

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

**REPLY DECLARATION OF PHIL S. BARAN, Ph.D. IN SUPPORT OF
PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 9,884,885**

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I, Phil S. Baran, declare as follows:

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

2. I have since given a deposition in this proceeding, and have reviewed additional materials, including Patent Owner's Response (POR), the Declaration of Dr. Hrdlicka (Ex. 2008) submitted in support of the POR, "Patent Owner's Motion to Amend Claims under 37 C.F.R. § 42.121," and supporting materials submitted with those documents, and the exhibits cited in this my second declaration. I also attended the December 20, 2023 deposition of Dr. Hrdlicka.

3. I submit this my second declaration in this proceeding to respond to the POR and Dr. Hrdlicka's declaration and deposition testimony. For brevity, I refer to Dr. Hrdlicka and Chemgenes herein collectively as "Chemgenes."

I. SUMMARY

4. As detailed and explained herein, it remains my opinion that all claims (1-5) of the '885 Patent are invalid. None of the information or arguments presented by Chemgenes undermines my opinion.

II. POSA

5. I disagree with Chemgenes' proposed POSA definition. (POR 18-19; Ex. 2008 ¶¶90-91.) Chemgenes' POSA definition is flawed because it excludes

highly skilled practitioners in the field of oligonucleotide chemistry, such as people with a strong background in synthetic organic chemistry. It does this by requiring the POSA to have work experience (or Ph.D. study focus) not just in “synthetic organic chemistry...including the development of oligonucleotide therapeutics, diagnostics, or building blocks” as per my proposed definition of a POSA, but more specifically in “the development and syntheses of nucleosides, nucleotides, and nucleic acids, including...the syntheses of oligonucleotides through [SPOS] pursuant to P(III) chemistry.” (Compare Ex. 1003 ¶24 with POR 18-19 and Ex. 2008 ¶¶90-91.)

6. As a result of my experience and expertise, I am capable of assessing the issues in this case from the perspective of a POSA under my POSA definition and under Chemgenes’. I have done so, and my opinions are the same regardless of which definition is applied. Dr. Hrdlicka has also stated that his opinions are the same under either definition. (Ex. 2008 ¶91.)

7. The POR asserts that I “do[] not appear to have a deep background in the P(III) chemistry at bar.” (POR 17.) I note that Dr. Hrdlicka did not state this; it appears to be attorney argument. It is not correct. I have an extensive background in P(III) chemistry, among other synthetic organic chemistry concepts, modalities, reactions, reagents, and mechanisms exploited by practitioners in making and using nucleosides, nucleotides, nucleic acids, and oligonucleotides via

P(III) chemistries, among others. My extensive background and expertise in these areas is amply demonstrated in my first declaration, reflected in my c.v., illustrated in my publications, and employed in my teaching, consulting, and serial entrepreneurship in the field of oligonucleotide synthesis. (Ex. 1003 ¶¶2-11 and Appx. A.) I elaborated on some of this during my deposition. (Ex. 2009 36:13-40:10; 41:6-12; 42:5-59:5; 62:11-65:5; 65:22-90:13.)

8. Chemgenes also asserts that “only 14 of [my more than] 250 papers...relate to oligonucleotide synthesis and the earliest of those papers was just five years ago.” (POR 17; Ex. 2008 ¶86.) Chemgenes then asserts that the most prominent of those 14 papers relates to P(V) chemistry, not P(III) chemistry. (POR 17; Ex. 2008 ¶86.) In this way, Chemgenes appears to suggest that I am somehow a late entrant to the field and/or not deeply familiar with the technology of the '885 Patent. Such suggestions are false. As I explained in my opening declaration, I am deeply familiar with this field. (Ex. 1003 ¶¶2-11, 23.) As I also explained in my deposition, I was exposed to nucleoside chemistry as an undergraduate in 1996 (Ex. 2009 at 36:13-20), and in the 2003-2009 period, I taught classes and consulted with companies in the area of nucleotide synthesis. (Ex. 2009 at 41:6-12.) Moreover, as I explained in my deposition, to characterize me as a late entrant into the field is to take a myopic view of my career only through the lens of my publications. (Ex. 2009 at 75:5-21.) Finally, as I also

explained in my deposition, my groundbreaking work on P(V) chemistry for oligonucleotide chemistry built on, and required a deep understanding of, P(III) chemistry. (Ex. 2009 at 45:4-11; 107:16-109:8.) I have received several prestigious awards based on my oligonucleotide work, including the 2022 Royal Society of Chemistry (RSC) Horizon Prize and the 2023 Edison patent award, which I received after submitting my first declaration. It is the highest prize given for a patent. (Ex. 2009 at 69:25-70:7.) Attached hereto as Exhibit 1034 is an updated version of my c.v. reflecting that development.

III. RESPONSE REGARDING THE STATE OF THE ART

9. Chemgenes asserts that I have not described “how complex and inherently unpredictable” the science of SPOS was in 2009, and that I have “greatly oversimplifie[d] the complexity of the synthetic chemistry involved and the challenges that a POSA would have faced” in 2009. (POR 6-8; Ex. 2008 ¶¶65-70.) While I agree that SPOS was complex and involved some degree of unpredictability, a POSA in 2009 would have been well-equipped to manage that, and I disagree that I have understated or downplayed any aspect of it in my analysis.

10. First, as explained in my opening declaration and above, a POSA was highly educated, trained, and experienced, and the level of skill in the art was

therefore very high. (Ex. 1003 ¶24.) This is true under both my and Chemgenes' definition of a POSA.

11. Second, as also explained in my opening declaration, the state of the art was highly advanced by 2009. (Ex. 1003 ¶¶48-63.) Chemgenes cites a 1991 review by Beaucage cataloging examples of what Chemgenes refers to as “adversity in developing SPOS,” but as Chemgenes, acknowledges, many of those “hurdles” had been overcome by 2009. (Ex. 2008 ¶¶66-67.) Indeed, the Beaucage paper describes how each of those issues were addressed, and does not refer to ongoing “adversity.” Rather, it conveys that as even as of 1991, the field was replete with *successful* efforts, and was heavily studied and highly advanced.

12. Notably, as early as its 1999 catalogue, Chemgenes stated that “[c]hemical synthesis of RNA has been perfected to the extent that long sequences...and multi-milligram quantities can be produced efficiently [citing papers from 1991 and 1992].” (Ex. 2029 at 51.)

13. Notably, Chemgenes' depiction of the field of nucleic acid synthesis as of 2009 cannot be squared with the description of the field as early as 2001 by Pitsch, which states:

[M]any research groups have *successfully* contributed to the development of a *reliable* chemical synthesis of nucleic acids. As a consequence, the synthesis of DNA oligonucleotides is probably *the most evolved chemical process known so far and has almost reached perfection in terms of efficiency and automation.*

(Ex. 1018 at 3773 (emphases added).) Pitsch then explained that phosphoramidite chemistry methods were being used almost exclusively and that those “methods can, in principle, also be applied to the synthesis of the structurally very similar RNA oligonucleotides.” (Ex. 1018 at 3774.) And as detailed below, Pitsch then reported a successful synthesis of acetyl-protected phosphoramidite and its use in highly successful RNA oligonucleotide synthesis. (Ex. 1018, *passim*.)

IV. GROUND I

14. In my opening declaration, I explained why Claim 1 of the '885 Patent is anticipated by the '039 Patent. (Ex. 1003 ¶¶87-107.) It appears that Chemgenes does not dispute this. (POR20-21; Ex. 2008 ¶¶92-98.)

15. I understand that Chemgenes has instead moved to replace Claim 1 with Substitute Claim 6. I have prepared a separate declaration addressing the patentability of Substitute Claim 6.

V. GROUND II

A. The “lead compound” framework is not consistent with how a POSA would have approached the selection, design, and synthesis of building blocks for SPOS of oligonucleotides.

16. In my opinion, the “lead compound” framework for assessing obviousness, which has been explained to me by attorneys, is primarily relevant to the field of drug discovery in the pharmaceutical arena, where it pertains to the identification and patenting of novel chemical compounds with therapeutic

potential. This concept involves the assessment of structure, activity, and utility of potential lead compounds in the development of new drugs.

17. In contrast, in the field of making *reagents* used in the production of oligonucleotides as of 2009, the “lead compound” approach is not particularly informative or relevant. As I explained in my opening declaration, oligonucleotide reagents, and more specifically the monomeric “building blocks,” such as phosphoramidites, are not themselves therapeutic compounds. (Ex. 1003 ¶¶40, 48.) Rather, they are reagents used to make oligonucleotides. As such, their development, improvement, and synthesis focuses on the optimization of chemical processes and purity to ensure the reliable and consistent production of high-quality reagents, rather than the identification of lead compounds for drug development. Indeed, Dr. Hrdlicka testified that he is not aware of describing his development approach in any of his writings as involving the selection of a lead compound. (Ex. 1035 at 192:11-193:16.)

18. Further differentiating the field of oligonucleotide reagent development and drug development, even the oligonucleotides made using those reagents often were not used as therapeutics in 2009. Rather, as explained in my opening declaration, oligonucleotides had diverse applications, many being used in DNA sequencing, genetic research, and molecular diagnostics. (Ex. 1003 ¶¶49, 56.) The properties of the oligonucleotide are often driven by the targeted

sequence and not necessarily by the properties of the individual building blocks used to synthesize them. Accordingly, there are myriad motivations at play for a POSA in developing and improving upon oligonucleotide building blocks. Which set of motivations might be at play in a given context will depend on the intended use case and could shift depending on the stage of development and scale of production. For instance, relatively small amounts of oligonucleotide are needed for biological research, as compared to amounts needed for clinical trials.

(Ex. 1009 at 11.)

19. As another example, it can be helpful to introduce various chemical modifications to the nucleoside building blocks to enhance the pharmacokinetic and pharmacodynamic properties of the oligonucleotide. Common modifications include 2'-O-methyl, 2'-O-methoxyethyl, 2'-fluoro, or phosphorothioate groups to improve stability, nuclease resistance, and cellular uptake. (*See, e.g.*, Ex. 1017 at 4:5-13 (noting that nucleoside can be “modified to improve at least one of its pharmacokinetic properties, its binding characteristics to target RNA or to modify its charge.”), 11:25-35 (noting that nucleosides can be functionalized “to increase the nuclease resistance” of the oligoribonucleotide, but that “for non-cellular uses, such as use of oligomeric compounds...as research reagents and as diagnostic agents, such nuclease stability may not be necessary.”), 11:52-12:31 noting that 2' substituent group modifications, specifically 2'-fluoro substitutions, are preferred

and “particularly useful for increasing the binding affinity...”.) Dr. Hrdlicka seems to agree that the selection of substituents on nucleoside building blocks “depends on the planned applications of the molecules that one is synthesizing” and said there was “no way” to conclude that one substituent group would be better than all the others because “[t]hat completely depends on context” and “different substituents could work.” (Ex. 1035 at 91:16-93:6.)

