UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SHANGHAI HONGENE BIOTECH CORPORATION,

Petitioner,

v.

CHEMGENES CORPORATION,

Patent Owner.

IPR2023-00490
U.S. Patent No. 9,884,885 B2

DECLARATION OF PATRICK J. HRDLICKA, Ph.D. IN SUPPORT OF PATENT OWNER RESPONSE

CHEMGENES EXHIBIT 2008
Shanghai Hongene v. ChemGenes
Case IPR2023-00490

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I. INTRODUCTION

1. By and through the witness services firm Rubin Anders and their engagement with counsel for ChemGenes Corporation ("Patent Owner" or "ChemGenes"), I have been retained to analyze Shanghai Hongene Biotech Corporation's ("Petitioner" or "Hongene") petition for *inter partes* review ("IPR") of Claims 1-5 of U.S. Patent No. 9,884,885 ("the '885 Patent") (Ex. 1001) ("Petition") (Pet.), the declaration of Phil S. Baran, Ph.D. provided in support of the Petition (Ex. 1003), and related exhibits, and provide my expert opinions in support of Patent Owner's response ("Response") to the Petition. I am being compensated for my time at my usual and customary consulting rate of $600 U.S. dollars per hour. My compensation is not affected by the outcome of this IPR and my opinion is not influenced in any way by my compensation.

II. BACKGROUND

A. Experience and Qualifications

2. I am currently a Professor in the Department of Chemistry at the University of Idaho. I graduated from the University of Southern Denmark, in Odense, Denmark in 2000 with a B.Sc. in Chemistry, where I worked under Professor J.J.L. Iversen. I then obtained an M.Sc. in Chemistry from the University of Southern Denmark in 2004, where I worked under Professor Jesper Wengel. I

then obtained a Ph.D. in Chemistry in 2006 from the University of Southern Denmark, where I worked, again, under Professor Wengel.

3. My training at the University of Southern Denmark afforded me a comprehensive background in chemistry, molecular biology, and microbiology. I received training in technical microbiology and natural products isolation in connection with my B.Sc. dissertation; protecting group, carbohydrate and nucleoside chemistry, medicinal chemistry, and computer simulations of nucleic acids during my M.Sc. work; and protecting group, carbohydrate, nucleoside and oligonucleotide chemistry, and fluorescence spectroscopy during my Ph.D. studies. My graduate training at the Nucleic Acid Center at the University of Southern Denmark - an interdisciplinary Center of Excellence comprised of five research groups and ~50 scientific coworkers focused on advancing the frontiers of nucleic acid chemistry - enabled me to specialize in protecting groups, nucleosides, nucleotides, oligonucleotides, and nucleic acid chemistry, i.e., the central areas of this IPR.

4. The title of my Ph.D. dissertation was "Functionalized LNA Analogs - Building Blocks for Nucleic Acid Based Therapeutics and Diagnostics." Broadly described, this project entailed the synthesis of numerous nucleoside phosphoramidites, their use as reagents to make chemically modified oligonucleotides via automated P(III)-based solid phase oligonucleotide synthesis

(SPOS) protocols, and biophysical characterization of the resulting chemically modified oligonucleotides via a range of techniques including UV-Vis and steady-state fluorescence emission spectroscopy and computer simulations. Particular emphasis was placed on the synthesis and characterization of oligonucleotides modified with conformationally restricted nucleotides and/or pyrene-modified nucleotides. As part of these studies, I gained extensive experience designing, planning and executing complex multi-step synthetic schemes to challenging nucleoside phosphoramidites, which entailed many protection/deprotection steps. I also supervised a group of technicians and B.Sc/M.Sc/Ph.D. students working on such projects. I published 10 peer-reviewed journal papers, and four conference proceedings from this dissertation.

5. After my Ph.D., I went on to become an Assistant Professor in the Department of Chemistry at the University of Idaho from 2006 to 2011. I then became an Associate Professor in the Department of Chemistry at the University of Idaho from 2011 to 2017. In 2017, I became a Professor of Chemistry at the University of Idaho, and still hold that position to this day.

6. I have served in other roles in addition to my regular appointment at the University of Idaho. Thus, I was an adjunct faculty in the Department of Chemistry at Washington State University from 2011 to 2014 and an Affiliate Faculty in the Department of Biological Sciences at the University of Idaho since 2013. Between

2015-2018, I served as a member, elected vice-chair, and elected chair of the Faculty Senate at the University of Idaho. Between 2018 to 2019, I was appointed Special Assistant to the Provost's Office at the University of Idaho.

7. My work has been recognized as follows: In 2010, I received the Early Career Faculty Award from the University of Idaho. In 2012, I received the President's Inaugural Mid-Career Faculty Award from the University of Idaho. In 2013, I received the Excellence in Research and Creative Activity Award from the University of Idaho. In 2022, I received the College of Science, Advisory Board Faculty Fellowship and the Donald Crawford Graduate Faculty Mentoring Award, both from the University of Idaho.

8. The overarching goal of my research laboratory is to develop novel chemically modified oligonucleotides for biomedical applications. Recently, we have focused on the development of oligonucleotides that enable sequence-specific recognition of chromosomal DNA. The scientific community has long sought to solve this challenge, fueled by the prospect for tools that will enable modulation of gene expression at the DNA level, detection of specific chromosomal DNA targets, and manipulation of genomic DNA. Other areas pursued by my laboratory include the development of: RNA-targeting antisense oligonucleotides with optimized hybridization and pharmacokinetic profiles and probes for detection of nucleic acid targets harboring single nucleotide polymorphisms. All of these projects rely on the

design and synthesis of complex, bespoke nucleoside phosphoramidites, which entails many protection/deprotection steps.

9. I have published 72 peer-reviewed journal articles (including five cover articles), two peer-reviewed book chapters, eight patent publications (three issued), 36 conference proceedings/abstracts, and one book review. The vast majority of these articles, book chapters, patent publications, and proceeding/abstract are related to protecting groups, nucleosides, nucleotides, oligonucleotides, and nucleic acid chemistry. My H-index is currently 26 and my work has been cited over 1900 times. As a devoted research and faculty member, I have been involved in securing seven external grants (totaling over $2 million) and several internal grants (totaling ~ $200,000). I am committed to research student supervision and training, and am or have been the primary supervisor to 17 Ph.D. and Masters students, two postdoctoral fellows, 28 undergraduate students, and been a committee member for 15 graduate students.

10. I teach (or have taught) semester-long courses within the areas of organic chemistry, medicinal chemistry, and nucleic acid chemistry and biology on many occasions (more than 30 occasions). Of particular relevance to this matter, I have offered courses entitled “Introduction to Nucleic Acid Chemistry” and “Nucleic Acids: Synthesis and Applications” on at least four occasions, in which topics such as protecting group chemistry, nucleoside chemistry, and principles of

oligonucleotide chemistry are covered. Moreover, each semester, I lead a seminar-style class that focuses on aspects of nucleic acids chemistry and biology, during which students present self-selected original research articles, which are discussed in plenum. The discussed articles often detail synthesis of new nucleoside phosphoramidites and oligonucleotides. This highly specialized seminar-style class has been offered on at least 20 occasions.

11. I have worked as a consultant and expert in several cases. I worked as a consultant for ISIS Pharmaceuticals (now Ionis Pharmaceuticals) from 2011 to 2012. I concurrently worked as a consultant for Minitube of America (now MOFA Global) from 2011 to 2015. Since 2016 to the present, I have been retained as a subject matter expert on several litigation matters pertaining to DNA, nucleoside and sequencing technologies.

12. As reflected in my C.V., I have been involved in a consultant in a number of litigations, including:

(A) United States International Trade Commission action 337-TA-1032 involving Certain single-molecule nucleic acid sequencing systems and reagents (representing Oxford Nanopore);

(B) *Inter Partes* Review of U.S. Patent No. 9,738,929 IPR2018-01792 (representing Oxford Nanopore);

(C) Pacific Biosciences of California, Inc., v. Oxford Nanopore Technologies, Inc. district court matters (C.A. No. 17-01353-LPS and C.A. No. 17-00275-LPS) (representing Oxford Nanopore);

(D) CGI Matters Adverse to Illumina (Case No. 1:19-cv-00970-MN (D. Del.); Case No. 19-cv-03770-WHO (N.D. Cal.); Case No. 20-cv-01465-WHO (N.D. Cal.) (representing CGI); and

(E) Twinstrand Biosciences, Inc., & University of Washington v. Guardant Health, Inc (Case No. 1:21-cv-01126-LPS (D. Del.) (representing Twinstrand.)

13. In formulating this Declaration, I have relied upon my training, knowledge and experience in the relevant art for over 20 years. My curriculum vitae attached as **Appendix A** to this Declaration provides a comprehensive description of my academic and employment history to date.

14. I reserve the right to supplement my opinions to address any information obtained, or positions taken, based on any new information that comes to light throughout this proceeding.

B. Materials Considered

15. In conducting the analysis and forming my opinions as reflected in this declaration, I have relied upon my education, training, and experience, and considered the Petition, declaration submitted by Dr. Baran in support of the

Petition, including all of its exhibits, as well as other literature referenced herein and listed in **Appendix B** and **Appendix C**.

III. SUMMARY OF MY OPINIONS[1]

16. Claim 1 of the ’885 Patent, as Patent Owner has proposed it to be amended, claims compounds not anticipated or obvious over the cited prior art.

17. Claim 2 of the ’885 Patent would not have been obvious over U.S. Patent No. 5,898,031 (Ex. 1017) in view of Pitsch (Ex. 1018) and Fan (Ex. 1019).

18. Claim 2 of the ’885 Patent would not have been obvious over U.S. Patent No. 7,879,991 (Ex. 1020) in view of Pitsch.

19. Claim 3 of the ’885 Patent would not have been obvious over U.S. Patent No. 5,898,031 in view of Pitsch, Fan, and Scaringe (Ex. 1022).

20. Claim 4 of the ’885 Patent would not have been obvious over Scaringe in view of Pitsch and Fan.

21. Claim 5 of the ’885 Patent, as Patent Owner has proposed it to be amended, claims compounds not anticipated or obvious over the cited prior art.

IV. LEGAL BASES FOR MY OPINIONS

22. I am not an attorney or a patent agent nor have I independently researched the law on patentability. ChemGenes’ attorneys have explained the

[1] The summary of my opinions is in no way intended to be limiting, and I more completely discuss my opinions below.

relevant legal standards to me that I have relied on in forming my opinions set forth in this declaration.

A. Patent Claims in General

23. I have been informed that patent claims are the numbered sentences at the end of each patent. I have been informed that the claims are important because the words of the claims define what a patent covers. I have also been informed that the figures and text in the rest of the patent provide a description and/or examples and help explain the scope of the claims, but that the claims define the breadth of the patent's coverage.

24. I have also been informed that an "independent claim" expressly sets forth all of the elements that must be met in order for something to be covered by that claim. I have also been informed that a "dependent claim" does not itself recite all of the elements of the claim but refers to another claim for some of its elements. In this way, the claim "depends" on another claim and incorporates all of the elements of the claim(s) from which it depends. I understand that all of the claims of the '885 Patent are written in Markush format. I understand that the '885 patent contains five independent claims: 1, 2, 3, 4, and 5 and that Petitioner has challenged all of these claims.

B. Person of Ordinary Skill in the Art (POSA)

25. I understand that the POSA is a hypothetical person who is presumed to have known the relevant art at the time of the invention. Factors that may be considered in determining the level of ordinary skill in the art may include: (A) the type of problems encountered in the art; (B) prior art solutions to those problems; (C) rapidity with which innovations are made; (D) sophistication of the technology; and I educational level of active workers in the field. In a given case, every factor may not be present, and one or more factors may predominate.

26. I understand that a POSA is also a person of ordinary creativity, not an automaton. I further understand that the hypothetical person having ordinary skill in the art to which the claimed subject matter pertains would, of necessity, have the capability of understanding the scientific and engineering principles applicable to the pertinent art.

C. Claim Construction

27. I understand that the scope and meaning of the Challenged Claims must be determined before invalidity of those claims can be determined. I understand that in *Inter Partes* Review proceedings, claim terms are given their ordinary and customary meaning as understood by a POSA as of the earliest effective filing date of the claim in question. I also understand that claims are construed in the context of the specification and prosecution history of the patent application.

28. I understand that extrinsic evidence may also be useful in interpreting patent claims when the intrinsic evidence (specification and prosecution history) is insufficient. I understand that extrinsic evidence may include dictionaries and other resources available a POSA as of the earliest effective filing date. I understand that claims may also be construed according to a prior claim construction determination in a civil action or a proceeding before the international trade commission that is timely made of record in the proceeding.

29. I understand that the context of a term used in a claim or claims may inform the meaning of a claim term. I understand that since the specification is a primary source for the meaning of a claim term, a proper construction of a claim term should be consistent with how the term is used in the specification. I understand that references cited by the application or incorporated by reference into the specification may indicate how a POSA would have understood certain terms and concepts.

30. I understand that a preamble term or phrase is not limiting where a Challenged Claim defines a complete invention in the claim body and uses the preamble only to state an intended use or purpose for the invention. I understand generally that a term or phrase found in the introductory words or preamble of the claim should be construed as a limitation if it recites essential structures or steps, or is necessary to give meaning to the claim. More specifically, I understand preamble

language may limit claim scope: (i) if dependence on a preamble phrase for antecedent basis indicates a reliance on both the preamble and claim body to define the claimed invention; (ii) if reference to the preamble is necessary to understand limitations or terms in the claim body; or (iii) if the preamble recites additional structure or steps that the specification identifies as important. I understand that such a determination should be made in the context of the specification and prosecution history of the patent application.

D. Burden of Proof

31. I have been informed that each claim of an issued patent is presumed to be valid. To overcome that presumption of validity, the party challenging the claim's validity must establish unpatentability by a preponderance of the evidence.

E. Anticipation

32. I have been informed that a patent challenger may contend that a patent claim is anticipated if someone else has already made the same invention. If an invention is not new, then the invention has been "anticipated" by the prior art. A claim is "anticipated" by the prior art if each and every limitation of the claim is disclosed in a single item of prior art.

33. I have also been informed that a prior art reference may disclose a claim feature expressly or inherently. I understand that something is inherent only if the missing descriptive feature must necessarily be present and would be recognized as

such by a person of ordinary skill in the art. I also understand that inherency cannot be established by possibilities, and that the fact that something may result from certain circumstances is not sufficient to show inherency.

34. I further understand that in order for a patent to be invalid by anticipation, a single prior art reference must describe every single element of the claimed invention, such that a person of ordinary skill in the art could practice the invention without undue experimentation.

F. Obviousness

35. I have been informed that a patent challenger may contend that a patent claim is invalid by arguing that it would have been obvious to a POSA at the time of the claimed invention. I understand that a claim is invalid for being obvious if, before the effective filing date, all the elements required by the Challenged Claim were known in the prior art, and one skilled in the art could have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to a POSA. I understand that obviousness should be evaluated over the prior art based on the claimed invention as a whole and from the perspective of a POSA as of the effective filing date. I have been informed that a finding of obviousness cannot be based on improper hindsight reasoning. That is, that a finding of obviousness must rely only on knowledge which was within the level of ordinary skill in the art at the

time the claimed invention was made, and that the reasoning must not rely on knowledge gleaned only from the patent's disclosure.

36. I further understand that an obviousness analysis includes consideration of the following factors: (1) the scope and content of the prior art; (2) the differences between the prior art and the Challenged Claims; (3) the level of ordinary skill in the pertinent art; and (4) additional considerations of objective indicia of non-obviousness.

