. 25, 2023), available at https://www.bio-itworld.com/pressreleases/2023/10/26/new-expert-advisory-board-appointments-set-to-drive-growth-and-innovation-at-hongene
2041	LinkedIn.com, Hongene Biotech Corporation post announcement, available at https://www.linkedin.com/posts/hongene-biotech-corporation_hongene-advisory-board-activity-7123353670590558208-IXFl?utm_source=share&utm_medium=member_desktop
2042-2044	Exhibit numbers not used
2045	Dr. Phil S. Baran 9/13/2023 Deposition Transcript from IPR2023-00490 (Ex. 2009)

Patent Owner ChemGenes Corporation (“Patent Owner” or “ChemGenes”) respectfully submits this response (“Patent Owner Response” or “Response”) to Petitioner Shanghai Hongene Biotech Corporation’s (“Petitioner” or “Hongene”) petition (“Petition”) asserting that Claims 1 and 2 of U.S. Patent No. 8,309,707 (“the ’707 Patent”) are unpatentable.

I. INTRODUCTION

In response to the Petition, Patent Owner has concurrently filed herewith a Motion to Amend Claims Under 37 C.F.R. § 42.121 (“Motion to Amend”). As discussed in the Motion to Amend and the Declaration of Patrick J. Hrdlicka, Ph.D. (Ex. 2001) in support of this Patent Owner Response and the Motion to Amend, and as further discussed below, the proposed substitute claims to replace original Claims 1 and 2 of the ’707 Patent renders Grounds I and II set forth in the Petition moot.

II. CHEMGENES AND THE ’707 PATENT

ChemGenes Corporation is a Massachusetts-based company that has been an innovator in the field of nucleoside, P(III) phosphoramidite reagent, and oligonucleotide syntheses since 1981, at the dawn of the modern solid-phase oligonucleotide synthesis (“SPOS”) era.

ChemGenes has invented numerous novel nucleosides, phosphoramidite reagents, and oligonucleotides, which it has sold to pharmaceutical companies, biotechnology companies, academic institutions, and other partners since its

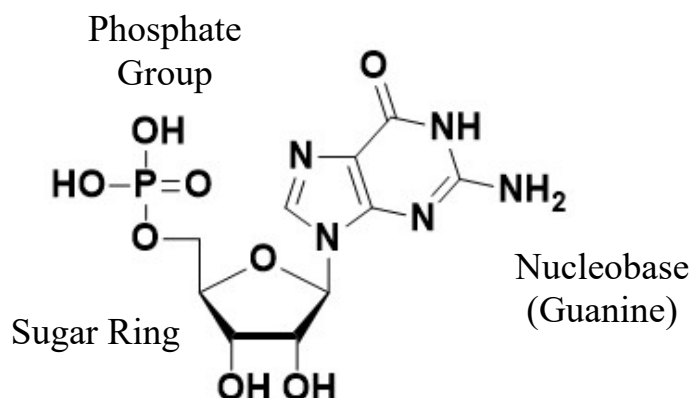
founding. ChemGenes has consistently applied for and been granted patents in the U.S. and throughout the world over the years for its novel compounds.

Claims 1 and 2 are directed to innovative compounds useful for synthesis of RNA in the reverse 5' → 3' direction. Ex. 2001, ¶36. More specifically, the Claims are directed to new types of 3'-dimethoxytrityl (DMT)-5'-cyanoethyl (CE) ribonucleoside phosphoramidites, which can be used to synthesize high purity RNA in the reverse 5' → 3' direction. *Id.*

III. TECHNOLOGY BACKGROUND

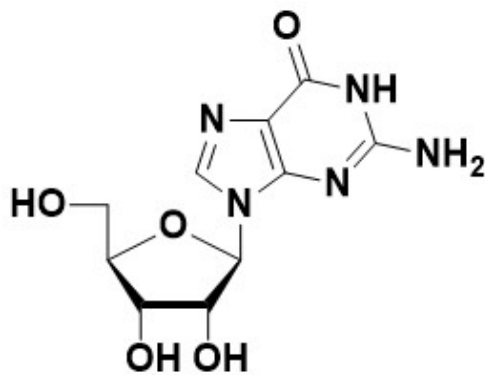
Nucleic Acids. Nucleic acids are macromolecules, which are essential to all known living organisms. Ex. 2001, ¶38. Examples of nucleic acids include DNA and RNA. *Id.* DNA and RNA are carriers of genetic information. *Id.* DNA and RNA are long polymers of 2'-deoxyribonucleotides and ribonucleotides, respectively. *Id.*

Nucleotides. Nucleotides are comprised of (1) a five-carbon sugar ring; (2) a phosphate group; and (3) one of four major nitrogen “nucleobases” (i.e., adenine (“A”), cytosine (“C”), guanine (“G”) in DNA and RNA; thymine (“T”) in DNA; and uracil (“U”) in RNA). *Id.*, ¶39. The nucleotides of RNA are called ribonucleotides and feature a hydroxyl (-OH) group at the 2'-position that points downwards. *Id.* The nucleotides of DNA are called 2'-deoxyribonucleotides and feature a hydrogen (-H) in place of the (-OH) group at the 2'-position. *Id.* An exemplary ribonucleotide, having a guanine nucleobase, is shown as follows:



Id.

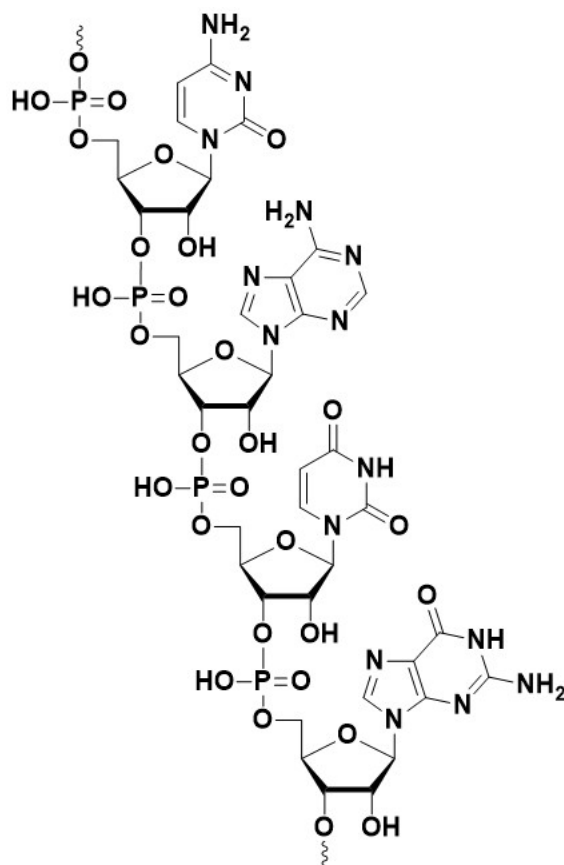
Nucleosides. Nucleosides are nucleotides without a phosphate group; an exemplary ribonucleoside having a guanine nucleobase, referred to as guanosine, is shown as follows:



Id., ¶40.