20. As another example, depending on the application, desired base pairing characteristics of the oligonucleotide may be very different. For some applications, such as diagnostics, it can be important to have a high degree of binding specificity and strength, whereas when looking to modulate gene expression, such as with antisense oligonucleotides, some degree of mismatch may be desirable.

21. Notably, the selection of protecting groups for the exocyclic amine of a nucleobase was not a one-size-fits-all or either/or exercise, and there was broad and multifaceted motivations in 2009 to use various protecting groups depending on the use case. (Ex. 2017 at 363 (noting that their motivation was to “offer an assortment of suitable N-acyl groups for nucleoside bases” to “help in planning oligonucleotide synthesis in more meaningful terms.”); *see also* Exhibit 2016 at 2.1.1. (noting that “[t]he choice of nucleobase protecting groups and deprotection protocols ...is dictated by many considerations.”).) The Chemgenes catalogues

from 1999 (Ex. 2029) and 2009 (Ex. 2030) both illustrate the many varied structures, activities, and uses of nucleosides and phosphoramidites and the many varied uses to which they were put at the time, including as basic research tools. (See, e.g., Ex. 2029 at 26-32; Ex. 2030 at 25-42 (listing variety of phosphoramidites and supports).)

B. There was ample reason to select compound x of the '031 Patent.

22. Regardless of whether a POSA would approach the design and synthesis of phosphoramidites in the manner suggested by Chemgenes (they would not), a POSA would have had nevertheless ample reason to select Compound x of the '031 Patent for modification.

23. Chemgenes asserts that I have made “no showing as to why a POSA would have selected Compound x – out of the scores of nucleosides identified in the '031 Patent and thousands of other nucleosides available in the prior art – as the most promising to modify in order to improve upon its activity.” (POR 22-23; Ex. 2008 ¶101.) Chemgenes’ assertions are both misguided and incorrect.

24. First, for the reasons explained above about how a POSA would have approached the selection and improvement of building blocks for SPOS, I disagree with the premise embedded in Chemgenes’ assertions that a POSA would undertake to select a *single* nucleoside, or to select “*the* most promising” nucleoside. (POR 21-24; Ex. 2008 ¶¶99-106.) And as explained to me, even the

“lead compound” framework for evaluating obviousness does not require selecting a *single* lead compound.

25. Second, contrary to Chemgenes’ assertions, I *did* explain why a POSA would have selected Compound x, and how that is reflected in the ’031 Patent. For example, I explained that a POSA would immediately have recognized the utility of Compound x, and that the ’031 Patent specifically contemplates its use in SPOS. (Ex. 1003 ¶¶111-116.) In my opinion, as explained above, given the nature of nucleosides as building blocks for a wide variety of compounds that themselves have a wide variety of uses, this clear utility of Compound x alone would have been reason sufficient for a POSA to select Compound x for use and potential improvement.

26. As another example, I explained that the ’031 Patent identified Example 4 as showing how to make nucleoside amidites that were used to make oligoribonucleotides and oligoribonucleosides of the invention, and that Compound x was the end product of Example 4. (Ex. 1003 ¶111.) As a matter of simple logic, this necessarily would have suggested to a POSA to select Compound x.

27. I also noted that the ’031 Patent discloses several nucleoside amidites that “had useful properties,” “clearly describes how monomeric phosphoramidites” such as Compound x “can be prepared,” “and the ways these compounds can be

used to synthesize oligonucleotides with therapeutic potential.” (Ex. 1003 ¶111.) Indeed, the ’031 Patent repeatedly identifies 2’-fluoro substituted nucleosides as preferred and being used to make preferred oligomers with enhanced binding affinity. (Ex. 1017 at 4:5-13, 4:41-48, 4:54-58, 11:52-60, 12:3-31 (“A further particularly useful 2’-substituent group for increasing the binding affinity is the 2’-fluoro group.”).)

28. Notably, Compound x is the only 2’-fluoro guanosine phosphoramidite disclosed in the ’031 Patent. Dr. Hrdlicka confirmed this in his deposition. (Ex. 1035 at 90:9-22.)

29. Chemgenes asserts that the ’031 Patent does not provide any reason to select Compound x, because it does not provide any “data showing Compound x being used as a reagent to incorporate 2’-fluoro-2’deoxyguanosine monomers into any oligonucleotides.” (Ex. 2008 ¶102.) Chemgenes is not correct. As I explained at length in my deposition, the ’031 Patent provides five examples expressly contemplating making oligoribonucleotides using 2’-fluoro monomers in the form of 2’-fluoro phosphoramidites. (Ex. 2009 at 116:10-134:6.) Specifically, Examples 12.iii, 13.iii., 13.v, 14.i, and 16.vii all refer to preparing compounds having “2’-fluoro nucleosides” in their “wing” segments, and conducting those preparations “in the manner of Example 8.” (*Id.*; Ex. 1017 at 43:63-44:4, 44:26-32, 44:41-49, 44:59-45:5.)

30. As I explained in my deposition, and contrary to Dr. Hrdlicka's deposition testimony that a POSA would have been "confused" by the cross-reference to Example 8 in Examples 12.iii, 13.iii., 13.v, 14.i, and 16.vii (Ex. 1035 at 67:4-75:19), POSA would have understood that Example 8 presents a general synthetic process for oligonucleotide synthesis, and a POSA would immediately understand how to deploy the appropriate 2'-fluoro phosphoramidite reagents in that process to make the oligoribonucleotides of Examples 12.iii, 13.iii., 13.v, 14.i, and 16.vii. (Ex. 2009 at 116:10-134:6.)

31. As I also explained in my deposition, to a POSA, four of those five examples (12.iii, 13.iii, 13.v, and 14.i) *necessarily* describe using Compound x to make oligonucleotides. (Ex. 2009 at 117:22-118:6, 128:5-11.) This would have been clear to a POSA from the face of the '031 Patent. A POSA would also understand that Compound x would necessarily be used to introduce a guanine monomer when making the oligoribonucleotides of those examples, because Example 8 (a) describes using phosphoramidites to introduce 2'-fluoro monomers in the wing segments of the oligonucleotides, (b) describes introducing guanine monomers, and (c) Compound x is the only 2'-fluoro guanosine phosphoramidite disclosed in the '031 Patent.

32. Chemgenes asserts that because the figures of the '031 Patent contain "data" on oligoribonucleotides containing 2'-OH and 2'-OME monomers, but not

data on any oligoribonucleotides containing 2'-fluoro monomers, a POSA would have selected the former and not the latter as "a lead compound." (POR 23; Ex. 2008 ¶¶102, 105.) I disagree. First, Chemgenes seems to be confusing the exercise of selecting *oligoribonucleotides* (not claimed in Claim 2 of the '885 Patent) with the exercise of selecting of phosphoramidite *reagents* used to synthesize oligonucleotides. Those are different exercises. Second, Chemgenes' assertion presents a false choice. A POSA would understand that that the Figures present *illustrative* data, and a POSA would not rely on the unexplained choice of which illustrative data to present in the figures as a reason to discount or disregard the advantages of using 2'-fluoro monomers, which are repeatedly emphasized in the '031 Patent, as discussed above.

33. Chemgenes asserts that a POSA would not select Compound x as a reagent because the '031 Patent does not disclose deprotection rates for Compound x. (POR 23; Ex. 2008 ¶104.) I agree that the '031 Patent does not disclose a deprotection *rate* for Compound x, but as I explained in my opening declaration, it does indicate that they used a 24-hour deprotection reaction period (Ex. 1003 ¶119), and I disagree that the absence of deprotection rate data would dissuade a POSA from selecting Compound x for use and for modification to improve deprotection speeds. First, as explained in my opening declaration, in the '031 Patent itself, and above, a POSA would have had ample reason to select

Compound x. Second, in my opinion, a POSA would not have regarded the lack of deprotection rate information for Compound x *per se* as a reason to disregard Compound x. Third, as explained in my opening declaration and deposition, SPOS is run in multiple cycles, each of which requires a deprotection step (Ex. 1003 ¶¶58-60, 121) and a POSA is motivated to shorten reaction duration. (Ex. 1003 ¶¶58-60, 63, 121 (noting in ¶63 that improvements in SPOS as having been “centered around” reducing, among other things, the “time associated with” preparation) (citing Ex. 1007 at 2293 as noting the need for “faster preparation”); *see also* Ex. 1007 at 2255 (“The rapid deprotection of the nucleobases under basic conditions is particularly important in oligoribonucleotide synthesis to minimize chain scission...”).) Accordingly, a POSA looking to develop a phosphoramidite with improved properties in early 2009 would naturally have been prompted by the ’031 Patent’s use of a 24-hour deprotection period to consider whether and how that period could be shortened.

34. Accordingly, I disagree with Chemgenes’ assertion that I employed any hindsight in determining that a POSA would have selected Compound x for use and further improvement. (POR 24, Ex. 2008 ¶106.)

35. Further, I note that Chemgenes itself in 2009 offered 2’-fluoro phosphoramidites for sale in its own catalogue, characterizing them as being “for

modified RNA synthesis.” (Ex. 2030 at 61.) That Chemgenes catalogue expressly acknowledged the well-known utility of such phosphoramidites, stating as follows:

A number of 2'-deoxy-2'-fluoro nucleosides have been found to display significant biological activity as nucleosides and as triphosphates, and are used as versatile probes for DNA and RNA polymerases [citing 1999 book chapter and 1990 article]. The incorporation of the deoxyfluoronucleosides into oligonucleotides imparts many interesting biological properties to fluorinated oligomers [citing a 1997 article].

(Ex. 2030 at 61.) This further illustrates that a POSA would have been interested in 2'-fluoro phosphoramidites in 2009, and thus would have good reason to select Compound x for use and/or improvement.