37. I have been further informed that objective indicia of non-obviousness are considered when assessing whether an invention would have been obvious at the time of the invention, as a check against "hindsight bias"—the inclination after a problem has been solved to see the solution as obvious or predictable when it was not. I have been informed that objective indicia of non-obviousness may include: unexpected, surprising, or unusual results; substantially superior results; synergistic results; long-felt, but unmet, need; commercial success; copying by others; industry skepticism; and failure of others. I have also been informed and understand that there must be a connection or nexus between these additional factors and the scope of the claim language.

38. I understand that multiple prior art references may be combined to show that a Challenged Claim would have been obvious if a reason existed as of the earliest effective filing date that would have prompted a POSA to combine elements

taught in one or more prior art references in order to arrive at the alleged invention with a reasonable expectation of success. I understand that this requirement is referred to as "motivation to combine," "suggestion to combine," or "reason to combine," and there are several rationales that meet this requirement.

39. I understand that the motivation to combine prior art references can be found in the prior art references themselves or by the common sense of a POSA as of the earliest effective filing date. I further understand that market demand, rather than scientific literature, may provide a motivation to combine references.

40. I understand that to rely on a prior art reference in an obviousness analysis, the prior art reference must either be from the same field of endeavor as the alleged invention (even if it is directed to solving a different problem), or the reference must be particularly pertinent to the problem being solved by the alleged invention (even if it is not in the same field of endeavor). For example, I understand that obviousness includes applying known techniques, components, or additives to other systems, processes, or formulations to improve them in an expected or known way. Further, I understand that obviousness includes a predictable variation of a known technique even if the technique originated in another field of endeavor. I understand that design incentives and other market forces can prompt variations of known techniques, and predictable variations are not the product of innovation, but rather ordinary skill and common sense.

41. I understand that a combination of prior art elements may be obvious if it was obvious to try the combination. I understand that this may include recognizing a design need or market pressure to solve a problem when there are a finite number of predictable solutions, and that a POSA has a good reason to pursue the known options within his or her technical grasp if there is a reasonable expectation of success. However, I understand that it may not be obvious to try a combination of unpredictable technologies.

42. I understand that the obviousness analysis focuses on what was known or obvious to a POSA as of the earliest effective filing date. Therefore, I understand that an unmet need or known problem in the relevant field of endeavor may provide a reason to combine prior art elements in the same way as the alleged invention.

43. I understand that some exemplary rationales that can support a conclusion that a Challenged Claim would have been obvious, include:

(A) combining prior art elements according to known methods to yield predictable results;

(B) simply substituting one known element for another to obtain predictable results;

(C) using known techniques to improve similar devices (methods or products) in the same way;

(D) applying a known technique to a known device (method or product) ready for improvement to yield predictable results;

(E) choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success—in other words, whether something is "obvious to try;"

(F) using work in one field of endeavor to prompt variations of that work for use in either the same field or a different one based on design incentives or other market forces if the variations are predictable to one of ordinary skill in the art; and

(G) arriving at a claimed invention as a result of some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings.

44. I understand that the teachings combined from multiple prior art references need not fit perfectly together. Rather, I understand that obviousness analysis takes into account inferences, creative steps, common sense, and practical logic and applications that a POSA would employ under the circumstances.

45. I understand that when considering obviousness, one should consider whether a teaching, suggestion, or motivation in a prior art reference would lead a person of ordinary skill in the art to modify the reference or combine references. I

understand that this includes references that "teach away" from the invention, by leading a person of ordinary skill in a different direction from that taken by the patentee and would lead the person of skill to believe that the direction taken by the patentee was unsuitable.

46. I understand that in an obviousness analysis, secondary considerations may also refute a finding of obviousness. I understand that examples of secondary considerations include commercial success, industry praise, long-felt but unsolved needs, failure of others, and unexpected results. I understand that as long as these considerations are tied to the claimed features, a patent owner is entitled to a presumption of a nexus between the secondary considerations and the patent.

47. I further understand that in situations involving a new chemical compound, one must employ a "lead compound" analysis. I understand that a lead compound is defined as a compound in the prior art that would be most promising to modify in order to improve upon its activity and obtain a compound with better activity. I understand that a reason or motivation to select a compound as a lead compound must be based on prior art evidence, rather than mere structural similarity. I understand that it is improper to rely upon *ex post* reasoning to rely solely on structural similarity. I further understand that to support a finding of obviousness, a person of ordinary skill would need to be able to use the prior art to modify the lead compound with a reasonable expectation of success.

48. I am also informed that a basis to combine teachings need not be stated expressly in any prior art reference. However, I understand that there must be some evidence showing an articulated reasoning with rational underpinnings to support a motivation to combine teachings and to support the legal conclusion of obviousness.

49. In addition, I am informed and understand that in order to establish that an element of a claim is "inherent" in the disclosure of a prior art reference, or a combination of prior art references, it must be clear to one skilled in the art that the missing element is necessarily present in or the inevitable outcome of the process and/or thing that is explicitly described in the prior art. I understand that to establish inherency, it is not enough that a certain result or characteristic may occur or be present in the prior art, nor may inherency be established by probabilities or possibilities. I understand that the mere fact that a certain thing may result from a given set of circumstances is not sufficient to establish inherency. I understand that the claim limitation at issue must be the natural result of the combination of elements explicitly disclosed by the prior art. I understand that inherency must be established based on what is necessarily present in the prior art, not based on what would result due to optimization of conditions. Thus, a person of ordinary skill in the art would need to recognize that the disclosure of the prior art shows that the claim limitations necessarily would result from following the express disclosure of the prior art, as

opposed to showing that the limitation only might result from following the express disclosure of the prior art.

50. With regard to inherency, as applied to obviousness, I also understand that inherency cannot be applied to a claimed element that would have been unpredictable to a POSA. I also understand that evidence of unexpected results demonstrates that the result or effect of the claimed invention as a whole is not merely the predictable result of an inherent property.

51. I understand that when general conditions of a claim are disclosed in the prior art, it is not inventive to optimize or discover workable ranges by routine experimentation. I understand that if there is recognition in the prior art that a variable affects a relevant property or result, then the discovery of an optimal value or working ranges is obvious.

52. I further understand that for a claim to be found invalid based upon a motivation to combine or modify the teachings in the prior art, there must be a reasonable expectation of success to modify or combine those teachings in order to arrive at the claimed invention. I understand that the law only requires that a POSA would have had a reasonable expectation of success and not certain success in combining or modifying the prior art teachings as the claimed invention does.

G. Priority and Prior Art

53. I have been informed that in some circumstances, a patentee may have claimed priority to an earlier application filing date, the date of which is referred to as a "priority date."

54. I understand that references constituting "prior art" include information that was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention; or in a patent or patent application that names another inventor and was effectively filed before the effective filing date of the claimed invention.

55. Further, I have been informed that statements by a patent applicant or patentee, including statements in the patent that something is in the "prior art," can constitute prior art that can be used to anticipate or render obvious patent claims. That is, prior art can be created by admissions of the patent applicant or patentee.

56. I also understand that a POSA is presumed to have knowledge of the relevant prior art.

V. THE '885 PATENT

57. I have reviewed the '885 Patent, which was issued on February 6, 2018. Ex. 1001, 1. The cover of the '885 Patent indicates that the application that led to the issuance of the '885 Patent, U.S. Patent App. No. 13/261,029, was filed May 19,

2010 and that the ’885 Patent claims priority to U.S. Provisional Patent Application No. 61/216,491, which was filed on May 18, 2009. Id.

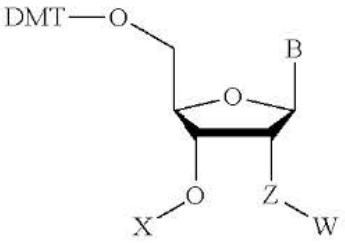
58. I have also reviewed the file history of the ’885 Patent, Ex. 1002, and understand the background and exchanges between the United States Patent and Trademark Office (“U.S.P.T.O.”) in the course of prosecuting the application that led to the issuance of the ’885 Patent. Id.

59. Based on the cover of the ’885 Patent, the ’885 Patent is titled: “Synthesis of Labile Base Protected-Modified Deoxy and Modified Ribo Nucleosides, Corresponding Phosphoramidites and Supports and their Use in High Purity Oligonucleotide Synthesis. Id.

60. The ’885 Patent has five claims, each of which is an independent claim, reproduced from the published copy of the ’885 Patent as follows (Ex. 1001, Cols. 25 and 26):

1. Derivatized nucleoside and phosphoramidite of general formula 1,

Formula 1



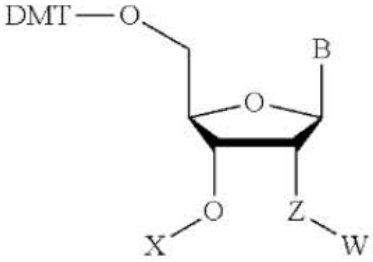
where B is selected from the group consisting of Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N-isobutyryl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl;

Z is Oxygen and W is methyl; and

X is cyanoethyl dialkyl phosphoramidite.

2. Derivatized nucleoside and phosphoramidite of general formula 1,

(Formula 1)



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

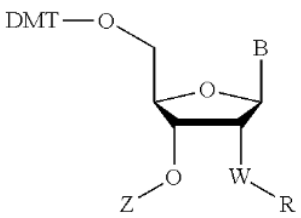
Z=ribo Fluoro or ara fluoro, and

W is absent; and

X is cyanoethyl dialkyl phosphoramidite.

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

(Formula 2)



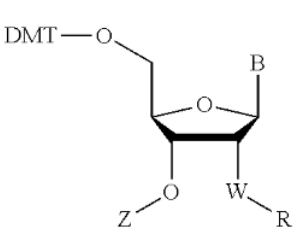
where B is Guanine-N-acetyl, or adenine-N-acetyl;

W=ribo fluoro or ara fluoro, and R is absent;

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

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

(Formula 2)



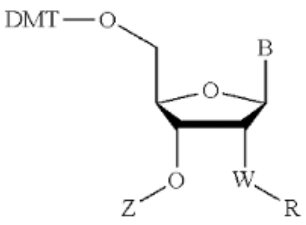
wherein, B is selected from the group consisting of Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N-isobutyryl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl;

W is Oxygen and R is selected from the group consisting of t-Butyldimethyl silyl, acetal levulinyl ester (ALE), pivaloyloxy, cyanoethylmethylene (CEM), dithiomethylene (DTM)); and

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

5. Derivatized nucleosides, succinates and supports of general formula 2,

(Formula 2)



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

W is Oxygen and R is methyl; and

Z is C(O)-M-C(O)—NH, where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl, and NH is C1-C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy.

61. I understand that several compounds are at issue in this case, which will be discussed throughout this declaration. I also understand that while Petitioner had the opportunity to challenge all of the compounds in the subject Markush groups of Claims 1-5, Petitioner only challenged one compound per claim, i.e.,

a. "B" as cytosine-N-acetyl for Claim 1;

b. "B" as guanine-N-acetyl and "Z" as ribo fluoro for Claims 2 and 3;

c. "B" as guanine-N-acetyl and "R" as t-Butyldimethylsilyl for Claim 4; and

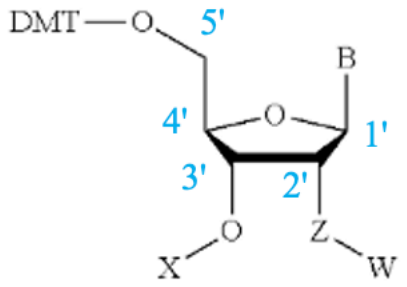
d. "B" as cytosine-N-isobutyryl for Claim 5.

Pet., 23, 30, 39, 41, 48, and 52.

62. I will highlight a few of the compounds of interest in connection with Claims 2 and 3 of the ’885 Patent, relating to Grounds II, III, and IV.

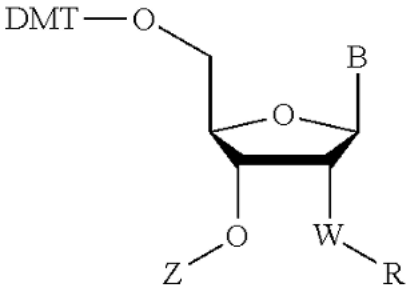
63. For example, as shown below, the Markush groups of Claims 2 and 3 cover phosphoramidites and succinates that features fluoro (F) at the 2'-position of the sugar ring and acetyl at the N2-position of the guanine base (hereinafter “N2-Acetyl-2’-F-2’-deoxyG”). The Claim 2 phosphoramidite where “Z” is ribo fluoro and “B” is guanine-N-acetyl is provided as follows:[2]

[2] The 1', 2', 3', 4' and 5' annotations are provided to denote the corresponding positions of carbon on the sugar ring of Formula 1 and this nomenclature will be used throughout this declaration when referring to the sugar rings of other nucleosides as well.

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

Ex. 1001, 25:44-64.

64. Similarly, the corresponding Claim 3 succinate where "W" is ribo fluoro and "B" is guanine-N-acetyl is provided as follows:

3. Derivatized nucleosides, succinates and solid supports of general formula 2,
(Formula 2) 
where B is **Guanine-N-acetyl**, or adenine-N-acetyl;
W=**ribo fluoro** or ara fluoro,
and R is absent;
Z is C(O)-M-C(O)—NH,
where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl,
and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1-C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy.

Id., 25:64-26:18. My opinions relating to Petitioners grounds for these compounds, and the other challenges compounds, are set forth as follows.

VI. STATE OF THE ART

A. The Petition and Dr. Baran's Declaration Oversimplify the Highly Complex and Unpredictable Chemistry Involved in Synthesizing Nucleosides, Phosphoramidites and Oligonucleotides Via P(III) Chemistry

65. While the Petition and Dr. Baran's Declaration cover certain aspects of the history of SPOS in its Petition, in my opinion, it does not describe how complex and inherently unpredictable this science was in the 2009 timeframe (and is today), and the chemistry involved in this exceedingly specialized field is by no means "simple" or "trivial," as the Petition and Dr. Baran's Declaration have portrayed it to be. Pet., 36.

66. On the contrary, as discussed by pioneers such as Serge L. Beaucage, synthetic chemists have faced a tremendous amount of adversity in developing SPOS over the decades. *See*, *e.g.*, Ex. 1007, 2223 (describing the hard-fought advancements relating to formation of internucleotide linkages, protection of the phosphate function, 5'-hydroxy function of nucleosides, nucleobases, and 2'-hydroxy function of ribonucleosides); 2223-33 (describing challenges relating to swelling of polystyrene solid supports, instabilities in succinate linkage between the oligonucleotide and solid support, and other challenges); 2233-42 (describing adversities relating to depurination of N2-isobutyryl 2'-deoxyguanosine under the acidic conditions required for the deblocking of the 5'-O-DMTr group); 2249-59 (describing challenges relating to developing proper nucleobase protecting groups and conditions to deprotect those groups safely during SPOS); and at 2259-93 (describing long coupling times and unpredictable reactions and strand cleavage

caused by, *inter alia*, O2'-protecting groups being too sterically hindered, and harsh deprotection conditions following SPOS).

67. In my opinion, while many hurdles have been overcome, and skilled artisans in this space have stood, and continue to stand, on the shoulders of giants, this science is still developing and inherently unpredictable, and that was certainly the case in the 2009 timeframe when the inventors of the ’885 Patent developed structures claimed in Claims 1-5. Then, and now, the syntheses of such structures and related oligonucleotides involve meticulous development, planning and execution of complex, multi-step synthetic routes, all subject to unpredictable outcomes and risk of failure, designed to produce high-quality, stable nucleoside phosphoramidite reagents for use in SPOS to produce oligonucleotides of correct identity with high purity and optimum yield.