Oligonucleotides. Oligonucleotides are short polymeric single strands of nucleotides. RNA-based oligonucleotides are referred to as “oligo**ribo**nucleotides” and are polymers of ribonucleotides. DNA-based oligonucleotides are referred to as “oligo**deoxyribo**nucleotides” and are polymers of 2'-deoxyribonucleotides. *Id.*, ¶41.

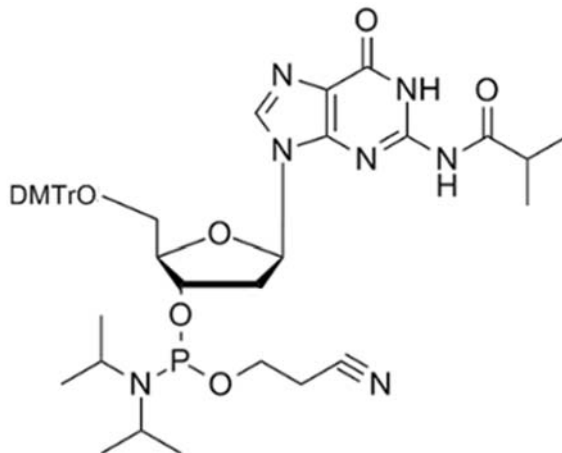
Oligonucleotides vary in length and sequences and can be comprised of a few, tens or hundreds of nucleotides, as compared to DNA and RNA that can comprise millions of 2'-deoxyribonucleotides and ribonucleotides, respectively. *Id.*, ¶42. The following is a depiction of an exemplary oligoribonucleotide:



Id. The umbrella term “oligonucleotide” or “oligo” encompasses oligoribonucleotides (RNA-based) as well as oligodeoxyribonucleotides (DNA-based). *Id.*, ¶43.

Phosphoramidites. Nucleoside phosphoramidites (or routinely just referred to as “phosphoramidites” or “amidites”) are derivatives of nucleosides that are used

as reagents for SPOS to obtain oligonucleotides. *Id.*, ¶44. An exemplary 2'-deoxyguanosine phosphoramidite is shown as follows:

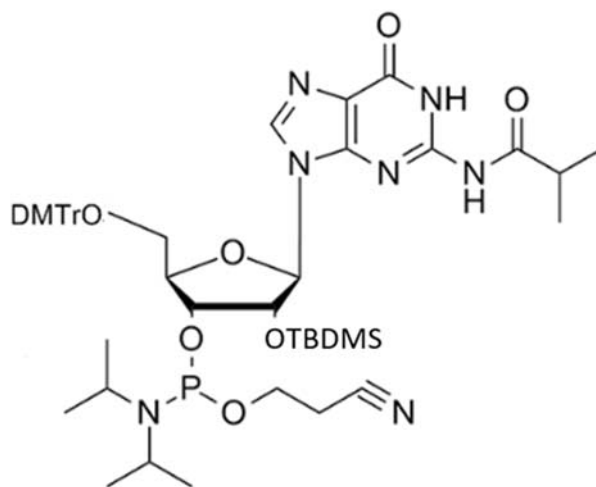


Id., ¶44.

As shown above, a phosphoramidite is characterized by having the general structure $(RO)_2PNR_2$, i.e., a phosphorus atom in a P(III) oxidation state having one P-N bond and two P-O bonds, and of the two oxygen-containing functionalities, one is usually a protecting group (typically a β -cyanoethyl group) and the other is a nucleoside. *Id.*, ¶45.

Phosphoramidites that are to be used in SPOS usually require additional protecting groups (in addition to the β -cyanoethyl group mentioned above), which shields reactive sites that would interfere with SPOS. *Id.*, ¶46. Commonly, but not universally, phosphoramidites feature a 4,4-dimethoxytrityl (DMTr, also commonly referred to as DMT) group at the 5'-position (shown above and below). *Id.* Typically, the exocyclic amines ($-NH_2$) of most nucleobases (e.g., A, C, G) must also be

protected (shown above and below as a N2-isobutyryl-protected guanine). *Id.* For RNA synthesis, the hydroxyl group (-OH) at the 2'-position of ribonucleoside phosphoramidites, also must be protected (most commonly, but not universally, as a *tert*-butyldimethylsilyl “TBDMS” group) to shield its reactivity during SPOS (shown below):



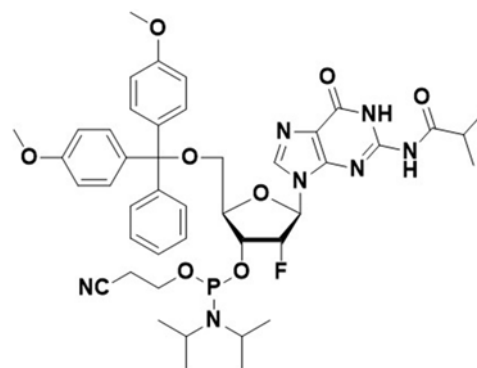
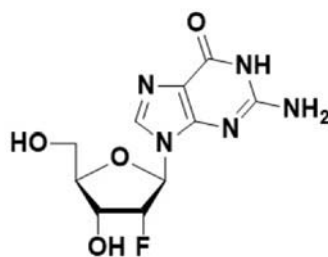
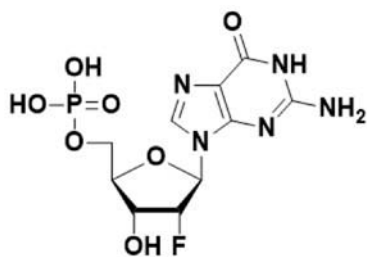
Id.