36. Finally, Dr. Hrdlicka agreed at his deposition that likely “a POSA would have known that 2 prime fluoros can be incorporated into oligonucleotides and increase affinity towards...certain target strands.” (Ex. 1035 at 76:20-77:11.)

C. There was ample motivation to modify Compound x by replacing the isobutyryl protecting group with an acetyl protecting group.

37. Chemgenes asserts that a POSA would not have been motivated by Pitsch or Fan to use acetyl as a protecting group for guanine on Compound x, and offers a series of purported reasons for this assertion. (POR 24-40; Ex. 2008 ¶¶107-141.) In my opinion, none of those reasons have any merit.

1. Purported instability of acetyl protecting groups.

38. Chemgenes asserts that the prior art taught away from using the acetyl protecting group, because it was known that acetyl protecting groups were unstable

under basic conditions. (POR 24-27; Ex. 2008 ¶¶107-111.) I disagree.

Chemgenes' position completely ignores the teachings of Pitsch, which teaches a robust and highly successful synthesis using the acetyl protecting group under basic conditions. Indeed, Pitsch affirmatively touts the use of the acetyl ("Ac") group under basic conditions and reports an extensive workup yielding data that according to Pitsch, "demonstrated that the Ac group, in combination with MeNH₂, is indeed *suited for a labile universal nucleobase protection*." (Ex. 1018 at 3778.)

Pitsch reported unvaryingly successful syntheses, noting (1) the 2'-protecting group they used (2'-O-tom) "was *completely stable* for a period of at least 48 h"; (2) their "first RNA synthesis with 2'-O-tom-protected phosphoramidites *showed very good coupling yields and indicated a very clean and reliable deprotection process*"; (3) that they "optimized all feasible reaction and deprotection parameters," and under their "robust deprotection conditions" which they optimized according to "scale and length" of oligonucleotide chain," they "*never observed indications of incomplete deprotection and/or concomitant strand scission*." (Ex. 1018 at 3778-3782 (emphases added).) Pitsch further reported that in all their analyses, the RNA sequences they prepared had "the correct sequence composition," and "*the complete absence of any unnatural connections*" and "*the full integrity of the nucleosides during the phosphoramidite synthesis, the sequence assembly, and the two deprotection reactions*." (Ex. 1018 at 3783 (emphases

added).) Thus, Pitsch alone refutes Chemgenes' suggestion that a POSA would avoid using an acetyl protecting group.

39. Chemgenes relies on a 1972 paper by Khorana (Ex. 2011), asserting that it taught away from (or would dissuade a POSA from) using an N-acetyl protecting group on a guanine phosphoramidite. (POR 24-25; Ex. 2008 ¶¶107-08.) In my opinion, this reliance is completely misplaced and misleading. In my opinion, as reflected in my opening declaration, Khorana's decision to pursue protecting groups other than acetyl were a product of the phosphodiester coupling chemistry being employed at the time in the early 1970's, well before the advent of phosphoramidite synthesis, and well before Pitsch. (Ex. 1003 ¶¶51-55.) The prolonged and harsh deprotection conditions used in phosphodiester synthesis were not used in SPOS using phosphoramidites. As explained below, a POSA in 2009 would have known this, and thus would not have been dissuaded by Khorana from using acetyl to protect the exocyclic amine of a guanosine phosphoramidite.

40. The irrelevance of Khorana's choice to explore protecting groups other than acetyl is clearly explained in later publications cited by Chemgenes and put into its proper historical and technological context. A 1987 paper by Schulhof begins by explaining that Khorana's choice of protecting groups for "the exocyclic amino functions of guanine," including isobutyryl, "dates back" to the phosphodiester methodology, and then notes that "[w]ith respect to the progress

achieved in the field of phosphotriester and phosphoramidite synthesis,” the protecting groups that Khorana used “present now a few shortcomings” such as requiring “a long and drastic deprotection step” that is “time-consuming,” and “forbids the synthesis of modified oligonucleotides containing alkali-sensitive bases.” (Ex. 2013 at 397-98.) Likewise, a 2000 publication explains that the choice of protecting group depends on the type of coupling chemistry employed, and that the “harsh reagents and conditions” used in phosphodiester syntheses require “sturdy” protecting groups like isobutyryl, and while noting that they have “remained popular” in SPOS using phosphoramidites, they also note that protecting groups like isobutyryl have downsides in that context. (Ex. 2016 at 9-10.)

41. A POSA would also have understood that the conditions used in the early 1970’s for phosphodiester synthesis were problematic for RNA oligonucleotide synthesis, which, unlike DNA oligonucleotide synthesis being explored by Khorana in 1972, required protection of the 2’-O position and milder conditions. (Ex. 1003 ¶¶43-44, 50; Ex. 2018 at 13 (explaining that for RNA, “there is a need for milder deprotection conditions” and that “[u]se of labile protecting groups not only facilitates DNA/RNA synthesis but also allows incorporation of modified and base sensitive nucleosides.”).)

42. This is consistent with Khorana's stated reason for exploring a protecting group other than acetyl. Khorana explained that they were driven by the "extended nature of the present task...". (Ex. 2011 at 221.) This included running reactions for multiple days, not just minutes or hours, as contemplated in Pitsch and the '031 Patent. (See, e.g., Ex. 2011 at 241 (noting that the N-benzoyl protected guanosine was shaken in pyridine (a basic environment) "for 110 hr").)

43. Chemgenes asserts that after Khorana, "a range of other base protecting groups were used...but acetyl was not one of those." (POR at 25-26; Ex. 2008 ¶109.) This is false. At a minimum, it ignores that Pitsch not only used acetyl, but heavily touted it in a leading journal. It also ignores Chemgenes' own patent No. 5,525,719, issued in 1996, identifying acetyl as an option for protecting guanosine and claiming acetyl-protected guanosine phosphoramidites. (Ex. 1043 at 4:35-37 (noting that "N²-Protection of guanosine is meant to include isobutyryl, acetyl, substituted acetyls, phenoxyacetyl, and related compounds") and claim 2 (claiming "N²-protected-2'-O-methyl-5'-dimethoxytrityl guanosine-3'-ethoxy N,N-dialkyl phosphoramidite") (emphasis added).) Chemgenes cites 11 publications to suggest that acetyl was not used. (POR at 25-27; Ex. 2008 ¶¶109-110.) I have reviewed this literature, and in my opinion, none of it, individually or collectively, would have dissuaded a POSA from using acetyl. None of it states or suggests that acetyl should not be used. None of it states or suggests that acetyl is

never used. None of it criticizes acetyl. Most of it predates the advent of phosphoramidite synthesis, the publication of Pitsch in 2001, or both. (Exs. 2011 (1972), Ex. 2020 (1972), Ex. 2017 (1981), Ex. 2021 (1986), Ex. 2013 (1987), Ex. 1007 (1991), Ex. 2018 (1993), Ex. 2016 (2001), Ex. 2019 (2004), and Ex. 2023 (2008).) Some of it actually explains potential shortcomings of isobutyryl protecting groups, thereby illustrating why a POSA would be interested in more base-labile protecting groups. (Ex. 2013 at 397-398 (isobutyryl requires “long and drastic deprotection step” that is “time consuming” and “forbids the synthesis of modified oligonucleotides containing alkali-sensitive bases.”); Ex. 2018 at 13 (explaining that for RNA, “there is a need for milder deprotection conditions” and that “[u]se of labile protecting groups not only facilitates DNA/RNA synthesis but also allows incorporation of modified and base sensitive nucleosides.”).)

44. Chemgenes’ assertions also ignore Compound 5 of the ’991 Patent, which employed acetyl PG. (Ex. 1020 at Fig. 16.)

2. Purported insolubility issue with using acetyl

45. Chemgenes asserts that a POSA would have been dissuaded from using an acetyl protecting group because it would reduce the solubility of the resulting guanosine in organic solvents. (POR 27-29; Ex. 2008 ¶¶112-116.) I disagree, for several reasons.

46. First, Chemgenes' assertion is squarely refuted by Pitsch, which used the acetyl protecting group to synthesize RNA oligonucleotides. As noted above, Pitsch conducted a thorough workup of various reaction conditions and reported a resounding success, and did not report any solubility problems. Chemgenes does not acknowledge or address this in making its assertions regarding solubility.

47. Second, even if solubility were a challenge when using an acetyl protecting group, this would not have dissuaded a POSA, who would have understood that in the relevant context of *solid phase* synthesis (SPOS), a high degree of solubility is not needed for the monomers and reagents as stock solutions are made and that solubility is a question of degree, not a binary result. Moreover, a POSA would also have understood how to make routine adjustments to the synthetic procedure to account for solubility issues, such as using admixtures of solvents for poorly soluble reagents and monomers. (See, e.g., Ex. 1036 at 3.10.8; Ex. 1037 at 701.)

48. Third, neither of the two publications cited by Chemgenes suggest that using an acetyl protecting group instead of an isobutyryl protecting group would cause solubility problems (POR 28-29; Ex. 2008 ¶¶113, 115 (citing Exs. 2018 and 2012)), and neither would have deterred a POSA from using an acetyl protecting group to protect a guanosine phosphoramidite in the relevant context of oligonucleotide synthesis incorporating 2'-fluoro-2'-deoxy monomers and/or RNA

monomers. Sinha (1993) alludes only to problems associated with DNA synthesis, not RNA synthesis, because it refers only to “deoxyguanosine-phosphoramidites.” (Ex. 2018 at 14.) Thus, Sinha (1993) does not suggest any problem using base labile N-protecting groups in oligonucleotide synthesis involving 2’-fluoro-substituted monomers (like Compound x) or RNA synthesis (as in Pitsch). Further, the statement in Sinha (1993) is vague and generalized. For example, Sinha (1993) does not say (a) what the unspecified problems are, (b) which deoxyguanosine-phosphoramidites experience those problems, (c) which labile N-protecting groups it is alluding to (and thus does not mention acetyl), (d) under what circumstances the unspecified problems arise, or (e) that the best or only way to address the unspecified problems is to not use those unspecified labile N-protecting groups. (Ex. 2018 at 14.)