68. In my opinion, synthetic routes for phosphoramidites, e.g., often include introduction of a diverse array of chemical reagents designed to transform a starting compound into a new compound (also called a synthetic intermediate), and in succeeding steps, a different array of chemical reagents are added to transform the newly created compound in the prior step into yet another new compound and so on. Phosphoramidite synthesis can involve in the range of 5, 10, 20 or more synthetic steps to attempt to reach the desired compound, and each step, requires carefully selected and controlled reaction conditions to successfully produce the desired

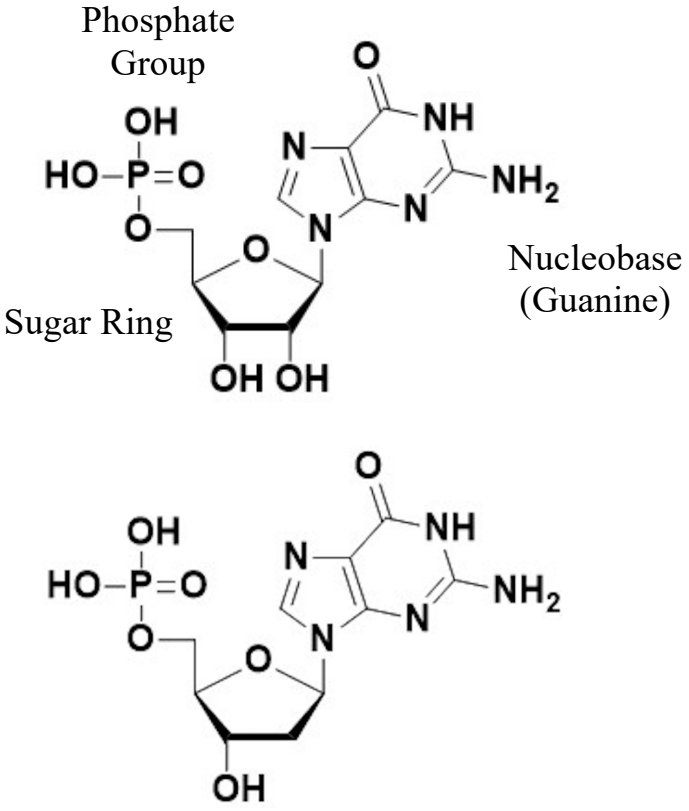
product. High levels of unpredictability exist at many of these stages, and even minor changes in either the molecular structure of a substrate or reagent, or in the reaction conditions, can trigger undesirable and unforeseen reactions and cause the planned synthetic transformations to fail.

69. Furthermore, in the event a novel phosphoramidite is successfully synthesized, it may still not be useful as a reagent in SPOS to synthesize an oligonucleotide. For example, a phosphoramidite may display low or no coupling efficiency during SPOS, a protecting group masking a reactive center may be prematurely removed resulting in undesirable production of branched or damaged oligonucleotides, or the resulting nucleotide monomer may be insoluble or unstable during the SPOS and/or deprotection conditions. Therefore, there are considerable variables and uncertainty in this work, and as highlighted above, skilled artisans in this space have experienced major challenges over the decades with SPOS, and continue to today.

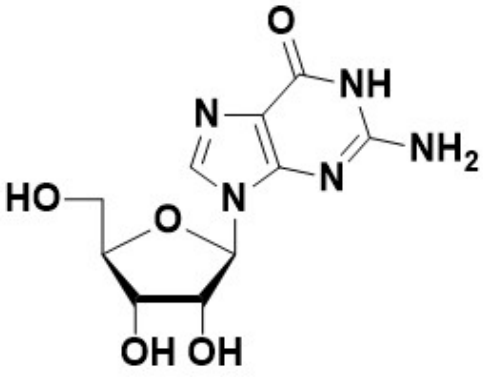
70. Accordingly, in my opinion, the statements in the Petition that a POSA would have found it "simple" or "trivial" to achieve the claimed inventions greatly oversimplifies the complexity of the synthetic chemistry involved and the challenges that a POSA would have faced over 14 years ago in the 2009 timeframe.

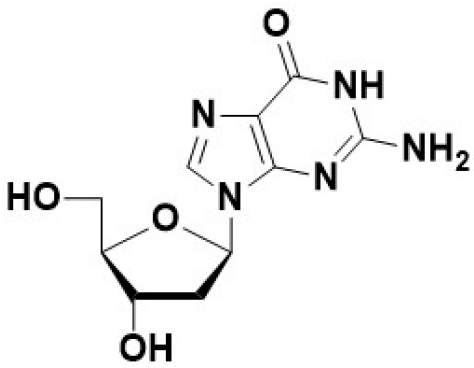
B. Overview of the Relevant Technology and Summary of Key Terminology Used in this Response

71. **Nucleotides**. Nucleo**t**ides 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"), thymine ("T"), cytosine ("C"), or guanine ("G") for DNA; and A, C, G, or uracil ("U")) for RNA). Two exemplary nucleotides, for RNA (2'-OH) and DNA (2'-H), having a guanine nucleobase, are shown as follows:

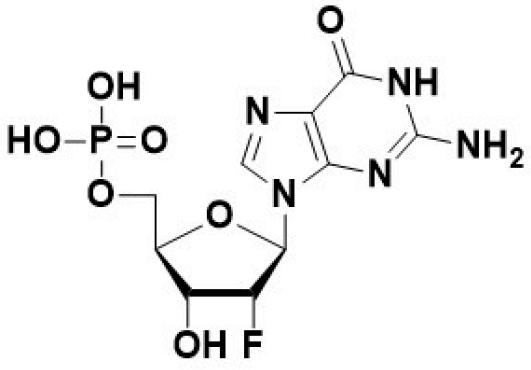


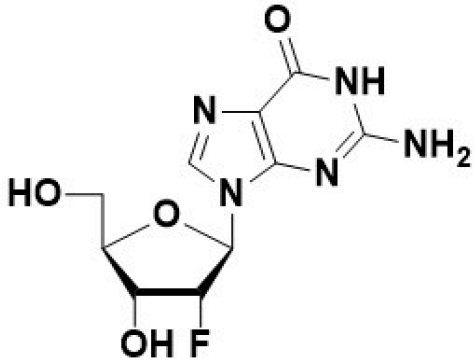
72. **Nucleosides.** Nucleo**s**ides are nucleo**t**ides without a phosphate group; two exemplary nucleosides having a guanine nucleobase, referred to as guanosine (2'-OH) and 2'-deoxyguanosine (2'-H) are shown as follows:





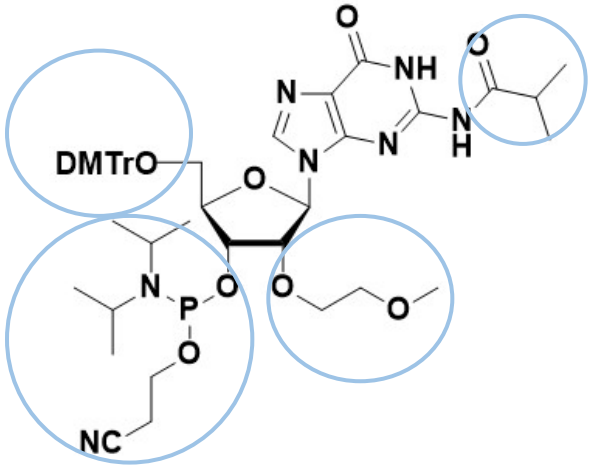
73. **2'-Fluoro Nucleotides and Nucleosides.** Importantly, a ribonucleic acid ("RNA") nucleotide has a hydroxyl (-OH) group at the 2'-position, and a deoxyribonucleic acid ("DNA") nucleotide has a hydrogen (-H), at the corresponding 2'-position. Both "modified" RNA and DNA sequences can have nucleotides with non-naturally occurring groups, like fluoro, at, e.g., the 2'-position, making 2'-fluoro-2'-deoxyribonucleotides and nucleosides versatile compounds for SPOS (2'-fluoro-2'-deoxyguanosine nucleotide shown on the left, and 2'-fluoro-2'-deoxyguanosine nucleoside shown on the right):





74. **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; an exemplary modified guanosine phosphoramidite is shown as follows:



75. 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.

76. Phosphoramidites can have a wide range of groups on the 2'-, 3'-, and 5'-positions of the sugar ring (here shown as methoxyethyl (MOE)) at the 2'-position, N,N-diisopropylamino-2-cyanoethoxyphosphinyl at the 3'-position, and 4,4-dimethoxytrityl (DMTr) at the 5'-position) and on the exocyclic amines ($-NH_2$) of the nucleobase (here shown as N2-isobutyryl-protected guanine).

77. Every position on the sugar ring can be additionally modified, such as the 2'-position which can have, e.g., a fluoro, methoxy, MOE, or other groups which

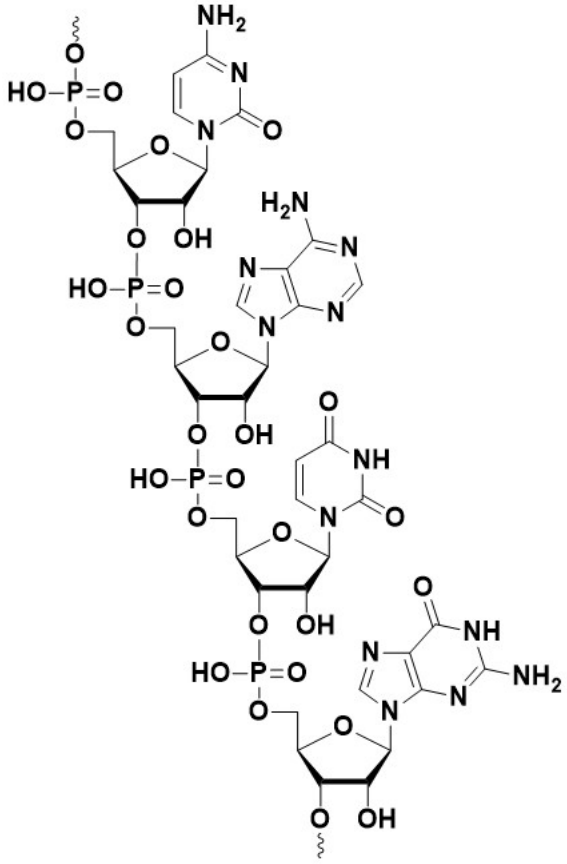
do not require protecting groups. For ***RNA synthesis***, the ribonucleotide will have a hydroxyl group (-OH) at the 2'-position, which, because of its reactivity during SPOS, must be protected with groups such as t-butyldimethyl silyl (TBDMS), acetal levulinyl ester (ALE), pivaloyloxy, cyanoethylmethylene (CEM), dithiomethylene (DTM), or (triisopropylsilyl)oxy-methyl (TOM). Most nucleobases (e.g., A, C, G) typically require the use of protecting groups for successful use in conventional SPOS, such as N2-isobutyryl-G, and phosphoramidites can feature non-canonical nucleobases and chemically modified nucleobases such as 5-methylcytosine.

78. In my opinion, 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 in the 2009 timeframe.

79. **Oligonucleotides**. Oligonucleotides are short polymeric single strands of nucleotides. DNA-based oligonucleotides are referred to as "oligo***deoxy***nucleotides" or "oligo***deoxyribo***nucleotides" and RNA-based oligonucleotides are referred to as "oligo***ribo***nucleotides," with RNAs having (-OH) at the 2'-position and DNAs having only (-H) (hence, the term "deoxy," or without oxygen).

80. Oligonucleotides vary in length and sequences and can be comprised of tens or hundreds of nucleotides as compared to DNA and RNA that can be strands

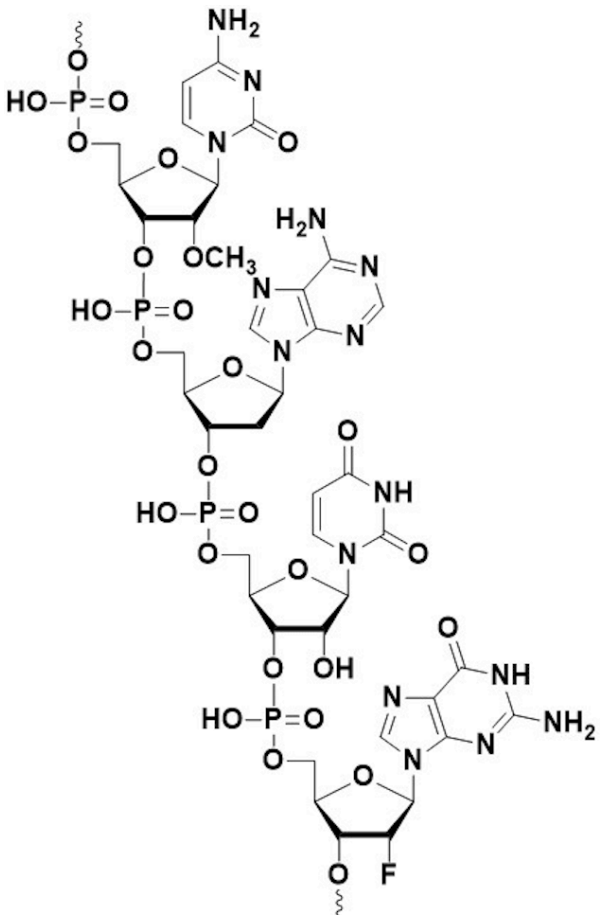
of millions of nucleotides. Following is a depiction of an oligoribonucleotide (i.e., RNA-based oligo):



81. The umbrella term "oligonucleotide" or "oligo" encompasses oligodeoxyribonucleotides (for DNA), oligoribonucleotides (for RNA), and "chimeric oligonucleotides" explained below. The first nucleotide in an oligonucleotide is typically attached via its 3'-position to a solid support through utilization of a succinyl and long chain amino alkyl (LCAA) linker. A POSA would have understood that "long chain spacers" and "lcaa" or "LCAA" spacers were commonly used spacers in solid phase oligonucleotide synthesis in which the long chain alkyl functions act as a spacer attaching an "amine" group (i.e., -NH-) to the

support. Long chain spacers of various lengths were commonly used in solid phase oligonucleotide synthesis including the ones illustrated in Ex. 1005, 3186, Fig. 1 (C3 alkyl spacer); Ex. 1007, 2228 (compound 35 showing a C3 alkyl spacer), Ex. 1014, 892 (compound 1a has R3 with a LCAA spacer), Ex. 1022, 5435, 5440 (using LCAA-CPG from CPG Inc., NJ), Ex. 2031, 3.1.5 ("This spacer can be as simple as a single methylene group (e.g., aminomethyl polystyrene) or it can be a lengthy alkyl or alkyloxy chain (e.g., long-chain alkylamine CPG"), p. 3.1.6 in Fig. 3.1.3 (showing LCAA spacer), Fig. 3.1.9 (showing a polyethylene glycol linker (H), and a combination of alkyl and ethyleneglycoxy (L)).

82. **Chimeric Oligonucleotides**. Chimeric oligonucleotides are oligonucleotides that feature 2 or more different types of nucleotides; following is a depiction of a "chimeric" oligonucleotide having four different types of nucleotides:



83. This exemplary chimeric oligonucleotide shows, starting from top to bottom, 2'-OMe-C (or 2'-O-Methylcytidine); 2'-deoxyadenosine (DNA); uridine (RNA); and 2'-fluoro-2'-deoxyguanosine. Chimeric oligonucleotides can have near limitless ranges of design and applicability, and non-natural nucleotides with, e.g., 2' groups like fluoro, can be used for synthesizing modified RNAs, DNAs, or oligonucleotides completely comprised of non-naturally occurring nucleotides (e.g., only having 2'-fluoro-2'-deoxyribonucleotides).

VII. CLAIM CONSTRUCTION

84. I agree with Dr. Baran that a POSA would have recognized that there were clear errors in Claims 3-5 of the '885 Patent. Specifically, I agree that a POSA would have understood "M" should be "ethyl" in Claims 3-5 and that the last clause in Claim 5 should be "and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1-C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy." Pet., 17-20.