Chemically Modified Nucleosides, Nucleotides, and Phosphoramidites.

Virtually every position on the sugar ring of a nucleoside, nucleotide, and phosphoramidite can be chemically modified, such as the 2'-position which can have, e.g., a halo atom (such as a fluoro). *Id.*, ¶47. Nucleosides, nucleotides, and phosphoramidites can also feature non-canonical nucleobases and chemically modified nucleobases such as 5-methylcytosine. *Id.*

Examples of chemically modified nucleosides, nucleotides, and/or phosphoramidites include 2'-fluoro-2'-deoxyribonucleosides, 2'-fluoro-2'-deoxyribonucleotides, and 2'-fluoro-2'-deoxyribonucleoside phosphoramidites where a downward pointing fluoro (-F) is at the 2'-position. *Id.*

A modified oligoribonucleotide (i.e., RNA-based oligonucleotide) can feature one or more chemically modified nucleotides, such as 2'-fluoro-2'-deoxyribonucleotides (2'-fluoro-2'-deoxyguanosine nucleotide shown on the left, 2'-fluoro-2'-deoxyguanosine nucleoside shown in the middle, and a 2'-fluoro-2'-deoxyguanosine phosphoramidite shown to the right):



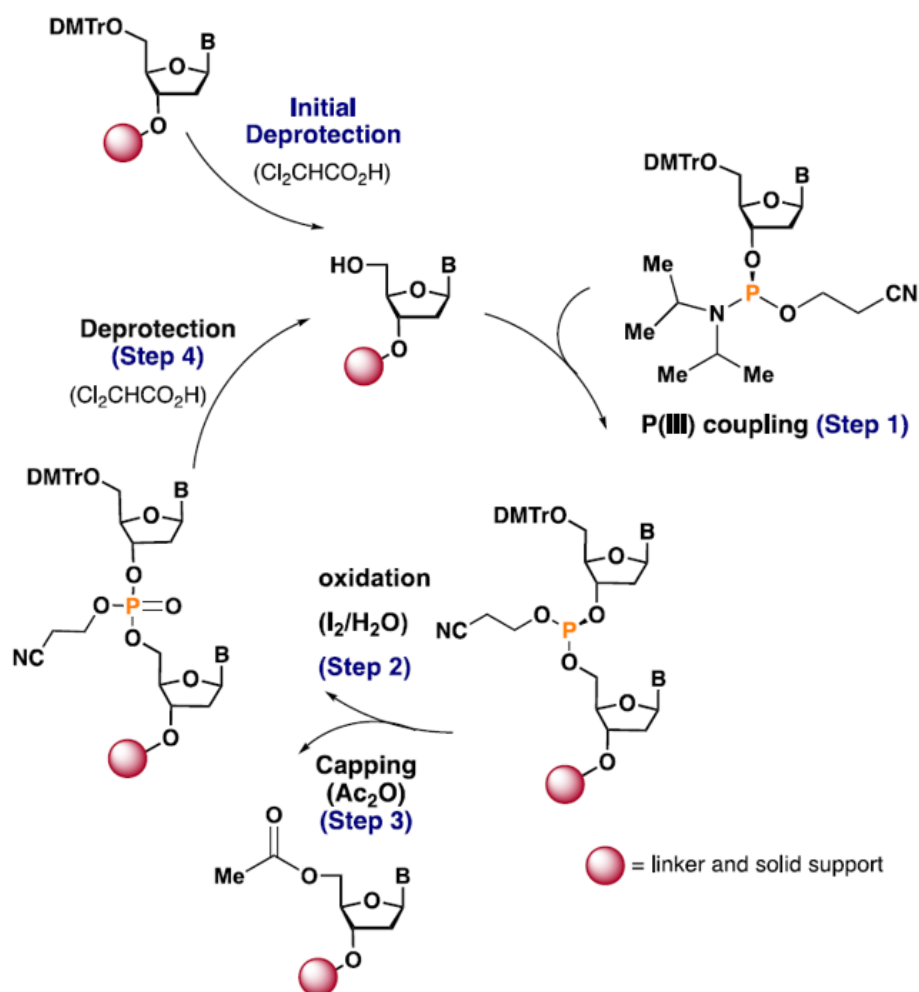
Id.

As Dr. Hrdlicka explains, given the variety of options for protecting groups, and chemically modified sugars and nucleobases, there were thousands of different phosphoramidites and nucleosides available to a POSA as of the date of the '707 Patent's inventions. *Id.*, ¶48.

Conventional DNA SPOS. The synthesis of oligodeoxyribonucleotides (DNA) via SPOS in the traditional 3' → 5' direction, uses conventional 2'-

deoxyribonucleoside phosphoramidites and is well-established. *Id.*, ¶49; Ex. 1010, 193-197.

As shown below, and as previously presented in Dr. Baran's Declaration, the traditional 3' → 5' SPOS cycle for DNA synthesis (i.e., canonical SPOS cycle), begins with deprotection of the 5'-DMTr group of the support-bound 2'-deoxyribonucleoside, which reveals a 5'-hydroxyl group ("OH") at the 5' position. Ex. 2001, ¶49; Ex. 1010, 194, 196.



Ex. 2001, ¶49.

In the presence of a suitable coupling reagent, the 5'-OH group then reacts with the phosphorus (“P”) of the phosphoramidite group of the incoming 2'-deoxyribonucleoside, which displaces the amine (i.e., diisopropylamino) and results in coupling of the incoming 2'-deoxyribonucleoside with the support-bound 2'-deoxyribonucleoside. *Id.*; Ex. 1010, 194, 196.

The next step involves oxidation of the phosphorus from its P(III) state to the P(V) state (i.e., the oxidation state of the phosphorus in DNA and RNA). Ex. 2001, ¶49; Ex. 1010, 194, 196. This step is typically accomplished by adding a mixture of iodine in water (i.e. I₂/H₂O), resulting in formation of a stable phosphotriester linkage between the two coupled nucleosides. Ex. 2001, ¶49; Ex. 1010, 194, 196.