49. A POSA in 2009 would not have considered Schaller relevant to the question of using acetyl to protect a guanosine phosphoramidite. First, Schaller was a paper from 1963, long before the advent of the phosphoramidite approach to oligonucleotide synthesis. Second, as noted above, Schaller did not address solid phase synthesis (SPOS) at all. Third, even if a POSA would consider Schaller’s statement relevant to the question of using acetyl to protect guanosine phosphoramidites (they would not), in the very next sentence of the Schaller footnote quoted by Chemgenes, Schaller reports that they had already since

successfully acetylated the guanine ring in deoxyguanosine by using a different solvent. (Ex. 2012 at 3822, footnote 21.) Thus, even to the extent a POSA would consider Schaller to be relevant (they would not) and consider Schaller specific enough to cause a POSA to question the use of acetyl as a protecting group (they would not), they would immediately see that there was a workaround.

50. Further illustrating that Chemgenes' purported solubility issues with the acetyl protecting group would not have dissuaded a POSA from using acetylated guanosine to synthesis RNA, Donga (2007) used acetylated guanosine phosphoramidite to build an RNA oligonucleotide using *solution-phase synthesis*. (See Ex. 1029 at 276, Scheme 3, bottom right.)

3. The differences between Compound x and aspects of Pitsch and Fan

51. Chemgenes points to certain differences between Compound x and certain subject matter of Pitsch and Fan, apparently to support the proposition that a POSA would not have applied the teachings of those references in looking to modify a 2'-fluoro, 2'-deoxyguanosine phosphoramidite such as Compound x. Specifically, Chemgenes asserts that the teachings of Pitsch and Fan were "not relevant" to "2'-fluoro-2'-deoxyribonucleotide phosphoramidites for modified oligonucleotide synthesis" because "the nucleosides and phosphoramidites disclosed in Pitsch and Fan would have been used for unmodified RNAs...not

modified oligonucleotides produced using Compound x having 2'-fluoro-2'-deoxynucleotides.” (POR 33-36; Ex. 2008 ¶¶123-129.) I disagree.

52. Chemgenes is restricting and compartmentalizing the teachings of Pitsch and Fan in manner that is (a) inconsistent with Pitsch itself and (b) is not how a POSA would engage with the teachings of Pitsch and Fan. Pitsch does not state or suggest that the acetyl protecting group could be used *only* for synthesizing RNA, or that it would not be useful in synthesizing modified oligonucleotides or chimeric oligonucleotides containing both RNA and DNA monomers (whether modified or not). To the contrary, Pitsch itself presents its work, and the use of the acetyl protecting group in particular, in broad terms and expressly integrates its discussion of DNA oligonucleotide synthesis and RNA oligonucleotide synthesis. For example, Pitsch begins by noting that they used “DNA coupling conditions,” to make their RNA oligonucleotides. (Ex. 1018 at 3773.) As another example, Pitsch broadly discusses “[t]he chemical synthesis of nucleic acids” and “the synthesis of DNA oligonucleotides,” and then explains that DNA synthetic methodology “can, in principle, also be applied to the synthesis of the structurally very similar RNA oligonucleotides.” (Ex. 1018 at 3773-74.)

53. Importantly, Pitsch explains that the acetyl protecting group “is indeed suited for a labile *universal* nucleobase protection.” (Ex. 1018 at 3778 (emphasis added).) Pitsch also presents data showing that a DNA oligonucleotide and their

RNA oligonucleotide underwent a “similar reaction course” and that DNA oligonucleotide and their RNA phosphoramidites achieved “comparable coupling efficiencies.” (Ex. 1018 at 3779-80.) Pitsch concludes by noting that they “adapted [their] RNA chemistry to the established DNA chemistry.” (Ex. 1018 at 3786.)

54. Thus, a POSA would naturally look to apply the teachings of Pitsch regarding the desirability of acetyl protecting groups *irrespective* of what resides at the 2' position of the nucleoside under consideration (in this case, Compound x). Contrary to Chemgenes' suggestion, nothing in Pitch states or suggests that the identity of the 2' substituent of the sugar has anything to do with, or would in any way affect, the desirable rapid deprotection speeds achievable with an acetyl protecting group. In fact, as I explained in my deposition, a POSA would have considered substitutions on the periphery of the sugar separately from considering what to use as the N-protecting group on the nucleobase. (Ex. 2009 at 153:23-154:5 (“[I]t’s really important [to] understand the logic of how oligonucleotides are made and how people think about the protecting group issue. They don’t equate the protecting group on the nitrogen relative to what is on the periphery of the sugar. That is dealt as a secondary consideration or separate from the N-protecting group.”).)

55. Indeed, a POSA would have known as a matter of common sense in 2009 that the exocyclic amine of the nucleobase and the 2' position on the sugar ring are, chemically speaking, remote from one another and not expected to affect the reactivities of one another. This is illustrated, for example, by Zhu (2003), et al., which shows that under substantially the same reaction conditions, there were little or no differences in silylation time and benzylation time of various nucleosides, regardless of which group was attached to the 2' position of the sugar ring. (Ex. 1038 at Table 1.)

56. Also contrary to Chemgenes' suggestion that a POSA would not apply teachings of Pitsch and Fan to Compound x, it was well known that 2'-fluoro-2'-deoxy nucleosides were "RNA-like" and had been incorporated into RNA to create "antisense" oligonucleotides with better target affinity. Indeed, the Kawasaki paper (Ex. 2025) cited by Chemgenes illustrates this close relationship, incorporation advantage, and significant utility of resulting antisense oligonucleotides. Kawasaki noted that "the application of oligonucleotides as antisense inhibitors of gene expression has generated much interest" because of its potential "far-reaching" impact on "fundamental research, chemotherapy, and agriculture." (Ex. 2025 at 831.) It explained that (a) such oligonucleotides may be useful antisense molecules, in part because "2'-deoxy-2'-fluoro homopolymers show characteristics more closely related to RNA than DNA;" and (b) such

nucleosides had been chemically incorporated into RNA by other researchers. (Ex. 2025 at 831-32.) Kawasaki summarized their findings by noting that their “modified 2’-deoxy-2’-fluoro phosphorothioate oligonucleotides...afforded antisense molecules with (1) high binding affinity and selectivity for the RNA target and (2) stability toward nucleases.” (Ex. 2025 at 836-37.) They concluded by stating that they were further investigating “[a]pplications of these types of antisense oligonucleotides against certain biological targets.” (Ex. 2025 at 837.) Kawasaki also referenced their own prior work incorporating 2’-deoxy-2’-fluoro nucleosides into chimeric oligonucleotides in which some regions had the 2’-deoxy-2’-fluoro nucleotides and some regions did not, and found that such “chimeric oligonucleotides are capable of activating mammalian RNase H in vitro upon hybridization with RNA and display potent antisense activity against RNA targets in cells.” (Ex. 2025 at 837.) Given the close relationship between oligonucleotides containing 2’-fluoro-2’deoxy nucleotides on the one hand, and RNA on the other hand, a POSA would naturally have looked to apply the acetylation protection teachings of Pitsch and Fan when looking to improve upon a 2’-fluoro-2’deoxyguanosine such as Compound x.

4. The purported degradation issue

57. Chemgenes asserts that a POSA would “not have been motivated” by Pitsch and Fan in regards to Compound x, because it was known that

oligonucleotides containing 2'-fluoro-2'-deoxyribonucleotides had a “persistent problem” of degradation and Pitsch and Fan did not teach how to resolve that problem. (POR 32-33; Ex. 2008 ¶121.) I disagree.

58. First, degradation of 2'-fluoro-2'-deoxyribonucleotides was not a “persistent problem,” as evidenced by the same two references Chemgenes relies upon. Sinha (2013) (Ex. 2024) does discuss the *potential* degradation of 2'-fluoro-2'-deoxyribonucleotides, but does not say it is a “problem,” let alone a “persistent problem.” Instead, Sinha (2013) notes merely that this potential “must be taken into consideration.” (Ex. 2024 at 83.)¹ Sinha provides “postulated” and “proposed” mechanisms for how degradation could occur *if* “methylamine or methylamine/ammonium hydroxide-based” conditions are used for cleavage and deprotection (“C&D”), but in the very same sentence, Sinha indicates that there is a simple workaround, stating that degradation “can often be minimized by using ethanolic ammonia solution (7M).” (Ex. 2024 at 83-86.) Thus, Sinha (2013) itself provides a proposed method of minimizing the supposed “persistent problem.” Consistently, Sinha (2013) does not cite any report of degradation (of any

¹ Notably, Sinha cites Kawasaki and touts the benefits of incorporating 2'-fluoro-2'-deoxy nucleosides into RNA. (Ex. 2024 at 83.)

oligonucleotide containing 2'-fluoro-2'-deoxyribonucleotides) actually having been a problem for anyone. (Ex. 2024 at 83-86.)²

59. The other paper relied on by Chemgenes (Kawasaki, discussed above) likewise does not support the notion that degradation was a “problem.” Instead, it notes the *potential* for degradation and reports that that they used “methanolic ammonia at room temperature.” (Ex. 2025 at 833.) They then report having confirmed a successful result based on NMR data and with compositional analyses of the synthetic oligonucleotides, noting that “protecting groups were cleanly removed by methanolic ammonia,” including from guanosine. (Ex. 2025 at 833.)

60. Notably, for all the syntheses described in the '031 Patent involving 2'-fluoro-2'-deoxyribonucleoside building blocks, deprotection is conducted exactly as described in Kawasaki: room temperature methanolic ammonia. Indeed, Examples 12.iii, 13.iii, 13.v, 14.i, and 16.vii of the '031 Patent each state that the corresponding oligoribonucleotide was prepared “[i]n the manner of Example 8.” (Ex. 1017 at 43:63-44:3, 44:26-32, 44:41-49, 44:63-45:5.) Example 8, in turn, states that “[t]reatment in methanolic ammonia for 24 hrs at room temperature was then done to deprotect all bases....” (Ex. 1017 at 40:48-52.)

² Sinha (2013) was published in 2013 and is not prior art to the '885 Patent. To the extent Chemgenes relies on Sinha (2013) as evidence of an alleged degradation problem with oligonucleotides containing 2'-fluoro-2'-deoxy monomers as of 2009, then Sinha (2013) also reflects a solution to that supposed problem as of 2009.

61. Second, even if a POSA were concerned about degradation of oligonucleotides containing 2'-fluoro-2'-deoxyribonucleotides, and even if Pitsch and Fan used methylamine and thus did not address that supposed "problem," that does not mean that a POSA would have disregarded the independently useful teachings of Pitsch and Fan regarding another important aspect of oligonucleotide synthesis, *i.e.*, how to protect exocyclic amine groups of nucleobases in a way that yields fast deprotection under mild conditions. In any event, even assuming degradation would have been a concern, a POSA would not have needed Pitsch or Fan to address it, because Kawasaki already had, and the '031 Patent employed that same deprotection approach.