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

85. I do not agree with Petitioner's and Dr. Baran's definition of a person of ordinary skill in the art ("POSA"), i.e., that a POSA would have had a Ph.D. in "organic or ***medicinal chemistry*** and 2 to 3 years of post-graduate work experience in ***medicinal chemistry***, synthetic organic chemistry, ***and*** nucleic acid chemistry, including the development of oligonucleotide ***therapeutics***, ***diagnostics*** or building blocks." Pet., 17 (emphasis added).

86. 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 has authored in his career relate to oligonucleotide synthesis, and the earliest of those papers is dated just 5 years ago. Ex. 2009, 75:22-24; 73:21-23; 97:23-98:1; 99:15-100:7 Furthermore, the focus of the most prominent of those papers appears to be on ***P(V) chemistry*** which, as Dr. Baran acknowledged, is a fundamentally

different synthesis platform than the P(III) chemistry at bar. *Id.*, 109:4-6 ("Q. But the focus of this paper [Ex. 2001] is on P(V)? A. the focus of this paper is awakening people to the difference between P(V) and P(III)."); Ex. 2010, 1 (Dr. Baran and the other authors describing "P(V)-based reagent platforms" as "as a fundamentally different approach" as compared to "phosphorus(III) [P(III)]-based reagent systems.").

87. I am, and was in the 2009 timeframe, highly skilled in developing synthesis schemes and directing the synthesis of nucleosides, nucleotides, and nucleic acids pursuant to P(III) chemistry, including, but not limited to, the synthesis of oligonucleotides through solid phase oligonucleotide synthesis ("SPOS"), and I am and was familiar with the level of skill of a POSA in the 2009 timeframe.

88. In my opinion, skilled artisans in the 2009 timeframe who developed synthetic schemes for (e.g., as discussed above), and who managed 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 whether the compounds claimed in the '885 Patent would have been obvious in the 2009 timeframe, including knowledge, skills, motivations and reasonable expectations.

89. In contrast, in my opinion, 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 managing or conducting the syntheses of, nucleosides, phosphoramidites or oligonucleotides pursuant to P(III) chemistry, are not as applicable to the central inquiries at bar, since the Claims in the '885 Patent are directed to nucleoside and phosphoramidite compounds themselves based on P(III) chemistry and not their therapeutic and diagnostic uses. Pet., 12; Ex. 2009, 93:14-94:5.

90. Accordingly, I propose the following alternative definition for a POSA, shown as redline changes to the definition that Petitioner and Dr. Baran proposed:

> As of May 18, 2009, a person of ordinary skill in the art ("POSA") would have had a Ph.D. (or equivalent degree) in organic ~~or medicinal~~ chemistry, and 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 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~~.

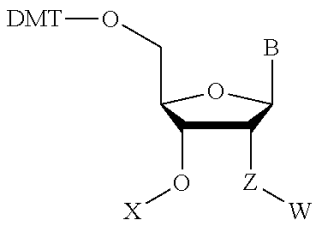
91. This definition, in my opinion, would not exclude medicinal or other chemists so long as the chemist in question met the above requirements. My opinions set forth in this declaration remain the same under either Petitioner's or the definition that I provided above for the level of skill.

IX. OPINIONS

A. Ground I: The Compounds of Substitute Claim 6 are Not Disclosed by the Prior Art.

92. In my opinion, the substitute Claim 6 as provided in Patent Owner's Motion to Amend, that removes "B" as "cytosine-N-acetyl" from Claim 1's Markush group, based upon the 5,808,039 patent ("Reddy") (Ex. 1016), is not disclosed by the prior art based on the reasons stated below.

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



Formula 1

where B is selected from the group consisting of Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-isobutyryl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl; Z is Oxygen and W is methyl; and X is cyanoethyl dialkyl phosphoramidite. The references cited in the Petition and Dr. Baran's Declaration do not disclose these limitations.

94. Petitioner and Dr. Baran cite to Reddy (Ex. 1016) as anticipating claim 1 because Reddy discloses a phosphoramidite molecule where the substituent group at the 1' position ("B") is cytosine-N-acetyl.

95. The Institution Decision stated that "Reddy expressly discloses and depicts the identical compound recited by challenged claim 1 in which 'B' is cytosine-N-acetyl and 'X' is 2-cyanoethyl N,N-diisopropyl phosphoramidite." Paper 7 at 17.

96. In my opinion, Substitute Claim 6 limits "B" such that it excludes "cytosine-N-acetyl" from the group "consisting of Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-isobutyryl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl." Reddy does not disclose a phosphoramidite group with any of the "B" species recited in Substitute Claim 6 and therefore does not disclose the compounds that are claimed in Substitute Claim 6.

97. It is my further opinion that Reddy does not disclose or suggest any phosphoramidites having a group at the "B" position other than cytosine-N-acetyl.

All of the compounds disclosed in Reddy have cytosine-N-acetyl at the "B" position (or a cytosine as in the starting material in Scheme I).

98. Reddy also does not, in my opinion, disclose or suggest modifying the group at the "B" position at all. Nothing in Reddy alone or in combination with any of the other references of record or references known to Patent Owner, which are encompassed by the materials that I have considered in preparing my opinions, would have provided a POSA with a reason or motivation to modify the "B" group of Reddy with a reasonable expectation of success.

B. Ground II: Claim 2 is not Obvious in View of the '031 Patent, Pitsch and Fan

1. A POSA Would Not Have Selected Compound x Disclosed in the '031 Patent as a Lead Compound in Any Event

99. I understand and have been advised that for new chemical compounds, courts consider whether the subject compound would have been obvious over prior art compounds pursuant to a "lead compound" analysis that applies the following two-part inquiry: (1) whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts, and (2) whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success.

100. The Petition and Dr. Baran's Declaration provide the following statement ostensibly to support why a POSA would have selected the compound listed in step "x" of Example 4-d from the '031 Patent ("Compound x") as a lead compound:

> Since the advent of phosphoramidite chemistry in oligonucleotide synthesis in the 1980s, a POSA would have recognized that the purpose of the above phosphoramidite was to serve as a building block for incorporating a guanine base into a growing oligonucleotide chain through automated SPOS, as illustrated above in Figures 5 and 6.

Pet., 33.

101. Based on a review of the record, Petitioner makes 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.

102. It is my opinion that a POSA would have known that the '031 Patent discloses over 50 nucleosides and over 40 different general oligonucleotide structures, and that it does not disclose any data showing Compound x being used as a reagent to incorporate 2'-fluoro-2'-deoxyguanosine monomers into any oligonucleotides. Ex. 1017, Col. 1-51. This was also confirmed by Dr. Baran during his deposition. Ex. 2009, 137:4-7 ("Q. Figure 1 shows 6 oligos; correct? A. Correct.

Q. None of this data relates to 2 prime fluoromonomers; correct? A. The data on this figure, I don't see it explicitly shown with the fluorine").

103. I also understand in determining whether a chemist would have selected a prior art compound as a lead, courts will consider evidence of the compound's pertinent properties, such as activity and potency, and other relevant characteristics in evidence, and absent a reason or motivation based on such prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection.

104. Neither the Petition nor Dr. Baran's Declaration discuss any of Compound x's properties, other than its being a phosphoramidite that can be used to build an oligonucleotide, and nothing in the '031 Patent would have provided a POSA with a reason or motivation to modify Compound x to improve upon its base deprotection rate. As Dr. Baran admitted, the '031 Patent does not disclose any base deprotection rates for Compound x. Ex. 1017; Ex. 2009, 145:5-146:4 ("what we don't know is what the absolute rate was").

105. In my opinion, if a POSA were to select any compound from the '031 Patent as a lead compound, a POSA would have selected the chimeric phosphorothioate oligoribonucleotides of the general structure: "[2'-OMe]-[RNA]-[2'-OMe]," discussed in Example 8, and 22-25 of the '031 Patent, which uses the phosphoramidites disclosed in Example 1 of the '031 Patent "2'-O-Methyl

nucleoside amidites" and "2'-OH (blocked as 2'-t-butyldimethylsilyl derivative) nucleoside amidites," which are ***not*** 2'-fluoro phosphoramidites like Compound x. Ex. 1017, 17:25-53. Those 2'-O-Methyl and 2'-OH compounds are the only ones that the '031 Patent provided data for, but no data was provided for Compound x.

106. Therefore, in my opinion, based on the above, a POSA would not have had a reason or motivation to select Compound x from the compounds disclosed in the '031 Patent or the "panoply of known" nucleosides or phosphoramidites in the prior art as "a natural choice for further development efforts" to improve upon its base deprotection rates or other activity, and Petitioner and Dr. Baran have instead used hindsight in selecting Compound x.

2. A POSA Would Not Have Been Motivated by Pitsch or Fan to Use Acetyl as a Protecting Group for Guanine on Compound x of the '031 Patent

i. A POSA Would Have Known That the Prior Art Taught Away from Using an Acetyl Group to Protect the N2-position of 2'-Deoxyguanosine and Neither Pitsch Nor Fan Would Have Motivated a POSA to Switch to an N2-Acetyl Group for Compound x

107. In my opinion, a POSA would have known that, long before Pitsch and Fan, oligonucleotide synthesis pioneers had attempted to use acetyl to protect the N2-position of the guanine nucleobase in nucleosides and nucleotides, but turned away from that approach for sound scientific reasons. Ex. 2011, 221. Specifically, a POSA would have known very well that Nobel Laureate Har Gobind Khorana

established that acetyl groups were not suitable to protect the N2-position of the guanine nucleobase in nucleosides and nucleotides due to the demonstrated instability of N2-acetyl groups under basic conditions, and that isobutyryl groups were superior.

> The N-acetyl group was introduced some years ago … and it has been used in all the synthetic work reported so far, ***but its disappearance to a significant extent during the course of synthetic and isolation procedures has repeatedly been observed*** … In view of the extended nature of the present task, the use of an alternative group was highly desirable … [Further investigation] showed the ***N-isobutyryl group to be considerably more stable than the N-acetyl group*** and this group has been used for the protection of all the deoxyguanosine residues in the present work …

Ex. 2011, 221 (emphasis added).

108. It is my opinion that based on these findings alone, a POSA in the 2009 timeframe would have been discouraged from using acetyl groups to protect the N2-position of the guanine nucleobase in nucleosides and nucleotides as the reference by Dr. Khorana explicitly taught away from that approach.

109. It is my further opinion that following Dr. Khorana's discovery, isobutyryl and a range of other base protecting groups, were used in the field to protect the N2-position of guanine nucleobases, but acetyl was not one of those groups, as evidenced by the breadth of literature spanning the following decades.

See, *e.g.*, Ex. 2011 (1972), 221 (describing acetyl as not stable for protecting the N2-position of 2'-deoxyguanosine derivatives and isobutyryl is used instead); Ex. 2020 (1972), 252 (same); Ex. 2017 (1981), 365 (describing numerous protecting groups for the N2-position of 2'-deoxyguanosine derivatives including isobutyryl, but not acetyl); Ex. 2021 (1986), 2047 (describing numerous protecting groups for the N2-position of 2'-deoxyguanosine derivatives including isobutyryl, but not acetyl); Ex. 2013 (1987), 401 (describing the use of phenoxyacetyl as a protecting group for the N2-position of 2'-deoxyguanosine derivatives, but not acetyl); Ex. 1007 (1991), 2256-58 (describing numerous protecting groups for the N2-position of guanine of nucleosides/nucleotides including isobutyryl, but not acetyl); Ex. 2018 (1993), 13-14 (describing the use of *t*-butylphenoxyacetyl as a protecting group for the N2-position of guanine of nucleosides/nucleotides over phenoxyacetyl, but not acetyl); Ex. 2016 (2001), 2.1.13 (describing isobutyryl as a "particularly valuable" protecting group for the N2-position of the guanine nucleobase in oligonucleotide synthesis, and listed numerous other N2-protecting groups, but not acetyl); Ex. 2019 (2004), 2.10.1 (identifying isobutyryl as a "standard" base protecting group for the N2-position of guanosine derivatives, but not acetyl); Ex.2023 (2008), 82 (identifying isobutyryl and PAC as a "standard" protecting groups for the N2-position of 2'-deoxyguanosine derivatives, but not acetyl).

110. In my opinion, even after the filing of the applications that led to the issuance of the ’885 Patent, experts in the field still regarded isobutyryl, but not acetyl, as a standard base protecting group for the N2-position of the guanine nucleobase. Ex. 2006 (2013), 327 (“Khorana et al. introduced protecting groups for the nucleosidyl exocyclic amines that are ***known today as standard protecting groups: isobutyryl (iBu) for guanosine***, and benzoyl (Bz) for adenosine and cytidine. Although others exist, ***these groups are those most commonly used***, with the possible exception of acetyl-protected cytidine, which is more readily and cleanly removed compared with Bz (Figure 1).”) (emphasis added); Ex. 2022 (2017), 2.1.22 (identifying isobutyryl as a ”popular” and “efficient” protecting group for the N2-position of guanine of nucleosides/nucleotides, but not acetyl). Dr. Baran acknowledged this during his deposition. Ex. 2009, 156:13-16 (“Okay. So is it fair to say that the standard protecting group for guanosine in the 2013 time frame was isobutyryl? A. For most applications, isobutyryl is fine.”).

111. A POSA would have therefore understood, in my opinion, that the deep-rooted scientific literature taught away from using acetyl groups to protect the N2-position of guanine of nucleosides/nucleotides like Compound x, and would not have been motivated by Pitsch and Fan which did not study 2'-fluoro-2'-deoxyribonucleosides like Compound x.

ii. A POSA Would Not Have Been Motivated to Switch from an Isobutyryl Group to an Acetyl Group to Protect the N2-Position of Guanine on Compound x Because Doing so Would Have Made Compound x Less Soluble in Organic Solvents

112. It is my opinion that a POSA would have considered solubility of nucleosides in organic solvents as critical during the synthesis of nucleosides and during SPOS. That is because numerous organic solvents are used, e.g., to solubilize nucleoside derivatives while transforming them into phosphoramidites, and to solubilize phosphoramidites for SPOS, and should a molecule have solubility problems during any of these reactions, or during purification of reaction mixtures, it would "drop like a rock" (i.e., precipitate) in the solution and cause catastrophic failure to the subject synthesis scheme. *Id*.

113. A POSA would have readily understood nucleosides with guanine moieties were notoriously insoluble in organic solvents and that lipophilic base protecting groups like isobutyryl or *tert*-butylphenoxyacetyl to protect the N2-position of nucleosides with guanine moieties would have enhanced the nucleoside's solubility. Ex. 2018, 14 ("Problems associated with solubility of deoxyguanosine-phosphoramidites using other labile N-protecting groups are eliminated with the use of the more lipophilic t-butylphenoxyacetyl groups.").

114. My opinion is that a POSA would have known that acetyl groups would have made nucleoside derivatives ***less soluble*** in organic solvents than isobutyryl

groups when used to protect the N2-position of the guanine of nucleosides/nucleotides. That is because acetyl groups are smaller, more polar groups, than isobutyryl groups and therefore less hydrophobic and less apt to solubilize nucleosides with guanine moieties, as Dr. Baran confirmed. Ex. 2009, 175:25-176:6 ("Q. And isobutyryl is more hydrophobic—isobutyryl group is more hydrophobic than an acetyl group; right? A. I would expect that to be the case, yes. Q. So an acetyl group is more polar than an isobutyryl group? That would be my expectation, yes.").