The next step is typically a capping step, which protects (and thereby inactivates) 5'-OH groups of any unreacted support-bound nucleosides, and thereby prevents undesirable elongation, which would lead to formation of shorter-than-desired oligonucleotides. Ex. 2001, ¶49; Ex. 1010, 194, 196.

Next, the DMTr protecting group at the 5'-position of the support-bound dinucleotide is removed, exposing the 5'-hydroxyl group (as in step 1), and setting the stage for the cycle to repeat. Ex. 2001, ¶49; Ex. 1010, 194, 196. The process repeats to add a 3rd, 4th, 5th, etc., nucleoside to produce a support-bound oligonucleotide. Ex. 2001, ¶49; Ex. 1010, 194, 196.

Once the desired oligonucleotide has been synthesized, the oligonucleotide is cleaved from the solid support and all protecting groups are removed. Ex. 2001, ¶49; Ex. 1010, 196.

Conventional RNA SPOS. According to Dr. Hrdlicka, development of canonical RNA SPOS proved far more challenging than canonical DNA SPOS, as it required development of suitable protecting groups for the 2'-OH group, alternative coupling reagents and deprotection protocols, and the use of longer coupling times and nuclease-free conditions. Ex. 2001, ¶50; *also see* Ex. 1009, 3862-3864.

At the time of the '707 Patent's inventions, synthesis of oligoribonucleotides via SPOS in the traditional 3' → 5' direction and using conventional ribonucleoside phosphoramidites was established (though not routine or predictable) for the synthesis and development of a vast variety of therapeutic grade RNA molecules. Ex. 1001, 1:35-39; Ex. 2001, ¶50. As described above, the ribonucleoside phosphoramidites require suitable protecting groups on the nucleobase (typically acyl groups such as, e.g., N2-isobutyryl for G), the 5'-OH position (typically DMTr), the 2'-OH position (typically TBDMS), and the 3'-phosphoramidite (typically a β-cyanoethyl group). Ex. 2001, ¶50; *also see* Ex. 1009, 3859, 3864.

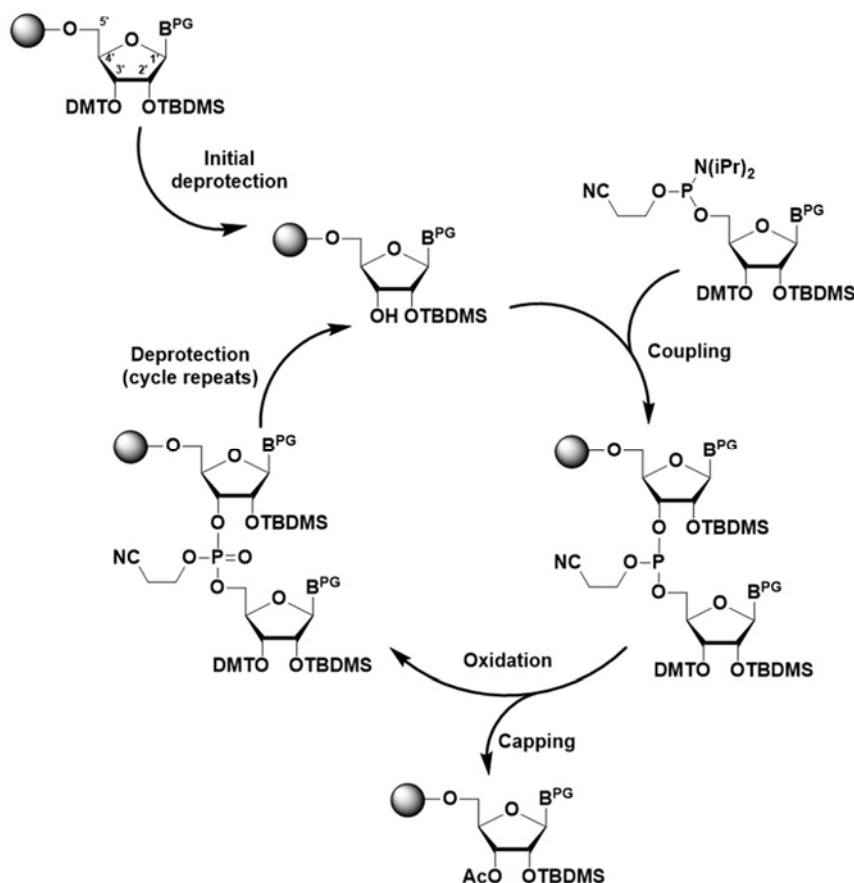
Fundamentally, the steps of the 3' → 5' RNA SPOS cycle are similar to the 3' → 5' DNA SPOS cycle. Ex. 2001, ¶50; *also see* Ex. 1009, 3864.

According to Dr. Hrdlicka, modification of the 3'-end of RNA with certain chemical entities is desirable for certain applications. *Id.*, ¶51. The synthesis of RNA modified at the 3'-end with lipophilic, long chain ligands or chromophores using the 3' → 5' synthesis methodology, is challenging and generally results in low coupling efficiency and purity of the final oligonucleotide, and additional purification steps are therefore needed. Ex. 1001, 8:25-32; Ex. 2001, ¶51.

Accordingly, as Dr. Hrdlicka explains, at the time of the '707 Patent's inventions, new synthetic methodologies were needed to efficiently synthesize RNA molecules quickly and in a manner that allowed for straightforward modification at the 3'-end of the oligonucleotide. Ex. 1001, 8:21-24, 34-39; Ex. 2001, ¶51.

Reverse RNA SPOS. In Dr. Hrdlicka's opinion, reverse RNA SPOS is an innovative approach to synthesize oligoribonucleotides in the 5' → 3' direction (i.e., the opposite direction of the traditional approach). Ex. 2001, ¶52. The use of reverse RNA nucleosides, phosphoramidites, and supports, like those claimed in the '707 Patent, allows for synthesis of high purity oligoribonucleotides and introduction of various modifications at the 3'-end. Ex. 1001, 4:1-4, 8:34-39; Ex. 2001, ¶52. The use of reverse RNA amidites, like those disclosed in the '707 Patent, in machine-assisted reverse SPOS leads to higher coupling efficiency per step, resulting in a greater ability to produce very long oligoribonucleotides of high purity. Ex. 1001, 4:1-4,

8:34-39; Ex. 2001, ¶52. An illustration by Dr. Hrdlicka of the reverse 5' → 3' SPOS cycle is shown below:



Ex. 2001, ¶52.