5. Chemgenes' assertions regarding deprotection rates and conditions

62. Chemgenes asserts that a POSA would not have been motivated by Pitsch and Fan to modify Compound x by using an acetyl protecting group instead of an isobutyryl group, because (a) the '031 Patent does not disclose a deprotection rate, (b) Pitsch does not report a protection rate for isobutyryl, (c) the deprotection conditions used in Pitsch and those used in Fan are different from those used in the '031 Patent, (d) Fan only compares deprotection of nucleoside derivatives and not of corresponding phosphoramidites or oligonucleotides, and (e) Fan uses deprotection conditions that are not used in oligonucleotide synthesis. (POR 36-40; Ex. 2008 ¶¶130-141.) In essence, Chemgenes is asserting that a POSA would

not rely on Pitsch or Fan because they do not facilitate a direct comparison of deprotection speeds of acetyl versus isobutyryl.

63. Chemgenes' assertions are meritless and do not reflect how a POSA would have approached and used the information at hand. First, as I have explained, regardless of Pitsch and Fan, a POSA would have been motivated to increase deprotection speeds to save time. (Ex. 1003 ¶¶63, 118-121.) Because Pitsch touts these very benefits of using an acetyl protecting group, this *alone* would have motivated a POSA to change the protecting group of Compound x from isobutyryl to acetyl.

64. Second, the common knowledge to a POSA at the time would have suggested that replacing the isobutyryl group on Compound x with an acetyl group would permit faster deprotection and permit the use of milder deprotection conditions, which had its own benefits. It was known that isobutyryl required a "long and drastic deprotection step" that is "time consuming" and "forbids the synthesis of modified oligonucleotides containing alkali-sensitive bases." (Ex. 2013 at 397-398), and that "[u]se of labile protecting groups not only facilitates DNA/RNA synthesis but also allows incorporation of modified and base sensitive nucleosides." (Ex. 2018 at 13.) Thus, to be motivated to make the switch from isobutyryl to acetyl, a POSA would not have needed rigorous data comparing deprotection speeds of those groups.

65. Third, the data in Fan would have suggested to a POSA that acetyl would almost certainly deprotect faster than isobutyryl. As explained in my opening declaration, the data in Fan showed acetyl as deprotecting four times faster than isobutyryl. (Ex. 1003 ¶120 (citing Ex. 1019 at 2556-57).) Dr. Hrdlicka admitted in his deposition that “acetyl likely would deprotect faster than isobutyryl.” (Ex. 1035 at 137:1-4.)

66. Chemgenes notes that absolute deprotection rates for nucleoside derivatives could “not have reliably transposed to a different nucleoside, never mind to a different corresponding oligonucleotide.” (POR 39; Ex. 2008 ¶138.) But a POSA would have understood that *relative* nucleoside deprotection speed is helpful information and likely predictive of *relative* deprotection rates for the corresponding phosphoramidites and for oligonucleotides made using such nucleosides or phosphoramidites. This expectation and predictive reliance is reflected in the very Schulhof paper that Chemgenes relies on and quotes. (POR 39; Ex. 2008 ¶138 (citing Ex. 2013 at 400).) Schulhof compared deprotection speeds of various protecting groups on various nucleosides. (Ex. 2013 at 399.) Based on this data, regarding the faster-deprotecting groups, the authors stated that “[t]hese groups should allow a gain of time in the preparation of DNA fragments...” (Ex. 2013 at 399.) They also indicated that “these groups exhibit correct values to expect a final removal from oligonucleotides within a few

hours...,” which they contrasted with the “long and drastic deprotection step” of 17 hours when using the slower protecting groups. (Ex. 2013 at 397, 400.) Thus, as reflected in Schulhof, and contrary to Chemgenes’ suggestion, a POSA would have considered the relative deprotection speed data on nucleosides reported in Fan as helpful information and predictive of obtaining faster deprotection of oligonucleotides by using acetyl-protected guanosine phosphoramidites than by using isobutyryl-protected guanosine phosphoramidites.

67. Fourth, Chemgenes’ critique of the conditions used in Fan misses the point. As I explained during my deposition, a POSA would have understood that the deprotection conditions in Fan were chosen intentionally to slow down the reaction to facilitate the comparison of isobutyryl and acetyl; they would not confuse those with conditions for oligonucleotide synthesis or otherwise view those conditions as a reason to disregard the relative deprotection speed data reported in Fan. (Ex. 2009 at 149:20-152:1 (“The solvent is different in [Fan] for a very specific reason.... That is...mock conditions that are chosen specifically to dramatically attenuate the rate of deprotection...so the solvent choice is solely to make the point of the differences in rate...whether [] the solvent they used are different or not is irrelevant to the mechanism of this reaction and the rate thereof. Completely irrelevant...Nobody would [try to deprotect oligonucleotide using the deprotection conditions of Fan]. That’s not the point of the study.”).)

D. There was a reasonable expectation of success in making the claimed compound.

68. As explained in my opening declaration, a POSA would have had a reasonable expectation of success in making the claimed compound, because it was well-known how to make a 2'-fluoro-2'-deoxyguanosine, acetylate it, and convert it to the corresponding phosphoramidite. (Ex. 1003 ¶¶110-124.)

69. Chemgenes asserts that a POSA would not have had a reasonable expectation of success in making the claimed compound. I disagree. Chemgenes makes several assertions attempting to refute this. None have any scientific merit, and none of them alone or together support a conclusion that a POSA would not have had a reasonable expectation of success.

1. Reasonable expectation of success based on '031 Example 4

70. First, Chemgenes asserts that a POSA would not have had a reasonable expectation of making the compound of Claim 2 because acetylation of guanosine derivatives was known not to work well. (POR 44-45; Ex. 2008 ¶151 (citing and quoting Ex. 1019 at 2555).) I disagree.

71. Chemgenes cites and quotes a portion of Fan where they reported obtaining dark reaction mixtures and unsatisfactory yields when trying to acetylate a guanosine derivative using the Biegelman procedure. (POR 44-45; Ex. 2008 ¶151.) Chemgenes fails to acknowledge, however, that *Fan overcame this issue and successfully acetylated guanosine*. Indeed, Fan reported acetylating guanosine

“smoothly” and “without generation of dark mixtures” when they treated a 3’,5’-di-tert-butylsilylene derivative with TMSCl (TMS Chloride). (Ex. 1019 at 2555-56.) Notably, this intermediate is similar to the ’031 intermediate “Compound i” in that both have a silyl group simultaneously protecting the 3’ and 5’ positions of the sugar ring. (Compare Compound 5 in Scheme 2 on page 2556 with ’031 Compound i.) The ’885 Patent itself refers to this same transient TMS Chloride as “standard reaction conditions.” (Ex. 1001 at 9:64-65.)

72. Further, as noted above, Donga (2007) used acetylated guanosine and did not report any difficulties obtaining it. (Ex. 1029 at 276.)

73. Second, Chemgenes asserts that removing the 5’-O,3’-O-silyl protecting group in step iii of Example 4.d of the ’031 Patent with TBAF “would have seriously risked” removing the acetyl groups. (POR 45-47; Ex. 2008 ¶¶154-57.) In support of this assertion, Chemgenes cites the Ober paper (Ex. 2015.) I disagree that this is a valid concern. In my opinion, it would not have undermined a POSA’s reasonable expectation of success in making the claimed compound. A POSA would have regarded the difficulty reported by Ober as being of questionable relevance. Ober reported difficulty deprotecting the 3’ and 5’ positions of its Compound 5. (Ex. 1015 at 18144.) Compound 5 had one TBDMS group each at the 3’ and 5’ positions, not a single siloxane group simultaneously protecting the 3’ and 5’ positions, as in the ’031 Patent Example 4.d. A POSA

would have known that TBDMS is more difficult to remove than a siloxane group, and thus would not have expected the same difficulty as reported by Ober. (See, e.g., Ex. 1039 at 1059-60, Scheme 141.) Moreover, to the extent a POSA was considering the difficulty reported by Ober, they would have known that *Ober overcame the difficulty* by using “pyridine buffered pyridine-HF complex in ethyl acetate.” (Ex. 2015 at 18144.) Thus, Ober could not have led a POSA to lack a reasonable expectation of success in making the compound of Claim 2.

74. Third, Chemgenes asserts that the lower solubility of the acetylated intermediate as compared to Compound iii of the '031 Patent would cause a POSA to have no reasonable expectation of success in making the claimed compound. (POR 47-48; Ex. 2008 ¶¶158-61.) I disagree. Chemgenes is merely speculating that a POSA “would have expected” that the lower solubility “could have negatively affected purification and caused the synthesis to fail.” (POR at 48; Ex. 2008 ¶160.) Chemgenes offers no support for this. And it is baseless, as explained further below. In my opinion, as a general matter, a POSA would have no reason to expect that removing 2 carbon atoms from a large nucleoside monomer (going from isobutyryl to acetyl) would have a solubility effect so profound that it would prevent the molecule from reacting in subsequent chemistry. Indeed, multiple papers use N-acetyl protected nucleosides, including Pitsch itself, and none of them mention solubility-induced reactivity challenges. (See, e.g., Ex. 1018; Ex.

1040 (passim); Ex. 1029 at 276.) Moreover, in the subsequent steps in the '031 Patent that Chemgenes contests would be problematic due to solubility constraints, all of the solvents employed are highly polar (THF, Dioxane, MeOH/H₂O, pyridine). Thus, a POSA would not expect the acetyl-protected variants to pose a solubility issue.

75. Fourth, Chemgenes asserts that using sodium hydroxide in step v. of Example 4-d would have cleaved the 2' acetyl and/or the N² acetyl and caused the synthesis to fail. (POR 49-50; Ex. 2008 ¶¶162-165.) I disagree. Pitsch used sodium hydroxide at the analogous step in its synthesis and obtained a 77% yield, and did not report any problems associated with its use of sodium hydroxide. (Ex. 1018 at 3787.) This alone refutes Chemgenes' assertion and demonstrates that a POSA would have had a reasonable expectation of success. Indeed, a POSA would understand that Pitsch used catalytic sodium hydroxide.