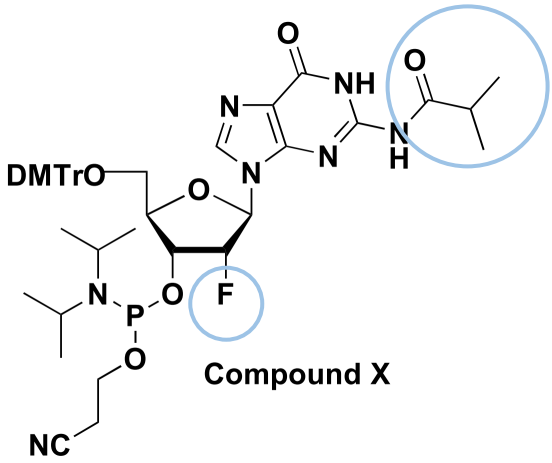
115. It is my opinion that a POSA would have understood that the literature demonstrated that adding acetyl to (i.e., acetylation of) 2'-deoxyguanosine caused solubility problems. Ex. 2012, 3822-26 (stating that "[a]cetylation of deoxyguanosine so as to prepare N,3',5'-triacetyldeoxyguanosine did not proceed satisfactorily … A part of the cause of failure to accomplish N-acetylation could be due to the insolubility of 3',5'-di-O-acetylguanosine which separates from the reaction mixture. … The lack of N-acetylation was probably due to the insolubility of 3',5'-di-O-acetylguanosine in the solvent. … In a parallel experiment benzoylation with [more lipophilic] benzoyl chloride did cause N-benzoylation as clearly shown ….").

116. In my opinion, a POSA would therefore not have been motivated to use acetyl over isobutyryl for Compound x which would have made Compound x ***less soluble*** in organic solvents.

iii. A POSA Would Not Have Been Motivated by Pitsch and Fan Which Did Not Study 2'-Deoxynucleosides or 2'-Deoxynucleotides and Would Have Produced Completely Different Oligonucleotides Than Produced By Compound x

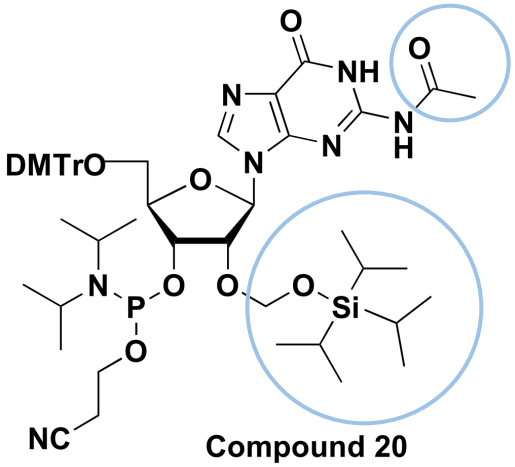
a. Pitsch and Fan Did Not Study 2'-fluoro-2'-deoxynucleosides Like Compound x Which Involved Known Degradation Issues When Used to Make Chimeric Oligonucleotides

117. A POSA would have known that Compound x from the '031 Patent, as shown below, was a phosphoramidite that had a fluoro (F) at its 2'-position and an isobutyryl group bound to the N2-position of guanine. Ex. 1017, 25:33-59.



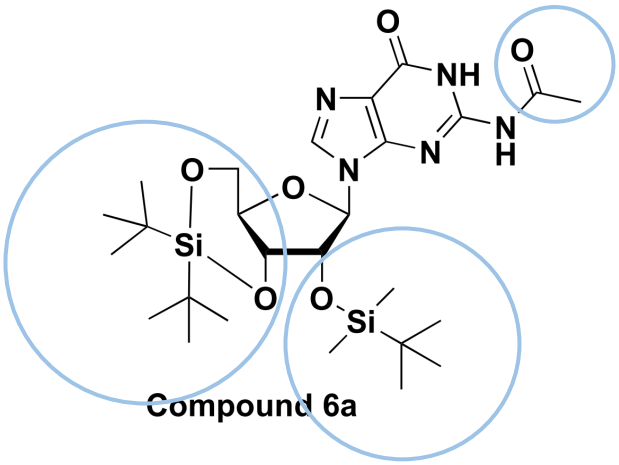
118. A POSA would have also understood that compound 20 from Pitsch ("Compound 20"), shown below, had an O2'-(triisopropylsilyl)oxy-methyl group, or

"TOM" group at its 2'-position (***not fluoro***) and an acetyl group bound to the N2-guanine. Ex. 1018, 3775 (Scheme 1).



Compound 20

119. A POSA would have further understood that compound 6a from Fan ("Compound 6a"), shown below, was a nucleoside derivative (not a phosphoramidite) that could not have even been used during SPOS unless transformed into a phosphoramidite (which is not described in Fan), and that had (1) *tert*-butyldimethylsilyl (interchangeably denoted as "TBS" or "TBDMS") to protect the hydroxyl (-OH) group at the 2'-position (***not fluoro***); and (2) 3',5'-*O*-di-*tert*-butylsilylene to protect the hydroxyl (-OH) groups at the 3'- and 5'- positions and an acetyl group bound to the N2-guanine. Ex. 1019, 2556.



Compound 6a

120. Therefore, a POSA would have understood that Pitsch and Fan did not teach 2'-deoxyribonucleotides (i.e., nucleotides lacking an (-OH) group at the 2'-position), yet alone, 2'-fluoro-2'-deoxyribonucleotides (i.e., nucleotides lacking an OH group at the 2'-position but having a 2'-fluoro substituent like Compound x), and instead only taught nucleosides with (-OH) at the 2'-position protected by TOM or TBDMS.

121. A POSA would have also known that in the 2009 timeframe a persistent problem existed with at least 2'-fluoro-2'-deoxyribonucleotides where oligonucleotides with those monomers would degrade. Ex. 2024, 83 (book chapter by Nanda D. Sinha et. al. stating that the 2'-F modification of chimeric oligonucleotides "is subject to depyrimidation [] especially with methylamine or ammonia/methylamine deprotection…"); Ex. 2025, 833 (observing "significant degradation of the 2'-deoxy-2'-fluorpyrimidine nucleosides" while under "the usual oligonucleotide deprotection conditions (concentrated NH_4OH, 55°C)"). A POSA would have also known that Pitsch discloses using methylamine (in ethanol and

water) and Fan uses methylamine (in ethanol and methylene chloride), i.e., the reagents that Ex 2024 identifies as causing damage. Ex., 1018, 3778. Ex. 1019, 2556.

122. Accordingly, in my opinion, a POSA would have recognized that the unique challenges associated with oligonucleotides with 2'-fluoro nucleotides would not have been resolved by the fundamentally different studies described in Pitsch and Fan, and would therefore not have been motivated by those references.

b. A POSA Would Have Understood That Pitsch and Fan Were Focused on RNA Which Would Not Have Been Applicable to a Study of 2'-fluoro-2'-deoxynucleoside for Use in Modified Oligonucleotides Like Compound x

123. A POSA would have also understood that the nucleosides and phosphoramidites disclosed in Pitsch and Fan would have been used for synthesis of unmodified RNAs (i.e., with (-OH) at the 2'-position), not modified oligonucleotides produced using Compound x having 2'-fluoro-2'-deoxynucleotides.

124. Below are illustrations of solid-support-bound oligonucleotides produced from Compound 20 (Fig. 1.a.) and a hypothetical phosphoramidite analogue of Compound 6a (Fig. 1.b.), showing each with acetyl at the N2-position of guanine and their different O2'-protecting groups (i.e., TOM and TBDMS) prior to base deprotection.[3]

[3] "Pg" in Fig. 1 is an abbreviation for "protecting group."

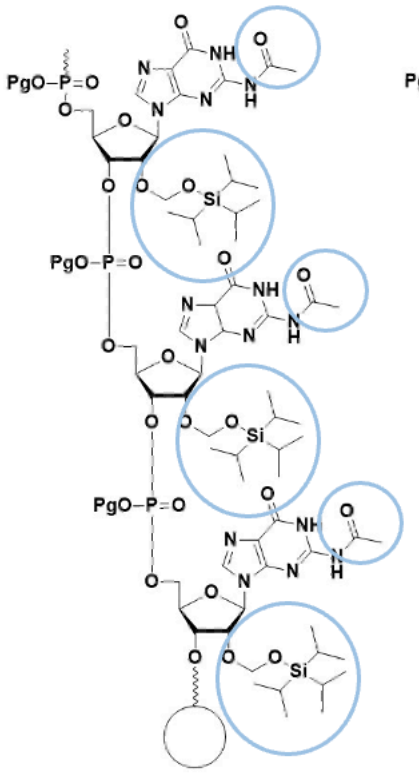


Fig. 1.a.

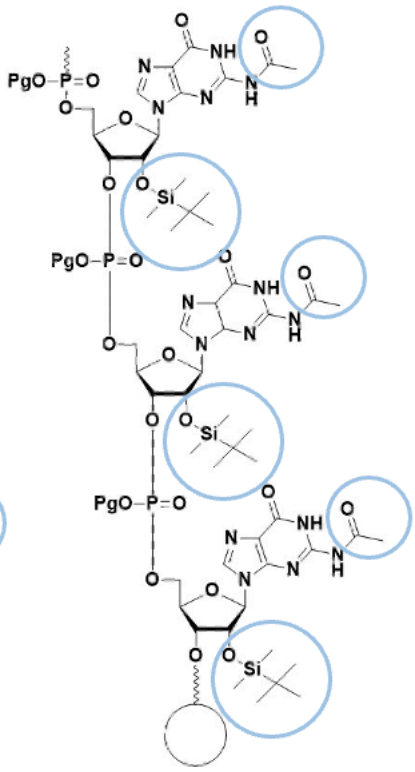


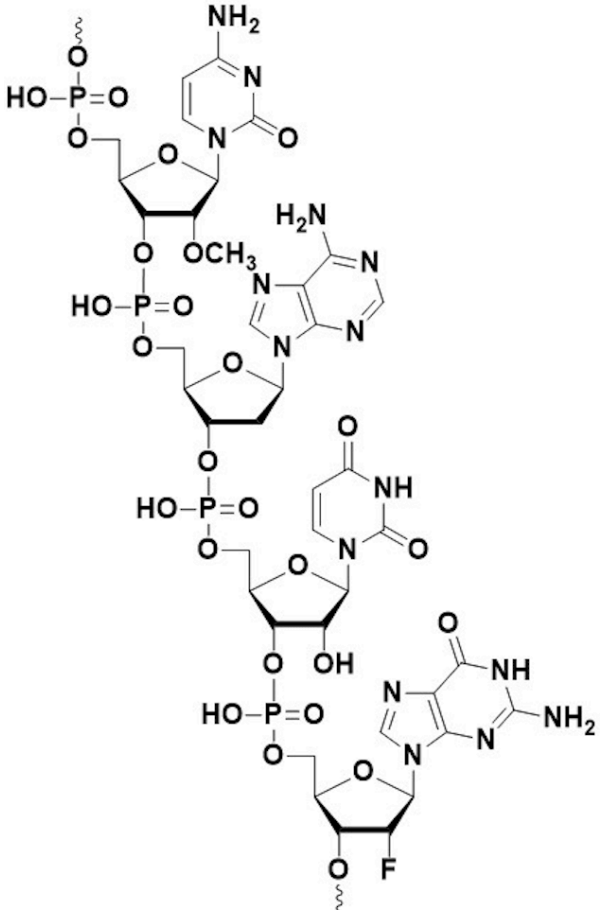
Fig. 1.b.

.

125. A POSA would have readily known that these oligonucleotides—incorporating the Pitsch and Fan monomers—are directed to RNA because of the (-OH) functional groups at their 2'-positions and the related disclosures in Pitsch and Fan that discuss "RNA" synthesis but not modified RNA or DNA or chimeric oligonucleotides. Exs. 1018; 1019. Ex. 1018, 3773; 1019, 2556. Ex. 2008, ¶125.

126. In contrast, a POSA would have understood that Compound x would have most certainly been used to incorporate modified nucleotides into oligonucleotides, like chimeric oligonucleotides, such as a chimeric oligonucleotide shown below with 2'-fluoro-2'-deoxyribonucleotides (i.e., 2'-F) and an assortment of

other nucleotides (i.e., from top to bottom: 2'-OMe-C (or 2'-O-methylcytidine); 2'-deoxyadenosine (DNA); uridine (RNA); and 2'-fluoro-2'-deoxyguanosine).



127. A POSA would have therefore found the limited teachings of Pitsch and Fan, which only applied to protected ribonucleosides and phosphoramidites for RNA synthesis, and not 2'-fluoro-2'-deoxyribonucleotide phosphoramidites for modified oligonucleotide synthesis, as not relevant (i.e., "apples and oranges") to efforts in modifying a 2'-fluoro-2'-deoxyribonucleoside phosphoramidite like Compound x.

128. In my opinion, a POSA would have expected that RNA-based phosphoramidites would have coupled differently during SPOS, and the different oligonucleotide structures would have had different deprotection characteristics when the base protecting groups were removed after the targeted oligonucleotide sequence was synthesized.

129. Accordingly, in my opinion, for at least these reasons, a POSA would not have been motivated by Pitsch and Fan, in view of the '031 patent, to produce N2-Acetyl-2'-F-2'-deoxyG as claimed in Claim 2.

iv. Petitioner and Dr. Baran Misapply the Teachings of Pitsch and Fan and a POSA Would Not Have Been Motivated by those References to Modify Compound x to Make the Claimed Invention

a. Neither Pitsch Nor the '031 Patent, Alone or in Combination, Compare Base Deprotection Rates of Acetyl and Isobutyryl

130. Petitioner and Dr. Baran also state that a POSA would have been motivated by Pitsch because the base deprotection rates of acetyl groups disclosed in Pitsch "compare [] favorably against the 24 hour deprotection period for the removal of the isobutyryl protecting group from the 2'-O-methyl G in Example 8 of the '031 Patent." Pet., 35. This argument is misleading.

131. Example 8 of the '031 Patent states:

> Treatment in methanolic ammonia ***for 24 hrs*** at room temperature was then done to deprotect all bases and sample was again lyophilized to dryness.

Ex. 1017, 40:48-51.

132. As Dr. Baran admitted, a POSA would have understood that Example 8 of the '031 Patent does not disclose base deprotection ***rates*** for the subject molecule it references but instead merely provides the procedure for how the subject molecule was deprotected. Ex. 2009, 145:5-13 ("Q. But the 24-hour deprotection period disclosed in example 8 of the '031 patent is not a rate of deprotection; right? A. I mean, that is the length of time it took them before they isolated and purified. So in an absolute sense, it is the time they took, but what we don't know is what the absolute rate was. Maybe they only needed seven hours. Maybe they needed 19.2. We don't know that.").

133. Petitioner and Dr. Baran also indicate that the subject molecule in Example 8 represents "2'-O-methyl G" monomers. But, in my opinion, that is not accurate either because the molecules disclosed in Example 8 are 2'-methoxy-2'-hydroxy-2'-methoxy phosphorothioate oligoribonucleotide "gapped" chimeric compounds, not simply O2'-methyl G monomers. Ex. 1017, 40:30-33 (subject molecule identified as "[2'-O-Me]/PS.[2'-OH]/PS.[-2'-O-Me]/PS oligoribonucleotide").

134. The Example 8 oligoribonucleotides also do not have 2'-fluoro-2'-deoxyribonucleotide monomers, yet alone 2'-fluoro-2'-deoxyguanosine monomers,

and Example 8 therefore does not correspond to an oligoribonucleotide synthesized using Compound x. Ex. 1017, 40:30-58.

135. Moreover, a POSA would have also recognized that Pitsch does not disclose base deprotection rates for isobutyryl, or even discuss isobutyryl as a base protecting group for the N2-position of guanine. Ex. 1018, 3778. A POSA would have also recognized that the base deprotection conditions of Pitsch and Fan are completely different from the deprotection conditions disclosed in the ’031 Patent, e.g., in Example 8 in Ex. 1017: "Treatment in methanolic ammonia for 24hrs at room temperature was then done to deprotect all bases and sample was again lyophilized to dryness." Ex. 1018, 3778 (disclosing “$MeNH_2$ (10M in H_2O/EtOH 1:1, 25º”); Ex. 1019, 2556 (disclosing 1.3% methylamine, 2.6% ethanol, and 96% methylene chloride by weight” to deprotect the N-acyl groups from the N2-position of the subject guanosine derivatives). Accordingly, a POSA would not be able to compare the teachings of Pitsch and Fan with any teachings of the '031 patent, with respect to deprotection rates. *Id*.