The reverse RNA SPOS cycle begins with deprotection of the 3'-DMTr group of the support-bound ribonucleoside, which reveals a 3'-hydroxyl group (“-OH”) at the 3' position. Ex. 2001, ¶52; *also see* Ex. 2004, 26:5-33, 122:55-123:13.

In the presence of a suitable coupling reagent, the 3'-OH group then reacts with the phosphorus (“P”) of the phosphoramidite group of the incoming reverse ribonucleoside phosphoramidite, which displaces the amine (i.e., diisopropylamino)

and results in coupling of the incoming ribonucleoside with the support-bound ribonucleoside. Ex. 2001, ¶52; *also see* Ex. 2004, 26:35-65, 123:15-61.

The next step typically involves oxidation of the phosphorus from its P(III) state to the P(V) state (i.e., the oxidation state of the phosphorus in DNA and RNA). Ex. 2001, ¶52; *also see* Ex. 2004, 27:3-22, 123:65-124:15. This step is typically accomplished by adding a mixture of iodine in water (i.e. I₂/H₂O), resulting in the formation of a stable phosphotriester linkage between the two coupled nucleosides. Ex. 2001, ¶52; *also see* Ex. 2004, 27:3-22, 123:65-124:15.

According to Dr. Hrdlicka, the next step is typically a capping step, which protects (and thereby inactivates) 3'-OH groups of any unreacted support-bound nucleosides, and thereby prevents undesirable elongation, which would lead to formation of shorter-than-desired oligonucleotides. Ex. 2001, ¶52; *also see* Ex. 2004, 27:1-2, 123:64. Next, the DMTr protecting group at the 3'-position of the support-bound dinucleotide is removed, exposing the 3'-hydroxyl group (as in step 1), and setting the stage for the cycle to repeat. Ex. 2001, ¶52; *also see* Ex. 2004, 27:24-45, 124:18-43.

The process repeats to add a 3rd, 4th, 5th, etc., nucleoside to furnish a support-bound oligonucleotide. Ex. 2001, ¶52; *also see* Ex. 2004, 27:50-28:51, 124:52-125:55.

Once the desired oligonucleotide has been synthesized, the oligonucleotide is

cleaved from the solid support and all protecting groups are removed. Ex. 2001, ¶52; *also see* Ex. 2004, 27:50-28:51, 124:52-125:55.

Petitioner's Assertions Regarding the Background Art for Reverse SPOS. Patent Owner addresses several inaccurate statements made in the Petition and in Dr. Baran's declaration with respect to the background art regarding reverse oligonucleotide synthesis, i.e., 5' → 3' oligonucleotide synthesis. Ex. 2001, ¶53.

Petitioner and Dr. Baran argue, without support, that “by the early 2000s, the advantages of oligonucleotide synthesis in the 5' → 3' or ‘reverse’ direction were well-recognized.” Ex. 1003, ¶54; Pet, 14-15; Ex. 2001, ¶53.

Dr. Baran and Petitioner then list several purportedly known advantages, such as “the ability to synthesize longer oligonucleotides” and the ability to “selectively remove[]” protective groups during synthesis to achieve higher purity. Ex. 1003, ¶55; Pet, 15; Ex. 2001, ¶53. To the extent that Petitioner and Dr. Baran argue that Wagner or Albert teach such advantages, Patent Owner disagrees. Ex. 2001, ¶53.

As support of the purportedly known advantages of 5' → 3' oligonucleotide synthesis, Dr. Baran and Petitioner cite to a paper by Wagner et al.¹ Ex. 1003, ¶55;

¹ T. Wagner & W. Pfleiderer, *Synthesis of 2'-Deoxyribonucleoside 5'-Phosphoramidites: New Building Blocks for the Inverse (5'-3')-Oligonucleotide Approach*, Helvetica Chimica Acta – Vol. 83 (2000), 2023-2035 (Ex. 1011).

Pet, 15; Ex. 2001, ¶54. Wagner paper that “very little is known in literature about the detailed specification of the synthesis of the appropriate 5'-phosphoramidites suitable for the built-up [*sic*] of oligonucleotides in the 5' → 3' direction.” Ex. 1011, 2023; Ex. 2001, ¶54.

Dr. Baran agreed with the Wagner authors' assessment of the state of knowledge concerning 5' → 3' oligonucleotide synthesis during his deposition, and further agreed that much research was needed to understand how to synthesize oligonucleotides through SPOS in the reverse 5' → 3' direction. Ex. 2003, 142:18-143:22; Ex. 2001, ¶54. Also noteworthy, Wagner pertains to reverse DNA SPOS, and not reverse RNA SPOS, as described and claimed in the '707 Patent. Ex. 2001, ¶54.

Petitioner and Dr. Baran also cite a paper by Albert et al.² Ex. 1003, ¶55; Pet, 15; Ex. 2001, ¶55. As Dr. Hrdlicka explains, the discussion in Albert, however, also related to the synthesis of DNA (not RNA). Ex. 2001, ¶55; Ex. 1012, 1 (“DNA microarrays have revolutionized nucleic acid analysis”), 6 (“The cycle yields for DNA synthesis of DNA in the 5' → 3' direction were reported in a previous study for T and C (13). Our results with T were identical to that reported earlier.”).

² T.J. Albert et al., *Light-directed 5'→3' synthesis of complex oligonucleotide microarrays*, Nucleic Acids Research (2003) Vol. 31, No. 7, 1-9 (Ex. 1012).

Accordingly, each of the Wagner and Albert references applied to reverse 5' → 3' synthesis for DNA, which is a different process than reverse 5' → 3' synthesis of RNA as described and claimed in the '707 Patent. Ex. 2001, ¶55.