76. Chemgenes cites data from Buchi showing de-acetylation of deoxyguanosine 5' phosphates over a two-hour period in sodium hydroxide. (POR 50; Ex. 2008 ¶164; Ex. 2020 at 279.) Buchi does not support Chemgenes' assertions. Buchi and Example 4-d of the '031 Patent both employ a molar excess of sodium hydroxide for the same two-hour exposure period. (Ex. 1017 at 26:49-50; Ex. 2020 at 279 (Table).) As shown in the Buchi data, after those two hours, only 18% of the compound had been de-acylated, and 82% of the acylated

compound remained. (Ex. 2020 at 279 (Table).) This is not a failure at all. To the contrary, this data confirms good yield at that step of the synthesis, and a POSA would simply account for such yield as they proceeded with their synthesis. They would not conclude that there was no reasonable expectation of succeeding in the synthesis.

2. Reasonable expectation of success based on Sivets

77. As I explained in my opening declaration, as another example, a POSA could easily have made the claimed compound by making the 2'-fluoro-2'-deoxyguanosine as disclosed in Sivets, then used standard methods to convert that to the claimed phosphoramidite. (Ex. 1003 ¶¶123-24.)³

78. As I also explained, a POSA would have expected those standard methods to work for converting a 2'-fluoro-2'-deoxyguanosine to the corresponding phosphoramidite, because they had worked in the prior art for converting a 2'-deoxyguanosine to the corresponding phosphoramidite. (Ex. 1003 ¶¶123-24.) Chemgenes does not assert that this is incorrect. Instead, Chemgenes suggests that during my deposition I did not provide any factual support for my suggestion that the standard methods would work to convert a 2'-fluoro-2'-deoxyguanosine to the corresponding phosphoramidite. (POR 52; Ex. 2008 ¶170.)

³ During my deposition, I corrected the typographical error in my report to refer to the correct compound in Sivets (15, not 17). (Ex. 2009 at 166:19-21.)

Chemgenes is incorrect. I explained that “[t]he 2’-fluoro reacts very similarly to the DNA...It’s a very, very small atom. It doesn’t require any protect[ing] group chemistry and is minimally disruptive to the...other parts of the molecule.” (Ex. 2009 at 167:11-17.)

79. Chemgenes then asserts that assuming 2’-fluoro-2’-deoxyguanosine would react similarly to 2’-deoxyguanosine, a POSA would have expected it to “suffer[] from similar solubility problems” during acetylation. (POR 52-53; Ex. 2008 ¶171.) I disagree. Clearly, as discussed above, the prior art, such as Pitsch and Pitsch #2, reports in detail how they successfully acetylated 2’-O-guanosine and does not report any solubility problems with those acetylations. (Ex. 1018 at 3775 (“A convenient synthesis of N²-acetylguanosine 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.”); Ex. 1021 at 8-9 (providing step-by-step instructions to “acetylate guanosine” and providing characterization data).)

80. Further, Chemgenes attempts to support the notion that 2’-guanosine had solubility problems during acetylation by citing Schaller. (POR 52-53; Ex. 2008 ¶171.) But as discussed above, Schaller reported *resolving* that issue, stating that “it has proved possible to acetylate the guanine ring in deoxyguanosine” by

solubilizing the nucleoside using tri-n-hexylethylammonium hydroxide and carrying out the acetylation over prolonged periods. (Ex. 2012 at 3822, fn.21.)

81. Chemgenes also suggests that having a fluorine instead of a hydrogen at the 2' position would give the two molecules "markedly different electronegativities, and would have expected those differences to have had a significant effect on the conformations of the resulting nucleosides and thus their reactivities." (POR 53; Ex. 2008 ¶171.) As noted in my opening declaration and again in deposition, I disagree; in my opinion, a POSA would not expect that difference to result in different "reactivities" of the molecules in the context of converting those nucleosides to the corresponding phosphoramidites using the standard techniques I cited. (Ex. 1003 ¶123; Ex. 2009 at 166:25-168:24 ("...my point is that their reactivity is very similar.")) As noted above, a POSA would not expect that the presence of fluorine at the 2' position would have any significant impact on the ability to acetylate the exocyclic amine of the nucleobase. This is supported by Zhu (2003), for example, where multiple different nucleosides were benzoylated at the exocyclic amine of the nucleobase with differing 2'-substituents. In the case of cytidine, the presence (entry 2) or absence (entry 7) of a hydroxyl group at 2' and even a hydroxyl group bearing the opposite (ara) stereochemistry (entry 5) required very similar conditions and led to high yields of benzoylated product. (Ex. 1038 at Table 1.) This is significant because it shows

how the nature of the substituent, its relative size, and even its stereochemical orientation have no practical effect on the distal reactivity of the exocyclic amine. In the case of guanosine the presence or absence of 2'-O (compare entries 3 and 10) had very little effect on the overall yield of the process (99% vs. 98% yield, respectively). (Ex. 1038 at Table 1.)

82. The Guschlbauer paper cited by Chemgenes is not to the contrary. It did not address or compare the *reactivity* of 2'-fluoro-2'-deoxyguanosine and that of 2'-deoxyguanosine. Indeed, a POSA would have recognized that Guschlbauer was a physical organic chemistry paper that did not address the reactivity of either species to the standard reagents used to convert nucleosides to N-protected phosphoramidites. (Ex. 2014.) Thus Guschlbauer would not have undermined a POSA's expectation of successfully making the claimed compound.

83. Moreover, Dr. Hrdlicka's suggestion that the 2'-F substituent would have a significant effect on reactivity and/or conformation is refuted by the data in Zhu (2003), because Zhu shows that an even more dramatic difference (the ara stereochemistry) had little or no effect on the nucleobase reactivity. (Ex. 1038 at Table 1.)

84. Chemgenes asserts that the protocols of Pitsch, Pitsch #2, and Example 4-d from the '031 Patent do "not make sense to cite" because they do not teach installation of protecting groups on 2'-deoxyguanosine or 2'-fluoro-

2'-deoxyguanosine. (POR 53-54; Ex. 2008 ¶¶172-73.) I disagree. A POSA would have expected the installation of protecting groups on of 2'-deoxy and 2'-fluoro-2'-deoxy monomers to be *easier* than protection of the more complicated monomers protected in Pitsch, Pitsch #2, and the '031 Patent, because, as I explained my opening declaration, the former do not have a reactive oxygen-bound substituent at the 2' position. (See, e.g., Ex. 1003 ¶50; Ex. 1018 at 3774 (“Compared to DNA,...each nucleotide unit within an RNA strand contains an additional 2'-OH group...which has to be protected during the assembly.”).)

85. Chemgenes asserts that “Pitsch is based on a flawed protocol because it discloses an insufficient amount of sodium hydroxide (‘0.2 mol’) to remove all of the O-acetyl groups of the peracetylated intermediate.” (POR at 54; Ex. 2008 ¶¶174-180.) I disagree. First, Pitsch clearly succeeded in making the acetylated guanosine, so the protocol was not “flawed.” Indeed, Pitsch disclosed extensive characterization data for that molecule, which could only be obtained from successful synthesis. (Ex. 1018 at 3787-793.) This alone refutes Chemgenes’ assertion. Second, a POSA would have understood that a base like sodium hydroxide could have hydrolyzed (removed) the O-acetyl groups catalytically (*i.e.*, without the need for molar equivalence), because O-acetyl groups are esters, and use of catalytic hydroxide in ester hydrolysis was well-known. (Ex. 1041 at 6045.) Third, even if a POSA were concerned that Pitsch did not disclose using enough

sodium hydroxide to remove all O-acetyl groups, they would have simply used more sodium hydroxide in that step, a trivial adjustment that would necessarily have been suggested by the supposed “flaw” itself. Fourth, even if a POSA did not make that adjustment, they would still expect to obtain *some* of the desired intermediate, just in lower yield than they might otherwise have obtained. As a matter of simple logic, getting a lower yield of an intermediate is not a failure to get the desired end product, and would not have undermined a reasonable expectation of success in doing so.

E. Secondary considerations do not support non-obviousness.

86. Chemgenes asserts that (a) there was a “longstanding need” in the industry to obtain pure chimeric oligoribonucleotides incorporating 2’-fluoro-2’-deoxyribonucleotides, (b) the ’885 Patent obtained unexpected results that satisfied this need in the form of the claimed compound, and (c) others had tried and failed to satisfy this need. (POR 54-61; Ex. 2008 at 184-196.) I disagree with each of those assertions.

87. As an initial matter, I note that Chemgenes relies on the ’885 applicants’ characterizations. Chemgenes does not point to any statements from any independent third-party asserting that any such need existed. Although the ’885 Patent refers to certain work by others, none of that work identifies a longstanding need to obtain pure chimeric oligoribonucleotides when using 2’-

fluoro-2'-deoxyribonucleotides. The '885 Patent cites two conference presentations as examples of this supposed difficulty, but does not provide any details about the reaction conditions used. (Ex. 1001 at 11:37-47.) Chemgenes, in turn, relies on this citation, but does not provide any more information about the conditions used, and does not provide copies of the presentations. (POR 57; Ex. 2008 ¶187.)

88. Chemgenes asserts that unspecified “observations” of these two undisclosed conference presentations (which are actually the '885 Patent's *characterization* of those presentations), “are corroborated by publications,” but Chemgenes cites only one publication, the Sinha (2013) chapter discussed above. (POR 57; Ex. 2008 ¶187 (citing Ex. 2024).) Sinha (2013) does not support any of the asserted secondary considerations. As an initial matter, Sinha (2013) was published in 2013, years after both the 2009 priority date of the '885 Patent and its corresponding 2010 PCT publication date. (Ex. 2024 at iv.) Thus, to the extent Chemgenes asserts that Sinha (2013) corroborates the existence of a difficulty (which I disagree with), then it also shows that the '885 inventors did not overcome that supposed difficulty. In any event, as detailed above, Sinha (2013) actually shows how to *avoid* degradation of oligonucleotides that contain 2'-

fluoro-2'-deoxyribonucleotides, by using different deprotection conditions. (Ex. 2024 at 83-86.) As also noted above, so does Kawasaki.⁴

89. Chemgenes also misinterprets the disclosure of the '885 Patent. According to the '885 Patent itself, the supposed “difficulty in obtaining pure chimeric oligoribonucleotides” containing 2'-fluoro-2'deoxy bases arose when using “*strongly basic conditions.*” (Ex. 1001 at 11:4-7.) But the '885 does not claim to have obtained pure chimeric oligoribonucleotides when using strongly basic conditions. Rather, the '885 Patent alludes to using “mild” deprotection conditions of methylamine. (Ex. 1001 at 22:50-51, 22:64-65, 23:13-14.)