136. Accordingly, in my opinion, neither the ’031 Patent nor Pitsch, alone or in combination, disclose any comparisons of base deprotection rates for isobutyryl vs. acetyl for any phosphoramidites, nucleosides, oligonucleotides, 2'-fluoro monomers, or any other molecules.

b. Fan Discloses Deprotection Rates on a Fundamentally Different Compound Than Compound x Under Deprotection Conditions That a POSA Would Have Never Used on an Oligonucleotide

137. In my opinion, Fan does not remedy the deficiencies of Pitsch and the '031 Patent. As discussed above, a POSA would have understood that Fan discloses synthesis and deprotection of nucleoside derivatives, which were completely different molecules than Compound x, and did not even teach the synthesis of a corresponding phosphoramidite, or the synthesis or deprotection of any oligonucleotides. Ex. 2019.

138. It is my opinion that a POSA would have therefore not have been motivated by the findings in Fan (or, for that matter, Pitsch) because, as any POSA in this field would have been well aware, data generated in connection with one nucleoside would not have reliably transposed to a different nucleoside, never mind to a different corresponding oligonucleotide. Ex. 2013, 400 ("[I]t is worth noting that the deprotection time of the free nucleoside may be quite different from that of the nucleoside inserted in the DNA chain.").

139. Moreover, in my opinion, a POSA would have also recognized that the Fan study used deprotection conditions that are ***incompatible with oligonucleotides***. For example, a POSA would have known that the Fan study used "1.3% methylamine, 2.6% ethanol, and 96% methylene chloride by weight" to deprotect

the N-acyl groups from the N2-position of the subject guanosine derivatives. Ex. 1019, 2556. A POSA would have understood that these were very unusual deprotection conditions that were not applicable for deprotection of oligonucleotides during SPOS.

140. It is my opinion that, as Dr. Baran acknowledged, a POSA ***would have never*** used methylene chloride (having the chemical formula CH_2Cl_2) as a solvent when deprotecting a resulting oligonucleotide because of the risk that the solvent would lead to precipitation of the oligonucleotide, thus failing to accomplish nucleobase deprotection. Ex. 2009, 151:22-152:1 ("Q. If you try to deprotect oligonucleotide using the deprotection conditions of Fan, it wouldn't work very well, would it? A. Nobody would do that. That's not the point of the study.").

141. Accordingly, for at least these reasons, a POSA would not have been motivated by art of record to have produced N2-Acetyl-2'-F-2'-deoxyG as claimed in Claim 2, and Petitioner's and Dr. Baran's reliance on the cited references to demonstrate motivation is instead based on hindsight reconstruction.

3. A POSA Would Not Have Had a Reasonable Expectation of Successfully Synthesizing the Compounds Claimed in Claim 2 of the '885 Patent

i. A POSA Would Have Expected That Using Acetic Anhydride in Step ii. of the Complex Synthesis Scheme Set Forth in Example 4-d of the '031 Patent Would Have Failed

142. Petitioner and Dr. Baran argue that a POSA would have "simply substituted acetic anhydride (for isobutyric anhydride) in step 'ii' and thereafter performed the remaining steps 'iii' through 'x'" in Example 4-d of the '031 patent and would have "regarded the conditions and yield for the installation of an acetyl protecting group as trivial and similar to those for an isobutyryl group." Pet., 36-37.

143. Petitioner largely relies on speculation by Dr. Baran in alleging that substituting acetic anhydride in step ii. of the complex 10-step process set forth in Example 4-d of the '031 Patent would have resulted in the claimed invention. *Id*.

144. Dr. Baran testified that he did not see a need to conduct any tests to prove his theory because he considered it "undergraduate level chemistry." Ex. 2009, 161:6-12 ("And my question was whether you went into the lab to prove that theory. A. No, because this is undergraduate level chemistry, so there would be no need to even contemplate doing something like that. So the answer is no.")

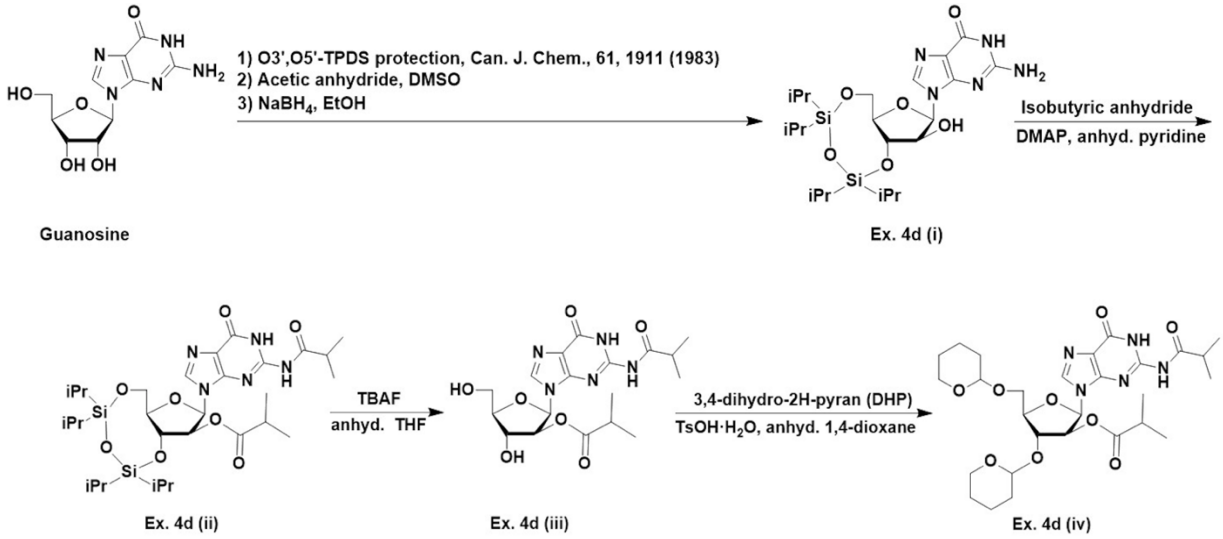
145. Petitioner and Dr. Baran do not provide any additional references, data, experimental evidence or technical reasoning to support Dr. Baran's theory that the

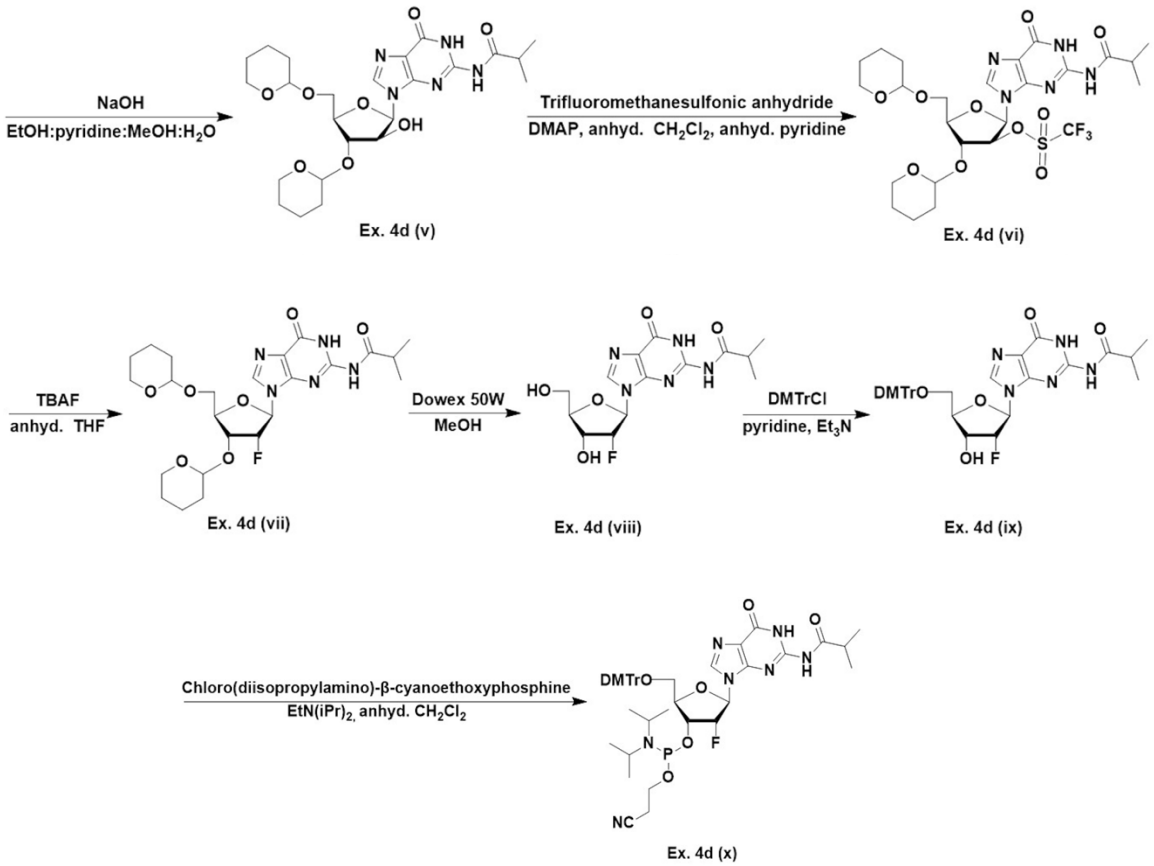
proffered modification to the Example 4-d scheme would have succeeded in resulting in the claimed compound.

146. Contrary to these unsubstantiated arguments, as supported by literature and my opinions set forth in the following subsections, it is my opinion that a POSA would have instead expected that substituting acetic anhydride for isobutyric anhydride in step ii. of Example 4-d in the '031 patent and executing the subsequent synthetic transformations (steps iii-x) would have resulted in failure.

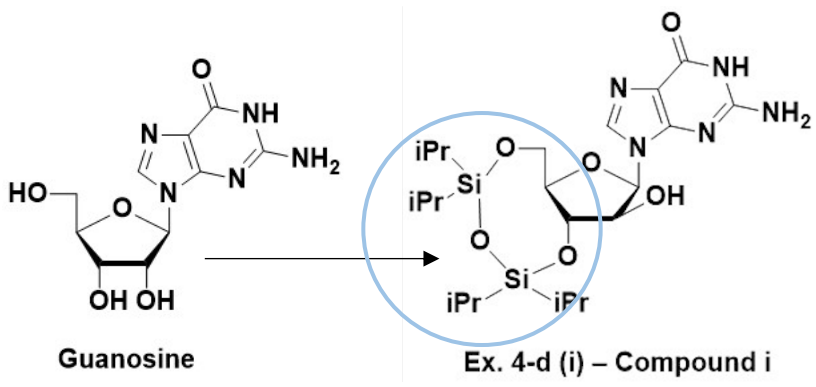
ii. A POSA Would Have Expected That Acetylating the Guanosine Derivative in Step ii. of Example 4-d of the '031 Patent Would Have Failed

147. Following is a schematic overview of the complex 10-step synthesis scheme described by Example 4-d of the '031 Patent that I generated:





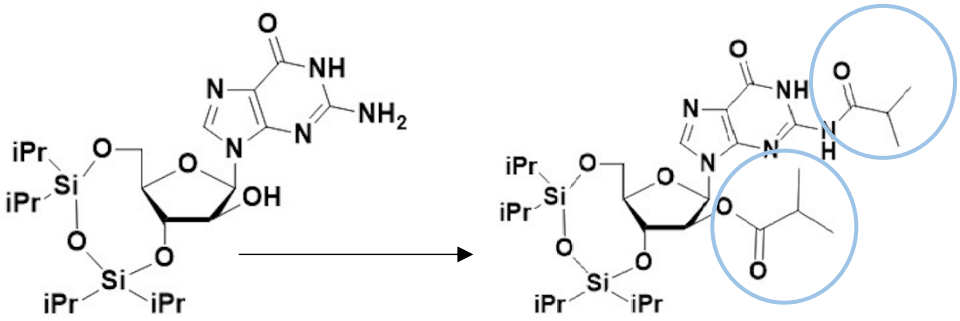
148. In my opinion, as shown below, a POSA would have understood that in step i. of Example 4-d of the '031 Patent, "9-(3', 5'-[1,1,3,3-Tetraisopropyldisilox-1,3-diyl]-β-D-arabinofuranosyl)guanine," ("Compound i") is synthesized from unprotected guanosine. Ex. 1017, 25:32-28:19.



Id., 25:34-38.

149. A POSA would have further understood that the resulting Compound i would have had a silyl group simultaneously protecting the 3'- and 5'-positions of the sugar ring, and the 2'-OH and the N2 amine (-NH_2) of the guanine base would not have been protected. *Id*.

150. A POSA would have observed, as shown below, that in step ii. of Example 4-d of the '031 Patent, Compound i would have then been converted to "N^2-Isobutyryl-9-(2'-O-isobutyryl-3',5'-[1,1,3,3-tetraisopropyldisilox-1,3-diyl]-β-D-arabinofuranosyl)guanine" ("Compound ii") by the introduction of, *inter alia*, isobutyric anhydride. *Id.*, 25:61-62.



Id. A POSA would have understood that the resulting modified guanosine Compound ii still would have had a 5'-O, 3'-O-silyl group protecting the 3'- and 5'-positions of the sugar ring, and the 2'-OH and the N2 amine (-NH_2) of the guanine base would have each been protected with isobutyryl groups. *Id*.

151. The statements in the Petition and Dr. Baran's Declaration that introducing an acetyl group via acetic anhydride in accordance with this step ii.

would be successful is belied by one of Petitioner's primary references, Fan, reporting that isobutyrylation (i.e., addition of isobutyryl groups) of guanosine derivatives (like Compound i) using isobutyryl in its scheme worked well, ***but acetylation (i.e., addition of acetyl groups) of guanosine derivatives did not*** ("the reaction mixtures were dark and the yields were unsatisfactory."). Ex. 1019, 2555.

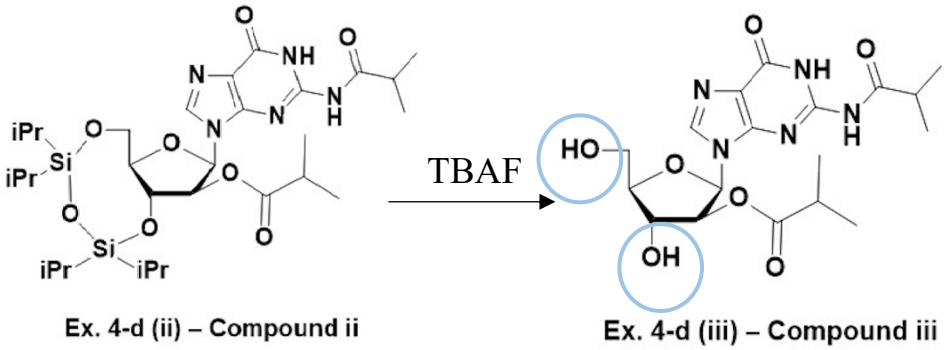
152. A POSA would have understood that a failure to attach acetyl groups (instead of isobutyryl groups) to the O2'- and/or N2-positions at this step would have completely derailed the subsequent synthetic transformations towards the N2-acetyl analogue of Compound x purported by Petitioner and Dr. Baran, as the reactive/nucleophilic O2'- and/or N2-positions would have reacted with reagents in some of the subsequent steps, to produce undesirable intermediates that would not have resulted in the synthesis of the N2-acetyl analogue Compound x. Ex. 1017, 25:32-28:19.