Further, according to Dr. Hrdlicka, no references cited by Petitioner or Dr. Baran teach that an advantage of 5' → 3' oligonucleotide synthesis is “the ability to synthesize longer oligonucleotides” because in “the traditional 3' → 5' direction, the buildup of protecting groups needed to prevent unwanted side reactions may limit the length of oligonucleotides.” Ex. 1003, ¶55; Pet, 15; Ex. 2001, ¶56. Again, Dr. Baran cites nothing in support of this statement. Ex. 2001, ¶56. To the extent Dr. Baran and Petitioner are arguing that this proposition was well-established in the art at the time of the inventions in the '707 Patent, Patent Owner disagrees. *See* Ex. 2001, ¶56.

Contrary to this unsupported testimony, Albert states that “[s]tepwise yields (for 5' → 3' synthesis) are slightly lower on average than 3' → 5' synthesis.” Ex. 1012, 4; Ex. 2001, ¶56. Albert also shows data in Table 1 in support of this statement. Ex. 1012, 2; Ex. 2001, ¶56.

According to Dr. Hrdlicka, a POSA would have therefore understood that the poorer coupling yields reported in Albert for oligonucleotide synthesis in the 5' → 3' direction, vis-à-vis synthesis in the 3' → 5' direction, would render synthesis of longer oligonucleotides less probable, not more probable. Ex. 2001, ¶56.

Therefore, to the extent Petitioner and Dr. Baran are arguing that Wagner and/or Albert teach that the synthesis of oligonucleotides in the 5' → 3' direction would produce longer oligonucleotides than in the 3' → 5' direction, Patent Owner disagrees. *Id.*

Further, Petitioner and Dr. Baran argue, citing to Wagner, that the “reverse 5' → 3' direction allows protecting groups to be selectively removed during synthesis to yield oligonucleotides of high purity, producing totally unprotected oligonucleotides that remain attached to the solid support.” Ex. 1003, ¶55; Pet, 15; Ex. 2001, ¶57. To the extent Dr. Baran and Petitioner argue that this proposition was known in the art at the time of Wagner, Albert or other prior art, Patent Owner disagrees.

As Dr. Hrdlicka explains, a POSA would have readily understood from Wagner that this purported advantage is not due to 5' → 3' oligonucleotide synthesis, but rather is due to the highly specialized nucleobase protecting groups used in Wagner. Ex. 2001, ¶57; Ex. 1011, 2023 (“Application of the npe/npeoc strategy (npe = 2-(4-nitrophenyl)ethyl, npeoc = [2-(4-nitrophenyl)ethoxy]carbonyl) allows also the inverse (5' → 3')-directed built-up [*sic*] of oligonucleotides of high purity starting with the appropriately protected 5'-phosphoramidites. ***By this strategy***, totally unprotected oligonucleotides still attached to the solid support are available” (emphasis added)).

Citing Wagner, Dr. Baran and Petitioner also state that the advantages of reverse 5' → 3' “have enabled the development of oligonucleotide-based nanotechnology such as oligonucleotide microarrays (a/ka DNA chips).” Ex. 1003, ¶55; Pet, 15; Ex. 2001, ¶58. This mischaracterizes Wagner, which does not teach that such technologies are predicated by reverse oligonucleotide synthesis. Ex. 2001, ¶58.

Wagner only lists oligonucleotide microarrays as an area of interest in the early 2000s. *Id.* There is nothing in Wagner tying oligonucleotide synthesis in the reverse (or any) direction to the development of oligonucleotide microarrays. *Id.*; *see* Ex. 1011 (“Beside the use of oligonucleotides in medicinal chemistry as potential antisense and antigene drugs, there is *increasing interest* in their use in oligonucleotide-chip technology, diagnostic tools, biological applications, and nanotechnology” (emphasis added)).

IV. CLAIM CONSTRUCTION: CLAIMS 1 AND 2 SHOULD BE CONSTRUED IN ACCORDANCE WITH THEIR ORDINARY AND CUSTOMARY MEANINGS

Claims 1 and 2 should be construed in accordance with “the ordinary and customary meaning of such claim[s] as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” 37 C.F.R. § 42.100.

V. PETITIONER'S DEFINITION OF A POSA SHOULD BE MODIFIED

Patent Owner does not agree with Petitioner's definition of a POSA, i.e., that a POSA would have had a Ph.D. 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." Pet, 16 (emphasis added); Ex. 2001, ¶59.

Dr. Baran has characterized himself as a professor in organic chemistry and an expert in medicinal chemistry, but testified that only 14 of the over 250 papers he authored in his career relate to oligonucleotide synthesis and the earliest of those papers was just 5 years ago. Ex. 2003, 183:13-16; Ex. 2045, 75:22-24; 73:21-23; 97:23-98:1; 99:15-100:7; Ex. 2001, ¶60.

Furthermore, the focus of the most prominent of those papers appears to be on *P(V) chemistry* which, as Dr. Baran acknowledged in a related proceeding, is a fundamentally different synthesis platform than the P(III) chemistry at bar. Ex. 2045, 109:4-6 ("Q. But the focus of this paper [Ex. 2032] is on P(V)? A. The focus of this paper is awakening people to the difference between P(V) and P(III)."); Ex. 2030, 1 (Dr. Baran et al. describing "P(V)-based reagent platforms" as "as a fundamentally different approach" as compared to "phosphorus(III)-based reagent systems."); *also see* Ex. 2032, 1268-69 (disclosing P(V)-based oligonucleotide synthesis not

involving phosphoramidites, and instead using completely different “PSI” reagents in a “fundamentally” different process, such differences including different reagents, solid supports, nucleobase protecting groups, coupling reagents, and no oxidation step as otherwise required by P(III) SPOS). Ex. 2001, ¶60.

Dr. Hrdlicka is, and was as of the date of the ’707 Patent’s inventions, highly skilled in developing synthesis schemes and conducting or directing the synthesis of nucleosides, nucleotides, and phosphoramidites pursuant to P(III) chemistry, including, but not limited to, the synthesis of oligonucleotides through SPOS, and is and was familiar with the level of skill of a POSA in that timeframe. Ex. 2001, ¶61.

According to Dr. Hrdlicka, skilled artisans as of the date of the ’707 Patent’s inventions, who developed synthetic schemes for, and who conducted or directed the syntheses of nucleosides, phosphoramidites and oligonucleotides in connection with P(III) chemistry, are those who would provide the most relevant viewpoints on aspects relating to the ’707 Patent. *Id.*, ¶62.