90. Chemgenes asserts that the “unexpected results” reported in the '885 Patent were that the inventors obtained “high quality full length RNA” containing 2'-fluoro-2'-deoxynucleosides by using acetyl-protected guanosine phosphoramidites. (POR 57-58; Ex. 2008 ¶188.) In my opinion, as explained throughout my opening declaration and above, this would not have been the least bit surprising to a POSA in 2009.

⁴ Chemgenes asserts that because Kawasaki, which was published in 1993, resolved the degradation problem by using a different solvent (methanolic ammonia rather than methylamine) rather than by using acetyl as a protecting group, this somehow demonstrates that the “overall degradation problem persisted in the industry for at least over 15 years.” (POR 59; Ex. 2008 ¶192.) This makes no sense. Kawasaki resolved its degradation issues. Thus, there was no “overall degradation problem.”

91. Chemgenes also seems to assert that the results obtained by the '885 applicants were unexpected because they solved the degradation “problem” by using acetylated 2'-fluoro-2'-deoxy phosphoramidites *while using methylamine*, a “problem” Chemgenes asserts was “observed” by Sinha. (POR 59-60; Ex. 2008 ¶¶193-94.) I disagree. First, Sinha states that it was published in 2013. (Ex. 2024 at iv.) To the extent it reflects that using methylamine was a “problem,” then it also reflects that the '885 Patent did not solve that “problem.” Second, contrary to Chemgenes' assertion, Sinha (2013) did not actually “observe[] problems using methylamine.” (POR 59; Ex. 2008 ¶194.) Rather, Sinha merely stated that “the 2'-F modification is subject to depyrimidiation” without citing any instance in the literature of that being a problem, then offered a “postulated mechanism” for that in the case of uridine, not guanosine. (Ex. 2024 at 83, 85.) Third, as I have explained, it was well-known by 2009 that “mild and shorter” base deprotection was preferred when synthesizing RNA because of the need to protect and deprotect the 2' oxygen of a ribonucleoside. (Ex. 1003 ¶¶43-44, 50; Ex. 2018 at 13 (explaining that for RNA, “there is a need for milder deprotection conditions” and that “[u]se of labile protecting groups not only facilitates DNA/RNA synthesis but also allows incorporation of modified and base sensitive nucleosides.”).) It was also well-known that acetyl protecting groups were useful for making RNA oligonucleotides because of their rapid deprotection even under mild deprotection

conditions. (Ex. 1018, *passim*.) Accordingly, a POSA looking to make a chimeric oligonucleotide containing both RNA monomers and 2'-fluoro-2'-deoxy nucleosides, for example, would naturally have used mild and shorter deprotection conditions and in doing so, would have naturally used an appropriate protecting group such as acetyl based on its known rapid deprotection at mild deprotection conditions. In other words, the choice of deprotection conditions and the choice of protecting group go hand-in-hand.

92. Further, I am informed that to support a finding of non-obviousness, alleged unexpected results must be commensurate in scope with the claimed invention. In my opinion, the asserted unexpected result of obtaining high-quality full-length RNA is not commensurate in scope with Claim 2. Indeed, Claim 2 claims phosphoramidite compounds *per se* according to the recited chemical structure, and does not claim oligonucleotides, RNA, or any process for synthesizing oligonucleotides or RNA. Nor does Claim 2 require purity of any kind or degree, let alone purity of oligonucleotides or RNA. Nor does Claim 2 require the use of any particular deprotection conditions, such as methylamine.

93. Finally, I disagree that Chemgenes has established any “failure of others” that would show non-obviousness of the claimed compound. I am informed that “failure of others” refers to a failure of others to make the claimed invention. In that regard, I note that Chemgenes has not shown that anyone tried

and failed to make the claimed compound. Chemgenes asserts only that “others tried but failed to satisfy the demand,” but Chemgenes does not clearly identify what that supposed “demand” was. If it is the same as the “need,” “problem,” or “difficulty” asserted by Chemgenes in connection with their asserted long-felt need and/or their asserted unexpected results, then for the reasons stated above, I disagree that Chemgenes has shown that there was such a “demand.” I also disagree that Chemgenes has demonstrated that anyone failed to satisfy such demand.

VI. GROUND III

A. Structural differences do not suggest non-obviousness

94. I agree with Chemgenes that Compound 5 in Figure 16 of the '991 Patent is a different molecule than the molecule of Claim 2 of the '885 Patent (where “B” is guanine-N-acetyl and “Z” is ribo Fluoro), which is why I did not offer the opinion that compound anticipates Claim 2.

95. I disagree with Chemgenes’ imprecise and subjective characterizations about the differences between these two molecules (*i.e.*, “starkly different”, “totally different,” “plainly different,” “drastic differences”). (Ex. 2008 ¶¶197, 198, 206, 207, 209, 211.)

96. As I explained in my opening declaration, a POSA would have known that Compound 5 was a 2'-fluoro *cytidine* phosphoramidite in the “L”

stereochemical configuration, whereas the compound of Claim 2 is a 2'-fluoro *guanine* phosphoramidite in the "D" configuration. (Ex. 1003 ¶127.)

97. I disagree with Chemgenes' assertion that Compound 5 and the compound of Claim 2 "would have to be prepared completely differently." (POR 63; Ex. 2008 ¶207.) A POSA would use the same procedures, simply using a *guanine* starting material in the D configuration instead of a *cytidine* starting material in the L configuration.

98. I disagree with Chemgenes' assertion that Compound 5 and the compound of Claim 2 "would have reacted completely differently during SPOS..." (POR 63-64; Ex. 2008 ¶207.) Chemgenes does not provide any basis for this assertion. It is not clear what they are referring to. To the extent Chemgenes is asserting that the compounds would react differently during protection of the exocyclic amine or its subsequent deprotection, I disagree, because the protecting group in each is the same. The conditions for nucleobase protection and deprotection of cytosine on the one hand, and that of guanosine on the other hand, are often the same. (See, e.g., Ex. 2016 at pages 7-9 and Fig. 2.1.7.)

99. To the extent Chemgenes is asserting that the compounds would react different because their stereochemical configuration is different, I disagree. As a matter of undergraduate chemistry, it is well known that enantiomers react the same, except in the presence of chiral reagents. Enantiomers have the same

chemical bonds, functional groups, and chemical reactivity. Because chemical reactions depend on the breaking and forming of bonds, enantiomers react in an identical manner when dealing with achiral reagents or conditions. Enantiomers have an inherent symmetry. The molecule and its mirror image share the same physical properties like melting point, boiling point, density, and refractive index. These properties are determined by the overall molecular structure and are not influenced by the spatial arrangement of atoms. (Ex. 1042 at 95.)

100. I disagree with Chemgenes' suggestion that a comparison between the structure and stereochemical configuration of Compound 5 and Claim 2 somehow suggests the non-obviousness of Claim 2. (POR 61-64; Ex. 2008 ¶¶197-207.) First, the different nucleobase employed in Compound 5 (cytosine) versus Claim 2 (guanosine) would not have been suggestive of non-obviousness. Rather, as I explained in my opening declaration, given the known purpose of phosphoramidite building blocks in SPOS, and the highly likely need to incorporate all four canonical nucleobases into an oligonucleotide, a POSA seeing the cytosine phosphoramidite of Compound 5 would have been motivated to make a guanosine version of it, so they could use it as a SPOS reagent to incorporate 2'-fluoro-2'-deoxy guanosine monomers as needed into an oligonucleotide. (Ex. 1003 ¶128.)

101. I also disagree with Chemgenes' assertion that there was no reason for a POSA to select Compound 5 in the '991 Patent. (Ex. 2008 ¶¶208-209.) As

discussed in my opening declaration and above, the advantages of oligonucleotides containing 2'-fluoro-2'-deoxy monomers were well-known, and a POSA would have immediately recognized the utility of Compound 5. This alone would have been sufficient reason to select it and consider making and using a guanosine version of it for SPOS.

102. Further, the '991 Patent itself highlights Compound 5 by describing its synthesis at length in Example 6 and illustrating that synthesis in Figure 16. (Ex. 1020 at Figure 16 and at 45:41-47:12.)

103. Chemgenes' asserts that a POSA would not have been motivated by the '991 Patent to make the compound of Claim 2 of the '885 Patent. (POR 65-67; Ex. 2008 ¶¶210-215.) As an initial matter, I am informed that for purposes of an obviousness analysis, motivation to make the claimed invention need not come from the prior art itself, and can come from other sources. Here, a POSA would have been motivated for the reasons I have stated. It thus does not matter whether the '991 Patent *itself* would have motivated a POSA to make the compound of Claim 2.

104. In any event, Chemgenes' mischaracterizes the teachings of the '991 Patent. Chemgenes asserts that the '991 Patent would not have motivated a POSA to make the claimed compound because the '991 Patent discloses a preference for 2'-fluoro modified *pyrimidines*, whereas the compound of Claim 2 contains a

guanosine nucleobase, which is a *purine*. (POR 65-67; Ex. 2008 ¶213.)

Chemgenes does say that this teaches away from the compound of Claim 2, and does not explain *why* the passage it cites means that a POSA would not be motivated to make the compound of Claim 2. In my opinion, a POSA would not read the '991 Patent in such a way. The passage cited conveys a preference that in the nucleic acids being made, the pyrimidines be 2'-fluoro modified. The passage Chemgenes points to is silent as to purines, and the preference it conveys is neither a preference for pyrimidines *per se*, nor a preference for pyrimidines over purines.