153. Accordingly, in my opinion, a POSA would not have had a reasonable expectation of success of synthesizing the N2-Acetyl-2'-F-2'-deoxyG of Claim 2 based on Petitioner's and Dr. Baran's theory for this reason alone.

iii. A POSA Would Have Expected That Using TBAF in Step iii. of Example 4-d of the '031 Patent Would Have Cleaved the Labile Acetyl Groups and Failed

154. In my opinion, a POSA would have understood that in step iii. of Example 4-d of the '031 Patent, as shown below, Compound ii would have been

converted to "N^2-Isobutyryl-9-(2'-O-isobutyryl-β-D-arabinofuranosyl)guanine" ("Compound iii") by the introduction of, *inter alia*, tetra-*n*-butylammonium fluoride ("TBAF").



Ex. 1017, 26:12-18. A POSA would have also known that the TBAF would have been used to cleave the 5'-O,3'-O-silyl protecting groups from the 3'- and 5'-positions of the sugar ring, while leaving the isobutyryl groups at the O2'- and N2- positions unharmed (i.e., with guanine remaining protected with an isobutyryl group). *Id.*

155. Even assuming, as per Petitioner's and Dr. Baran's theory, that acetyl groups could have been successfully introduced in step ii. in place of the isobutyryl groups protecting the O2'- and N2- positions of guanine (which for the reasons stated above they would not have been), a POSA would have expected, as supported by the literature, that removing the 5'-O,3'-O-silyl protecting groups in step iii. with TBAF also would have seriously risked the undesirable removal of the O2'- and/or N2-acetyl groups, given the basic/nucleophilic conditions disclosed. *See*, *e.g.*, Ex. 2015, 18144 ("The subsequent deprotection of the TBDMS groups proved to be difficult

due to parallel cleavage of the [N2] acetyl protecting group under basic fluoride deprotection conditions such as TBAF in THF.").

156. It is my opinion that a POSA would have expected that the undesirable removal of the acetyl group(s) at the O2'- and/or N2-positions at this step would have completely derailed the subsequent synthetic transformations towards the N2-acetyl analogue of Compound x, as the presence of a reactive/nucleophilic 2'-OH and/or 2-NH_2 groups would have reacted with reagents in subsequent steps to produce undesirable intermediates that would not have resulted in the synthesis of the N2-acetyl analogue Compound x as Petitioner and Dr. Baran allege. Ex. 1017, 25:32-28:19.

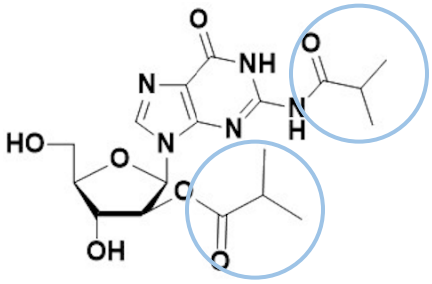
157. Accordingly, in my opinion, a POSA would not have had a reasonable expectation of success of synthesizing N2-Acetyl-2'-F-2'-deoxyG covered by Claim 2 for this additional independent reason.

iv. A POSA Would Have Expected the Acetyl Group to Have Rendered Compound iii Less Soluble in Organic Solvents and Cause the Synthesis to Fail

158. As discussed above, in my opinion, a POSA would have understood that unprotected guanosine and its derivatives are highly polar and are not functionally soluble in many organic solvents absent hydrophobic protecting groups like isobutyryl groups. Ex. 2009, 176:4-6. A POSA would have also known that acetyl groups are smaller and more polar (i.e., more water-loving) than isobutyryl

groups and would have therefore made guanosine derivatives less soluble in organic solvents. *Id*.

159. Therefore, a POSA would have understood that, according to Petitioner's and Dr. Baran's theory, Compound iii, shown here,



Ex. 4-d (iii) – Compound iii

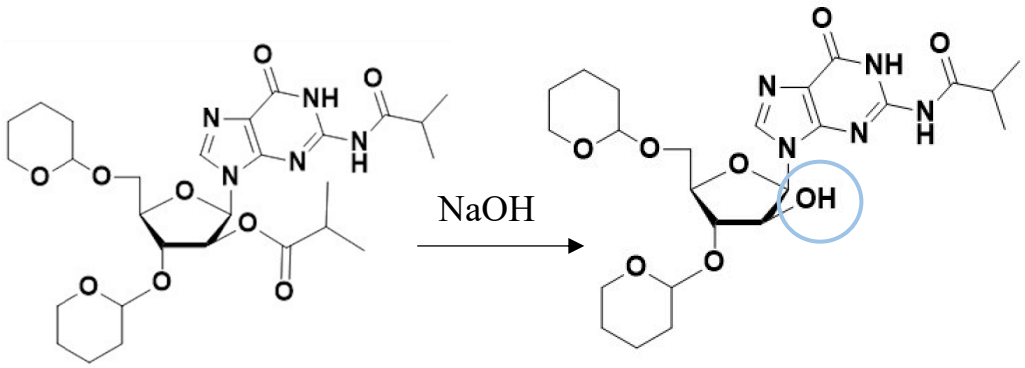
would have had two acetyl groups at the O2'- and N2- positions instead of the two isobutyryl groups. Ex. 1017, 25:32-28:19.

160. A POSA would have expected Petitioner's and Dr. Baran's proposed molecule to be less soluble in organic solvents than Compound iii, which a POSA would have expected could have negatively affected purification and caused the synthesis to fail. Additionally, a POSA would have also been concerned that the lower solubility of acetyl groups as compared to isobutyryl groups would have derailed the subsequent synthetic transformations and purifications (steps iv. – x.) of Example 4-d. Ex. 1017, 25:32-28:19.

161. Accordingly, in my opinion, POSA would not have had a reasonable expectation of success of synthesizing the N2-Acetyl-2'-F-2'-deoxyG of Claim 2 for this additional independent reason.

v. A POSA Would Have Expected That Using Sodium Hydroxide in Step v. Would Have Cleaved the 2' and/or N2 Acetyl Protecting Groups and Caused the Synthesis to Fail

162. In my opinion, a POSA would have known that in step v. of Example 4-d of the '031 Patent, "N^2-Isobutyryl-9-(2'-O-isobutyryl-3', 5'-di-O-[tetrahydropyran-2-yl]-β-D-arabinofuranosyl)guanine" ("Compound iv") is converted to "N^2-Isobutyryl-9-(3',5'-di-O-[tetrahydropyran-2-yl]-β-D-arabinofuranosyl)guanine" ("Compound v") by the introduction of, *inter alia*, NaOH ("sodium hydroxide").



Ex. 1017 at 26:42-59.

163. A POSA would have understood that the resulting Compound v, shown above, would have retained its tetrahydropyran-2-yl (THP) protecting groups at the 3'- and 5'- positions (installed during step iv.) and the isobutyryl protecting group at the N2-position, whereas the isobutyryl protecting group at the O2'-position was cleaved. *Id*. A POSA would have understood that this step indicates "selective

deprotection," where only certain protecting groups (here, just O2'-isobutyryl) are cleaved, whereas others remain intact. *Id*.

164. A POSA would have expected that, had two acetyl groups been present on Compound iv. (as per Petitioner's and Dr. Baran's theory), instead of the two isobutyryl groups, and the scheme had not already failed in prior steps (which, as discussed above, a POSA would have expected it would have), the use of sodium hydroxide to remove the O2'-acetyl group in step v. of Example 4-d would have caused concomitant removal of the N2-acetyl group given the basic/nucleophilic conditions disclosed, which include an over 10-fold molar excess of sodium hydroxide (NaOH) relative to the reactant nucleoside. Ex. 2020, 252, 279 ("the N-isobutyryl group showed, as might have been expected, considerably higher stability than the N-acetyl group" when deprotected "in a mixture of pyridine (0.4 ml.) and water (0.6 ml.) at 4°C [and] Sodium hydroxide (1 ml. of 2 M), which had been cooled to 4°C [and] added with vigorous agitation.").

165. Accordingly, in my opinion, a POSA would not have had a reasonable expectation of success of synthesizing the N2-Acetyl-2'-F-2'-deoxyG compound of Claim 2 for this additional and independent reason.

4. Petitioner's Additional Arguments for Reasonable Expectation of Success Lack Evidentiary Bases

166. Petitioner and Dr. Baran further state that instead of starting with Compound x, "a POSA could have also synthesized the molecule claimed in Claim

2 … by starting with 2'-fluoro-2'-deoxyguanosine, either acquired from a commercial source or synthesized according to Sivets (2007).” Pet., 37-38 (citing Sivets, Ex. 1028, compound 17).

167. In my opinion, Dr. Baran’s conclusory statement is not supported by any evidence (e.g., a product or catalogue disclosure) that shows 2'-fluoro-2'-deoxyguanosine was commercially available at the time of invention.

168. Second, it is my further opinion that a POSA would have known that compound 17 from Sivets (2007) (“Compound 17”) is not an ***N9-linked*** 2'-fluoro-2'-deoxyguanosine such as claimed in Claim 2, but is instead an ***isomeric N7-linked*** 2'-fluoro-2'-deoxyguanosine, and each are completely different molecules. Ex. 1028, 1821. When this was posed to Dr. Baran during his deposition, he changed his testimony and referred to compound 15 disclosed in Sivets (2007) (“Compound 15”), without providing any other bases for his opinions now relating to Compound 15. Ex. 2009, 166:15-21. In either case, in my opinion, Petitioner’s grounds are not supported.

169. Petitioner and Dr. Baran state that a POSA “would have reasonably expected that 2'-fluoro-2'-deoxyguanosine would react similarly to a ‘regular’ 2'-deoxyguanosine (*i.e.*, one with a 2'-H instead of the 2'-F substitution) in connection with the preparation of reagents for SPOS …” Pet., 38. However, The statements in the Petition rely solely on the conclusory testimony of Dr. Baran and no references,

data, or experimental evidence for the proposition that these completely different molecules "would react similarly" are provided. *Id*.

170. When asked about the basis for this testimony during his deposition, Dr. Baran testified that his testimony is based on "[t]ons of experience in the area and doing this chemistry through supervision and seeing it over the years" along with "literature" that he failed to identify in his declaration or during his deposition. Ex. 2009, 167:9-12. This testimony does not appear to be supported by facts or data.

171. Even if the argument that 2'-fluoro-2'deoxyguanosine would react similarly to a 'regular' 2'-deoxyguanosine was supported, which it is not, then it follows that a POSA would have understood that 2'-fluoro-2'deoxyguanosine would have suffered from similar solubility problems as "regular" 2'-deoxyguanosine during acetylation. Ex. 2012, 3822 (stating that "[a]cetylation of deoxyguanosine so as to prepare N,3',5'-triacetyldeoxyguanosine did not proceed satisfactorily … A part of the cause of failure to accomplish N-acetylation could be due to the insolubility of 3',5'-di-O-acetylguanosine which separates from the reaction mixture. … The lack of N-acetylation was probably due to the insolubility of 3',5'-di-O-acetylguanosine in the solvent. … In a parallel experiment benzoylation with [more lipophilic] benzoyl chloride did cause N-benzoylation as clearly shown ….") Furthermore, in my opinion, and contrary to these unsupported arguments, a POSA would have also known, at the very least, that the different 2'-substituents of 2'-fluoro-2'-

deoxyguanosine and 'regular' 2'-deoxyguanosine (i.e., 2'-F vs. 2'-H) would have had 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. Ex. 2016, 1421 (stating "[n]ucleoside conformation[s are] determined by the electronegativity of the sugar substituent…").

172. The rest of the statements in the Petition in Section VI.B.4. are illogical in my opinion. A POSA would have understood that neither Pitsch (Scheme 1, step "c)" molecule 3; step "d)", molecule 6); and Step "f)"); Pitsch #2 (2001) (Support Protocol 2); nor the '031 Patent (Example 4-d, Step "x") (Figure 3) teach the installation of protecting groups on "regular" 2'-deoxyguanosine. Pet., 38. Accordingly, in my opinion, it does not make sense to cite to those protocols as being useful for the synthesis of "regular" 2'-deoxyguanosine (or, for that matter, 2'-fluoro-2'-deoxyguanosine).

173. In is my further opinion that Petitioner's and Dr. Baran's reliance on Pitsch, Scheme 1, step "c)" is misplaced since Pitsch teaches installing acetyl on a completely different molecule than 2'-fluoro-2'-deoxyguanosine which is not instructive to synthesizing 2'-fluoro-2'-deoxyguanosine, and its teachings would therefore not have provided a POSA with a reasonable expectation of success in synthesizing the claimed compound.

174. Further discouraging a POSA, in my opinion, is that a POSA would have also recognized 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. Ex. 1018, 3787.

175. Specifically, even if a POSA had access to 2'-F-2'-deoxyguanosine, and had applied the protocol of Pitsch to install an N2-acetyl group on guanine (via peracetylation and subsequent selective *O*-deacetylation), a POSA would have understood that it would not have produced an N2-Acetyl-2'-F-2'deoxyguanosine. Ex. 2012, 3822.

176. Instead, the compound that would have been synthesized would have been a compound where, at a minimum, not all of the O-acetyl groups would have been removed.

177. That is because the protocol in Pitsch (Scheme 1, step "c)" molecule 3) uses an insufficient amount of sodium hydroxide to remove all of the O-acetyl groups of the peracetylated intermediate ("A mixture of guanosine (56.6 g, 0.2 mol) in DMF/Py/Ac_2O (250 ml each) was heated under reflux for 3 h….the intermediate (N^2,2'-*O*,3'-*O*,5'-*O*-tetraacetylguanosine)… was dissolved in THF/MeOH/H_2O 10:8:7 and treated with 10 M aq. NaOH (20 ml).") . Ex. 1018, 3787.

178. Even if peracetylation of guanosine was successful, which it may not have been, peracetylation of 0.2 mol of guanosine would have resulted in 0.2 mol of

N^2,2'-*O*,3'-*O*,5'-*O*-tetraacetylguanosine intermediate, which has four acetyl groups and, thus, 0.8 mol of acetyl groups, including 0.6 mol of O-bound acetyl groups. A POSA would have also known that 20 mL of 10 M aq. NaOH amounts to 0.2 mol of hydroxide (OH^-) ions, too little to successfully remove all of the O-bound acetyl groups. *Id*.

179. Furthermore, a POSA would have also understood that peracetylation of 0.2 mol 2'-fluoro-2'-deoxyguanosine, even if successful despite evidence to the contrary, would have yielded 0.2 mol of a putative N^2,3'-*O*,5'-*O*-triacetyl-2'-fluoro-2'-deoxyguanosine intermediate, which would have had 0.6 mol of acetyl groups, including 0.4 mol of O-bound acetyl groups. A POSA would have also known that 0.2 mol of hydroxide (OH^-) ions (i.e., 20 mL of 10 M aq. NaOH) is insufficient to successfully remove all of the O-bound acetyl groups.

180. Moreover, a POSA would have expected to have observed concomitant removal of the N2-acetyl group given the basic/nucleophilic conditions disclosed in Pitsch. *See*, *e.g.*, Ex. 2020, 252 ("the N-isobutyryl group showed, as might have been expected, considerably higher stability than the N-acetyl group" when deprotected "in a mixture of pyridine (0.4 ml.) and water (0.6 ml.) at 4°C [and] Sodium hydroxide (1 ml. of 2 M), which had been cooled to 4°C [and] added with vigorous agitation …").

181. The corresponding protocol in Pitsch #2 (2001) (Support Protocol 2) does not alleviate these concerns since the Pitsch #2 (2001) protocol is very similar to Pitsch #1 (2001) other than describing a smaller scale synthesis. Ex. 1021at 2.9.9.