In contrast, the viewpoints of those who instead have focused on using oligonucleotides for therapeutic and diagnostic purposes after their production, but who were not skilled in the art of developing synthesis schemes for, and conducting or directing the syntheses of, nucleosides, phosphoramidites or oligonucleotides pursuant to P(III) chemistry, are not as applicable to the central inquiries at bar, because the Claims in the ’707 Patent are directed to nucleosides, phosphoramidites

and solid supports for P(III) solid-phase synthesis of oligonucleotides and not the therapeutic and diagnostic uses of oligonucleotides. *Id.*, ¶63.

Accordingly, Patent Owner respectfully proposes the following alternative definition for a POSA, shown as redline changes to the definition that Petitioner proposed:

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

Alternatively, someone with a Ph.D. (or equivalent degree) in organic chemistry, and who focused on the development and syntheses of nucleosides, nucleotides, and nucleic acids, including, but not limited to, the syntheses of oligonucleotides through SPOS pursuant to P(III) chemistry during his or her Ph.D. studies.

Alternatively, someone with a Bachelor’s or Master’s degree in organic chemistry who had at least 5 years of extensive work experience in these fields, and who had gained a thorough

understanding of the ~~syntheses development~~ of nucleic acid-based materials ~~pursuant to P(III) chemistry~~, would also have qualified as a POSA ~~with a Bachelor's or Master's degree in organic chemistry or medicinal chemistry.~~

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

Further, during his deposition, Dr. Baran testified that there are “exceptions” to his proposed definition of a POSA, that his definition was “malleable,” and that he has “no problem” with other POSA definitions that have been proposed. Ex. 2003, 177:17-178:1; *Id.*, ¶65. Patent Owner respectfully submits that it would prevail under either definition of a POSA based on at least the reasons provided in this Response. Ex. 2001, ¶65.

VI. DR. BARAN’S BIAS

With regard to Dr. Baran’s ties to Hongene, it was recently discovered during Dr. Baran’s deposition in this case, that Hongene appointed Dr. Baran to its Advisory Board at least by October 16, 2023, a day before ChemGenes’ Patent Owner Response was due in related proceeding IPR2023-00490 (regarding the ’885 Patent) in which Dr. Baran is also testifying as an expert for Hongene. Ex. 2003, 121:15-22.

According to Dr. Baran, Hongene initially contacted Dr. Baran in July of 2023 regarding the appointment which was formally announced on October 25, 2023. Ex.

2003, 119:6-8, 120:2-17, *also see* Ex. 2040, 2 (October 25, 2023 BioITWorld Press Release announcing Dr. Baran's appointment to the Hongene Advisory Board); Ex. 2041 (Hongene's Linked-In page announcing same).

Dr. Baran testified that he executed a contract with Hongene regarding the Advisory Board appointment and that Hongene agreed to pay Dr. Baran \$70,000 per year. Ex. 2003, 121:3-4. This significant financial payment to Dr. Baran (independent of the \$750 per hour he is being paid to serve as a consultant on this case (Ex. 1003, ¶1)) should be taken into consideration when considering his bias in this case and the related IPR2023-00862 and IPR2023-00490 cases.

ChemGenes has repeatedly asked Hongene to provide voluntarily a copy of the contract between Hongene and Dr. Baran, as well as related communications, so as not to force ChemGenes to move for such documents, but Hongene has not provided those documents to ChemGenes or indicated that it would provide them to date.

VII. THE '696 PATENT

Petitioner has proffered U.S. Patent No. 5,869,696 (Ex. 1014) (the "'696 Patent") as an anticipatory reference. Ex. 2001, ¶66. According to Dr. Hrdlicka, the '696 Patent is not directed to synthesis of oligonucleotides (or RNA) in the 5' → 3' direction. *Id.* As shown on the face of the '696 Patent, the '696 Patent is directed to "[u]niversal solid support oligonucleotide synthesis processes, and reagents for

cleaving oligonucleotides from solid supports.” Ex. 1014, Abstract; Ex. 2001, ¶66. Universal supports are solid supports that allow a practitioner to synthesize oligonucleotides using a common solid support. Ex. 1014, 4:21-36; Ex. 2001, ¶66.

As Dr. Hrdlicka explains, SPOS in the traditional 3' → 5' direction typically requires the use of solid supports attached to the 3'-position of the first nucleotide in the chain of nucleotides comprising the subject oligonucleotide. Ex. 2001, ¶67; *also see* Ex. 1014, 1:19-21; Ex. 2003, 156:13-18 (“Q: And you agree that in solid phase oligonucleotide synthesis in the traditional 3 prime to 5 prime direction, typically requires the use of solid supports that have the 3 prime most nucleotide attached to it? A: Yeah, that’s how it works.”).

As an example, and as Dr. Hrdlicka testified, if an oligonucleotide sequence has a 2'-deoxyA (i.e., DNA-A) at its 3'-end, SPOS typically initiates with a solid support that is linked to a 2'-deoxyA nucleoside, from which the oligonucleotide sequence will proceed via a stepwise addition of phosphoramidites in the 3' → 5' direction. Ex. 2001, ¶67; *also see* Ex. 1014, 1:22-26.

Similarly, according to Dr. Hrdlicka, if an oligonucleotide sequence has an rG (i.e., RNA-guanine) at its 3'-end, SPOS initiates with a support that is linked to an rG nucleoside, from which the oligonucleotide sequence will proceed via a stepwise addition of phosphoramidites in the 3' → 5' direction. Ex. 2001, ¶67; *also see* Ex. 1014, 1:29-33.

Universal supports allow practitioners to use one type of support for oligonucleotide syntheses and avoid stockpiling different types of solid supports. Ex. 2001, ¶67; *also see* Ex. 1014, 1:34-43, 4:31-36. Dr. Baran agreed with this. Ex. 2003, 155:10-18 (“Q: And it is your understanding that the teachings of this reference indicate that the use of the disclosed universal solid support allows a practitioner to avoid stockpiling different solid supports? A: By universal, the goal would be, you know, to allow people to focus on using one for all their needs versus having, you know, multiple different types, so yeah.”); Ex. 2001, ¶67.