105. I also disagree with Chemgenes' assertion that the '991 Patent would not have motivated a POSA to make the claimed compound and would have discouraged a POSA from doing so because "the '991 Patent is directed to L-configured nucleic acids, not D-configured phosphoramidites" and "teaches instability of D-configured nucleic acids in aqueous solutions and biological systems." (POR 66; Ex. 2008 ¶214.) First, the '991 Patent clearly contemplates using *either or both* D-configured or L-configured nucleotides, and that the resulting nucleic acids can be wholly D-configured, wholly L-configured, or partially D- and partially L- configured nucleic acid, depending on the desired behaviors or functionalities. (Ex. 1020 at 11:32-67 ("The nucleic acids according to the present invention can either be D nucleic acids or L nucleic acids.") ("It is also possible that one or more parts of the nucleic acid are configured as D nucleic

acid(s), or at least one or more parts of the nucleic acid are designed as L nucleic acid. The term ‘part’ of the nucleic acid should describe as little as one nucleotide.”) (“[P]arts of these longer nucleic acids can be either a D nucleic acid or an L nucleic acid. Any combination can be used in conjunction with the present invention. This other part or respectively these other parts of the longer nucleic acid can have a function, which is different to binding and especially to binding CGRP[, such as] interaction with other molecules, e.g., for the purposes of allowing immobilizing, cross-linking, proof or amplification.”).) Accordingly, in my opinion, the ’991 Patent *would* have motivated a POSA to pursue both D-configured and L-configured phosphoramidites so they could build the various kinds of nucleic acids discussed in the ’991 Patent.

106. Further, although the ’991 Patent notes that D nucleic acids are not very stable in aqueous solutions and in particular biological systems, it also discusses ways to improve that stability, noting that “[t]he inventive nucleic acids can however also be present as double-stranded[, which] lends the nucleic acid a stability which is of advantage when the nucleic acid is present in the naturally occurring D form instead of the L form.” (Ex. 1020 at 12:27-32.)

B. Expectation of success

107. Chemgenes' asserts that a POSA would not have had a reasonable expectation of success in making the claimed compound. I disagree, for the reasons discussed in my opening declaration and above regarding Ground II.

108. Chemgenes asserts that I have not provided evidence or reasoning for reasonable expectation of success "based on the '991 Patent or Compound 5." (Ex. 2008 ¶¶216-17.) I am informed that to establish a reasonable expectation of success in making the claimed compound, I am not required to rely on the teachings of the '991 Patent.

109. In any event, I note that Chemgenes does not assert that a POSA would not have had a reasonable expectation of success in making the claimed compound using the teachings of the '991 Patent. Nor could Chemgenes correctly assert such a thing. Indeed, the '991 Patent provides detailed instructions for making Compound 5, and cites a number of publications by others, reflecting that such synthetic techniques were well-known to a POSA and could be easily applied to make the compound of Claim 2 of the '885 Patent. (Ex. 1020 at Example 6 (45:42-47:12).) The POSA, using the R-configured ribose as a starting material instead of the L-configured ribose, would have had a reasonable expectation of success in otherwise following Example 6 in the '991 Patent to make the compound of Claim 2 of the '885 Patent.

C. Secondary Considerations

110. Chemgenes relies on the same secondary considerations for Ground III as they do for Ground II. I have addressed those above and my opinions in this regard apply equally to Ground III.

VII. GROUND IV

111. For Ground IV, which addresses Claim 3 of the '885 Patent, Chemgenes appears to rely on its assertions regarding Claim 2. (POR 69-70; Ex. 2008 ¶¶220-29.) My responses and opinions regarding those are stated above, and it remains my opinion that Claim 3 would have been obvious to a POSA over the '031 Patent, Pitsch, Fan, and Scaringe.

112. Chemgenes also asserts that Compound 5c in Scaringe is “different from the molecules covered by Claim 3 and the various molecules disclosed in the '031 Patent, Pitsch, and Fan” because Compound 5c is not 2'-fluoro substituted and instead has an O2'-TBDMS group and an isobutyryl nucleobase protecting group, not acetyl, and does not disclose deprotection rates. (Ex. 2008 ¶¶225-227.) Chemgenes does not explain *why* those differences would lead to Chemgenes' conclusion that a POSA “would not have been motivated by Scaringe to synthesize the succinate claimed in Claim 3...with a reasonable expectation of success.” (POR 70; Ex. 2008 ¶227.) I disagree that such a difference would have lead a POSA to such a conclusion.

113. As I explained in my opening declaration, Scaringe is one of many examples in the prior art showing how to convert nucleosides to its corresponding phosphoramidite or succinylated derivative and attach that to a long chain alkylamine controlled pore glass. (Ex. 1003 ¶¶145-147.) The increased steric hindrance of the C-2' OTBDMS would mean to the POSA that if it worked in Scaringe, it would work even better with a 2'-F-substituted species, because fluorine is small and would render the C-3' OH site more reactive. Further, as explained above, a POSA would not regard the nucleobase protecting group as having any significant effect on the reactivity of the chemically distant ribose OH site.

114. Finally, in my opinion, it is irrelevant that Scaringe does not discuss deprotection rates. As discussed above, the '031 Patent, Pitsch, and Fan provide the relevant information regarding deprotection rates sufficient to motivate a POSA to use the acetyl to protect the exocyclic amine on the nucleobase.

VIII. GROUND V

A. Selection of Scaringe Compound 5(c)

115. Chemgenes asserts that I did not provide any reason to select Compound 5(c) from Scaringe. (POR 73; Ex. 2008 ¶234.) As an initial matter, Chemgenes seems to be operating from the premise that a “lead compound” analysis is required. As explained above, however, in my opinion, it is not,

because the claimed compound is a reagent for SPOS, not a candidate for a potential drug or therapeutic. Further, Chemgenes suggests that I would have to explain why Compound 5(c) was “*the* most promising” to select. (POR 73; Ex. 2008 ¶234 (emphasis added).) As I explained above, however, I am informed that even assuming the lead compound analysis applies, it does not require establishing a single lead compound.

116. In any event, Chemgenes is not correct. As I explained in my opening declaration, Scaringe discloses that Compound 5(c) can be attached to LCAA-CPG to prepare a solid support for SPOS. (Ex. 1003 ¶152, referring to ¶¶144-47 (“[A]s discussed above with respect to Claim 3 of the ’885 Patent, Scaringe (1990) also discloses the coupling of [Compound 5(c)] to LCAA-CPG to prepare the solid support for SPOS.”).) This clear utility alone would have been reason sufficient for a POSA to select Compound 5(c) in Scaringe.

117. Chemgenes also asserts that a POSA would not have selected Compound 5(c) of Scaringe, because the sequences reported in Scaringe did not have guanosine bound to the solid support. (POR73-74; Ex. 2008 ¶¶235-237.) I disagree. First, Chemgenes is not correct. Scaringe *did* report making sequences with Compound 5(c) bound to the solid support. On page 2, Scaringe states:

Syntheses were conducted...using derivatized...solid supports. These supports were prepared by the coupling of compounds **5a-d** to LCAA-CPG. Other reagents and details are described in the experimental section.

(Ex. 1022 at 5435 (emphasis in original).) Then again in the experimental section, Scaringe repeats this disclosure and also reports resulting data:

Derivatization of Controlled Pore Glass Supports

1000Å LCAA-CPG (CPG Inc., NJ) was derivatized with compounds **5a-d** following a published protocol (23). Final nucleoside loadings of 10-15 $\mu\text{mol g}^{-1}$ were obtained.

(Ex. 1022 at 5440 (emphases in original).)

118. Chemgenes does not acknowledge these disclosures in Scaringe, and instead discusses only Table 4, which discloses four sequences. (POR 73-74; Ex. 2008 ¶236.) But Scaringe does not state that they only made the four sequences depicted in Table 4. Rather, Scaringe explains that they chose those four sequences *for testing* to compare them to sequences previously-prepared by a different (enzymatic) method. (Ex. 1022 at 5434-35 (“To test our methodology with biochemical assays we prepared the sequences...shown in Table 4. These sequences were chosen because they have been previously prepared by the T7 transcription method and have well characterized biochemical activities...”).)

119. Second, even if Scaringe had not reported making solid supports bound to Compound 5(c), I disagree that a POSA would have approached Scaringe or the selection of a nucleoside succinate in the manner suggested by Chemgenes. Rather, a POSA would have appreciated that Compound 5(c) could be a useful

reagent for making a sequence starting with guanine, and would have selected Compound 5(c) for use or modification on that basis.

B. Motivation to Replace Isobutyryl Protecting Group with Acetyl

120. Chemgenes asserts that a POSA would not have been motivated to install an acetyl protecting group on Compound 5(c) instead of isobutyryl. (POR 75; Ex. 2008 ¶238.) Chemgenes relies on its assertions made in connection with Claim 2. I have addressed those above and they apply equally to Claim 4.

121. In my opening declaration, I noted that a POSA would have recognized that substitution of the protecting group on the exocyclic amine of the nucleobase would not have been affected by the 2'-O-TBDMS protecting group on the sugar ring. (Ex. 1003 ¶155.) In response, Chemgenes does not refute that statement. And as I explained in my deposition and above, those locations are chemically distant and respective substitution groups at those respective positions are chosen independently by a POSA.

122. Chemgenes asserts that Beaucage does not show that that substitution of the protecting group on the exocyclic amine of the nucleobase would not have been affected by the 2'-O-TBDMS protecting group on the sugar ring. (POR 75; Ex. 2008 ¶239.) This is beside the point; I cited Beaucage to show that 2'-O-TBDMS had been commonly used to shield the 2'-OH. (Ex. 1003 ¶155.)

C. Expectation of success and secondary considerations

123. Chemgenes asserts that I did not explain why a POSA would have had a reasonable expectation of success in making the compound of Claim 4. (POR 76; Ex. 2008 ¶240.) Chemgenes is incorrect. I explained in my opening declaration that “as discussed above with respect to Claim 3, a POSA would have (a) known how to couple the resulting succinate to the amine group of [LCAA-CPG] as disclosed in Scaringe (1990)...and (b) regarding a C6 alkyl as a suitable spacer...”. (Ex. 1003 ¶156.)

124. I note that Chemgenes does not affirmatively state that a POSA would not have had a reasonable expectation of success in making the compound of Claim 4, nor does Chemgenes offer any evidence or reasons why a POSA would not have had such a reasonable expectation of success.

125. I further note that Chemgenes does not offer any assertions or arguments regarding secondary considerations in connection with Claim 4.

IX. GROUND VI

126. In my opening declaration, I explained why Claim 5 is anticipated by Gaur. (Ex. 1003 ¶¶157-73.) It appears that Chemgenes does not dispute this. (POR 76-77; Ex. 2008 ¶¶242-248.)

127. I understand that Chemgenes has instead moved to replace Claim 1 with Substitute Claim 7. I have prepared a separate declaration addressing the patentability of Substitute Claim 7.

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

Dated: January 19, 2024



Phil S. Baran, Ph.D.