As Dr. Hrdlicka explains and as Dr. Baran acknowledged, the claims of the ’696 Patent are directed towards oligonucleotide cleaving reagents. *See* Ex. 1014, 33:59-36:14; Ex. 2003, 157:5-7 (“Q: Looks like all these claims are directed to a cleaving reagent is that fair to say? A: Looks like it, mm-hmm, yeah.”); Ex. 2001, ¶68.

Cleaving reagents are useful for removing oligonucleotides from the solid support on which they are synthesized. Ex. 2001, ¶68; Ex. 1014, 2:65-3:1; Ex. 2003, 157:8-11 (“Q: Is it fair to say that cleaving reagents are useful for [re]moving oligonucleotides from the solid support on which they are synthesized? A: Yeah.”).

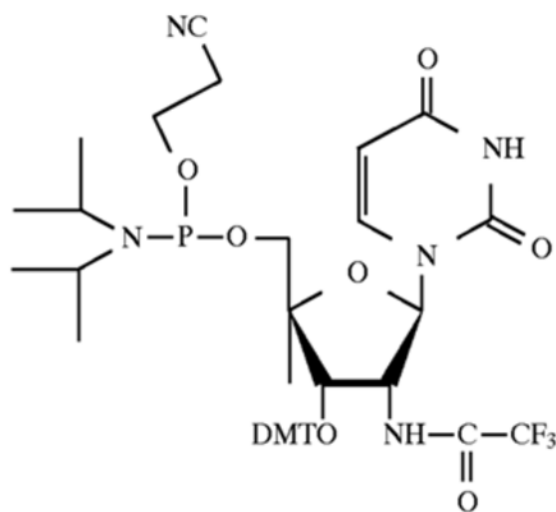
Accordingly, the claims of the ’696 Patent are not directed to oligonucleotide synthesis in either the 5' → 3' or 3' → 5' direction. Ex. 2001, ¶68; Ex. 2003, 158:6-10 (“Q: [T]he claims aren’t directed to 5 prime to 3 prime or 3 prime to 5 prime

synthesis, right? A: They could -- the claims don't have that written in them, correct.”). The claims are also not directed to any nucleosides, phosphoramidites, supports or any compounds that are linked to supports. Ex. 2001, ¶68; *also see* Ex. 2003, 158:11-21 (Dr. Baran admitting same).

VIII. THE CHALLENGED CLAIMS, AS AMENDED, ARE NOT UNPATENTABLE

A. Ground I is Moot Subject to Patent Owner's Motion to Amend

Petitioner has challenged one compound claimed in Claim 1's Markush group, based solely on anticipation under 35 U.S.C. § 102(b) by U.S. Patent No. 5,869,696 (Ex. 1014) (the “'696 Patent”). Example 3 of the '696 Patent discloses the following compound:



2'-Trifluoroacetamido-3'-O-(4,4'-dimethoxytrityl)-2'-deoxyuridine-5'-O-(N,N'-diisopropyl)-β-cyanoethyl-phosphoramidite (Ex. 1014, 13:23-67)

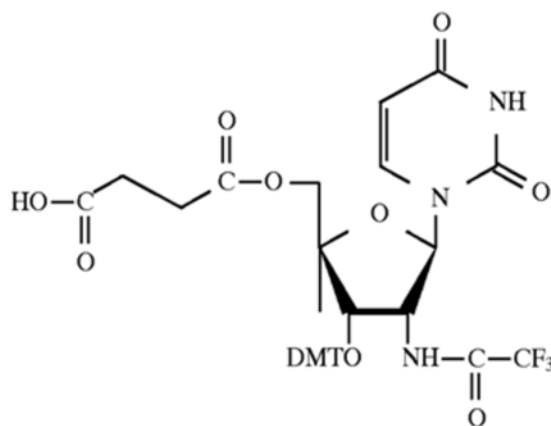
Ex. 2001, ¶71.

In response to this Ground, Patent Owner has contemporaneously filed its Motion to Amend under 37 C.F.R. § 42.121, which among other amendments, removes “W” as “N—H diradical” from Claim 1’s Markush group. Ex. 2001, ¶69.

Accordingly, subject to the Board’s ruling on Patent Owner’s Motion to Amend, and without prejudice to Patent Owner’s rights to the other patentably distinct compounds in Claim 1’s Markush group (e.g., where “W” in Formula 1 is an oxygen diradical or a fluorine radical), pursued through reissue or otherwise, Ground I is rendered moot. *See* Ex. 2001, Section IX.A.

B. Ground II is Moot Subject to Patent Owner’s Motion to Amend

Petitioner has challenged 2 distinct compounds claimed in Claim 2’s Markush group, based solely on anticipation under 35 U.S.C. § 102(b) by the ’696 Patent. Example 2 of the ’696 Patent discloses the following compound:



In response to this Ground, Patent Owner has contemporaneously filed a Motion to Amend, which among other amendments, removes “W” as “N—H diradical” from Claim 2’s Markush group. Ex. 2001, ¶78.

Accordingly, subject to the Board’s ruling on Patent Owner’s Motion to Amend, and without prejudice to Patent Owner’s rights to the other patentably distinct compounds in Claim 2’s Markush group (e.g., where “W” in Formula 2 is an oxygen diradical or a fluorine radical), pursued through reissue or otherwise, Ground II is rendered moot. *See* Ex. 2001, Section IX.B.

IX. CONCLUSION

For the reasons set forth above, and in its Motion to Amend, Patent Owner respectfully requests that the Board affirm the patentability of the challenged claims, as amended.

Dated: February 5, 2024

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

The undersigned certifies that this Patent Owner Response complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). This Patent Owner Response contains 5048 words as calculated by the “Word Count” feature of Microsoft® Word for PC Version 16.0.5426.1000, the word processing program used to create it. Pursuant to the Trial Practice Guide (August 2018 Update), the page and word count do not include the table of contents, table of authorities, mandatory notices under § 42.8, certificate of service, or appendix of exhibits or claim listings. The undersigned further certifies that this response complies with the typeface requirements of 37 C.F.R. § 42.6(a)(2)(ii) and typestyle requirements of 37 C.F.R. § 42.6(a)(2)(iii). This Patent Owner Response has been prepared in a proportionally spaced typeface using Microsoft Word 2016 word in Times New Roman 14-point font.

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CERTIFICATE OF SERVICE

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