182. Furthermore, in my opinion, McBride (Ex. 1006) does not disclose 2'-fluoro-2'-deoxyguanosine or a cyanoethyl dialkyl phosphoramidite as specified by Claim 2 (i.e., the phosphorous in McBride is connected to a methoxy group (-OCH_3), unlike N2-Acetyl-2'-F-2'-deoxyG in Claim 2 where phosphorous is connected to a cyanoethyl group (-OCH_2CH_2CN)). Ex. 1006, 245, 247.

183. Accordingly, in my opinion, a POSA would not have had a reasonable expectation of success of synthesizing the N2-Acetyl-2'-F-2'-deoxyG compound of Claim 2 for these additional reasons.

5. Secondary Indicia of Non-Obviousness Further Establish that Claim 2 is Not Obvious

184. In my opinion, in describing their invention in the '885 Patent's specification, the applicants explained that peers in the oligonucleotide industry were experiencing difficulty in obtaining pure chimeric oligoribonucleotides when using 2'-fluoro-2'-deoxyribonucleotides.

> When oligo ribonucleotide chimeras comprise [sic] of mixed bases composed of 2'-fluoro and 2'-ribo bases they present a challenge in obtaining pure chimera oligonucleotides. It has been well documented by several recent reports that oligonucleotide chimeras having 2'-

> fluoro-2;'-deoxy [sic] bases along with natural ribo bases present difficulty in obtaining pure oligos.

Ex. 1001, 10:65-11:4.

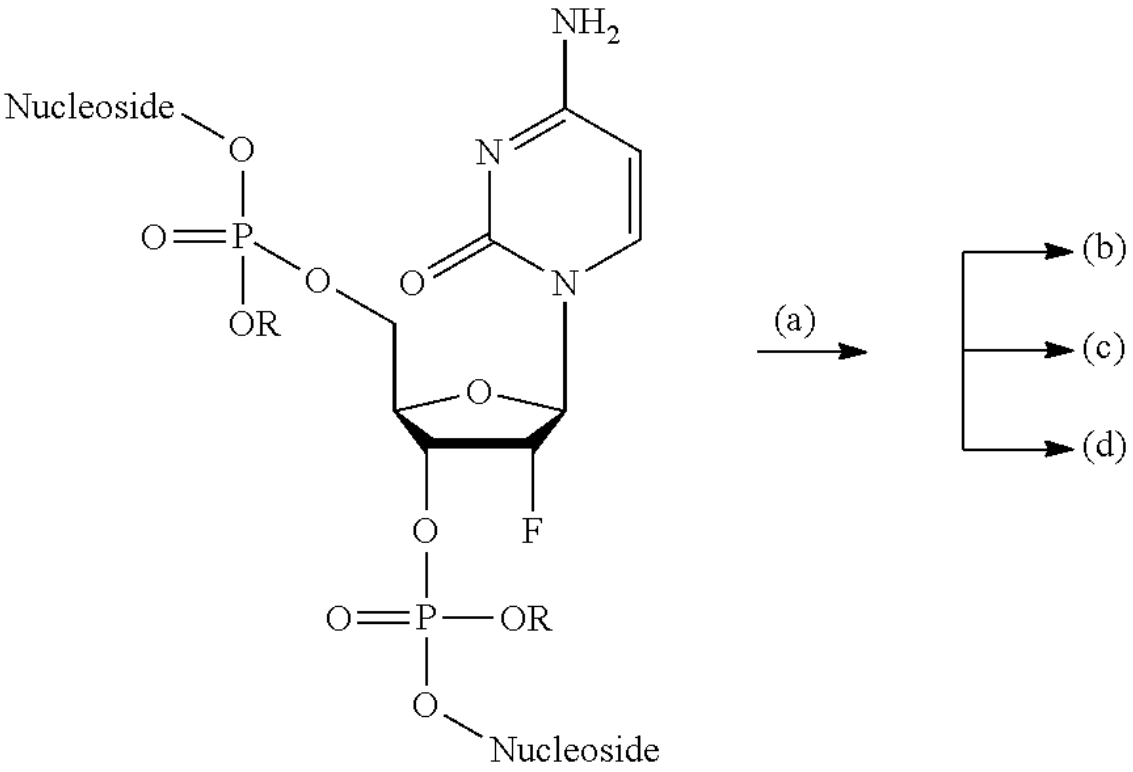
185. The applicants further explained that the 2'-fluoro atom on 2'-fluoro-2'-deoxyribonucleotide monomers of chimeric oligoribonucleotides was lost (as hydrogen fluoride (HF)) under "usual deprotection condition[s]," thus resulting in the formation of chimeric oligonucleotides with monomers lacking fluorine. Ex. 1001, 11:15-17.

186. The applicants also discussed the observed loss of pyrimidine nucleobases (i.e., uracil and cytidine) from 2'-fluoro-2'-deoxyribonucleotide monomers which caused damage to the nucleotides and the overall chimeric oligoribonucleotide products themselves.

> It has been shown that with strongly basic conditions, there is ***significant loss of fluorine*** as loss of Hydrogen Fluoride ("HF") is seen as M-20 peak in Mass spectral analysis. Besides it has also been shown that uracil and cytosine are eliminated to a significant extent, when oligo chimeras containing 2′-fluoro-2′-deoxy uridine and 2′-fluoro-2′-deoxy cytidine are part of chimeras (see scheme 3).

Ex. 1001, 11:4-11 (emphasis added). The applicants also provided the following scheme to illustrate the industry problem:

Scheme 3. Graphic Representation of effect on quality of oligonucleotides containing 2′-fluoro nucleosides: (a) deprotection using methyl amine, the usual deprotection condition of protecting groups of bases, (b) loss of fluorine leading to loss of HF, generating significant amount of M-20, (c) loss of cytosine and uracil, the pyrimidine bases is observed quite frequently, d) with the loss of pyrimidine, subsequent cleavage of chain occurs.



Ex. 1001, 11:12-35.

187. To further demonstrate the issue, applicants cited to studies presented at 2 conferences occurring in 2005 and 2007, where industry peers provided results demonstrating "depyrimidation of chimera oligonucleotides carrying 2'-fluoro-2'-deoxy pyrimidine in RNA's" and "Depyrimidation, as well as loss of HF and chain

cleavage in chimeras having 2'-fluoro-2'-deoxy pyrimidines in RNA sequences." The full passage from the '885 Patent is as follows:

> The studies as shown in scheme 3 were carried out independently by two groups recently. Ken Hill, Agilent Technologies, Boulder, Colarado [sic].; Identification of Process Related Impurities—Understanding Oligonucleotide Production, TIDES 2007, Las Vegas. Nev. The author showed depyrimidation of chimera oligonucleotides carrying 2'-fluoro-2'-deoxy pyrimidine in RNA's; and, Nanda D. Sinha, Avecia Biotechnologies Inc., Massachusetts—Depyrimidation, as well as loss of HF and chain cleavage in chimeras having 2'-fluoro-2'-deoxy pyrimidines in RNA sequences. Eurotides, 2005, Munich, Germany.

Ex. 1001, 11:36-47. These observations are corroborated by publications, including from one of the cited authors, Nanda D. Sinha. Ex. 2024, 83 (book chapter by Nanda D. Sinha et. al. stating that the 2'-fluoro-2'-deoxyribonucleotide of chimeric oligonucleotides "is subject to depyrimidation [] especially with methylamine or ammonia/methylamine deprotection…").

188. It is my further opinion that, in addressing this longstanding industry need, the applicants of the '885 Patent reported the following unexpected results:

> Our data shows that by utilizing ***n-acetyl-guanine protected ribonucleoside phosphoramidites***, used in oligo ***with 2'-fluoro*** substitution, high quality full length RNA were obtained. ***It is therefore imperative to utilize 2'-fluoro-2'-deoxy nucleosides and corresponding phosphoramidites with guanine protecting groups***

having N-2 acetyl guanine for mild and shorter base deprotection protocol.

Ex. 1001, 11:48-55 (emphasis added). The compounds referenced in this passage—i.e. "2'-fluoro-2'-deoxy nucleosides and corresponding phosphoramidites with guanine protecting groups having N-2 acetyl" – cover the exact N2-Acetyl-2'-F-2'-deoxyG phosphoramidite that Petitioner has challenged.

189. In my opinion, the cited results were unexpected as compared to the properties of what Petitioner and Dr. Baran have alleged is the closest prior art—Compound x from the '031 Patent. Based on the disclosures in the '885 Patent and other literature (e.g., Exs., 2024 and 2025) referencing oligoribonucleotide chimeras comprised of mixed 2'-fluoro and 2'-ribo bases presenting serious challenges in obtaining pure chimeric oligoribonucleotides, a POSA would have expected that using Compound x would have caused similar purity problems under usual oligonucleotide deprotection conditions. *Id*.

190. In my opinion, this is supported by at least Kawasaki, which observes "***significant degradation*** of the 2'-deoxy-2'-fluorpyrimidine nucleosides" while under "the usual oligonucleotide deprotection conditions (concentrated NH_4OH, 55°C)." Ex. 2025, 833. Kawasaki shows (in Scheme II) significant overlap with the synthesis schemes of Example 4-d of the '031 Patent and both publications identified

as originating from the same company (Isis Pharmaceuticals, Inc.). Ex. 1017, Cover; Ex. 2025, 831.

191. While Compound x is not shown as synthesized in Kawasaki, its precursors are, and the Compound x structure—"N2-Isobutyryl-2'-deoxy-2'-fluoro-5'-O-(4,4'-dimethoxytrityl)guanosine 3'-[β-Cyanoethyl N,N-diisopropylphosphoramidite]"—is described in the experimental protocols. Ex. 2025, 839. It therefore appears the work disclosed in Kawasaki and the '031 Patent may be related and, in any event, address the same structures including Compound x.

192. Kawasaki also states the authors used methanolic ammonia instead of NH_4OH, but did not modify the N2-protecting group, to address the degradation problem. Ex. 2025, 833. Given that this publication was dated in 1993, the overall degradation problem persisted in the industry for at least over 15 years before the filing of the application that led to the issuance of the '885 Patent.

193. Accordingly, the results obtained by the applicants by utilizing N2-acetyl on 2'-fluoro-2'-deoxyguanosine to address this problem using methylamine for deprotection were surprising and unexpected as compared to the prior art which did not disclose using the novel N2-Acetyl-2'-F-2'-deoxyG compound claimed by the '885 Patent to address the longstanding industry need. Ex. 1001, 11:15-17.

194. Moreover, POSAs routinely used methylamine to remove protecting groups from guanosine, but Sinha observed problems using methylamine, further demonstrating that the results using N2-Acetyl-2'-F-2'-deoxyG were unexpected. Ex. 2024, 83 (book chapter by Nanda D. Sinha et. al. stating that the 2'-F modification of chimeric oligonucleotides "is subject to depyrimidation [] especially with methylamine or ammonia/methylamine deprotection…"); Ex. 1001, 22:63-23:1 (using methylamine); Ex. 1018, 3778 (using methylamine); Ex. 1019, 2556 (using methylamine).

195. Since at least one of the molecules described in these passages of the '885 Patent as satisfying a long-felt industry need and demonstrating unexpected results is the same N2-Acetyl-2'-F-2'-deoxyG phosphoramidite claimed in Claim 2, my understanding is a presumption of a nexus between the asserted evidence and patent claim should apply because the compound *is* the invention disclosed and claimed. Furthermore, it is my opinion that the evidence referenced herein of long-felt need spanning over 15 years demonstrates both that a demand existed for the patented invention, and that others tried but failed to satisfy the demand.

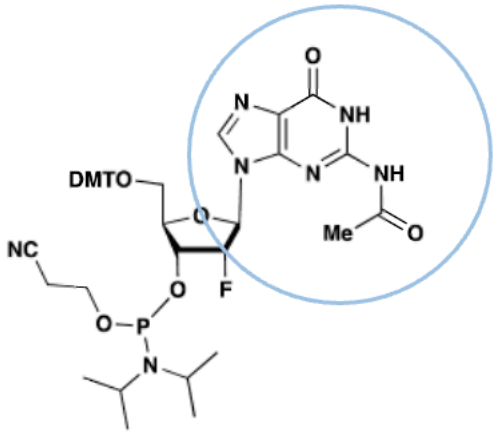
196. Accordingly, in my opinion, the inventors' advancement in developing the novel N2-Acetyl-2'-F-2'-deoxyG phosphoramidite, as claimed in Claim 2, was not obvious for this reason as well.

C. Ground III: Claim 2 Would Not Have been Obvious in View of U.S. Patent No. 7,879,991 and Pitsch

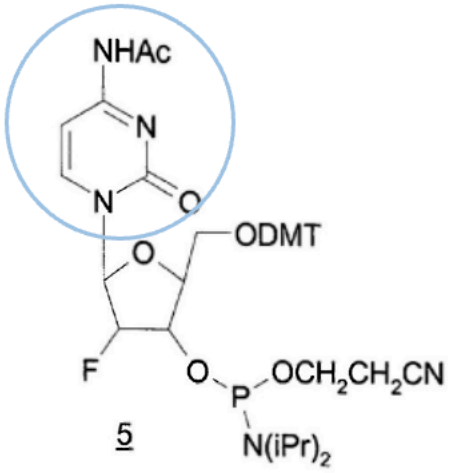
1. The ’991 Patent Discloses a Totally Different Molecule than Claimed in Claim 2 of the ’885 Patent

197. Contrary to Petitioner’s and Dr. Baran’s statements, the compound disclosed in Figure 16 of U.S. Patent No. 7,879,991 (the ’991 Patent) (“Compound 5”) is not “almost identical” to Claim 2 “where ‘B’ is Guanine-N-acetyl and ‘Z’ is ribo Fluoro,” and is instead starkly different. Pet., 40.

198. First, as shown in the figure below from the Petition, Claim 2 has a ***guanine*** base and Compound 5 has a ***cytosine*** base.



The ’885 Patent, Claim 2

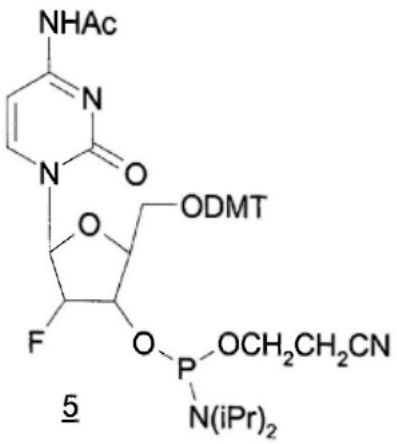


The ’991 Patent, Fig. 16 (#5)

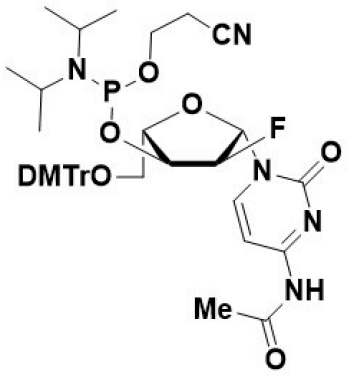
Pet., 39. In my opinion, a POSA would have therefore immediately known, for this reason alone, that Compound 5 was totally different from the compound claimed in Claim 2 where “B” is guanine-N-acetyl and “Z” is ribo fluoro, and therefore certainly not “almost identical.”

199. Further, a POSA would have also recognized that Compound 5 is an ***L-configured*** nucleoside, as Dr. Baran admits. Ex. 1003, ¶127 (stating the '991 Patent discloses "2'-fluoro-L-cytidine phosphoramidite" in Figure 16); Ex. 2009, 180:8-16 ("Q. Right. So does that clarify for you that figure 16 shows L configured cytosine? A. Yes."). Figure 16 from the '991 Patent states "FIG.16 shows the illustration of 2'-fluoro-L-cytidine phosphoramidite based on 2'-fluoro-L-uridine" and Example 6 of the '991 Patent states "The synthesis of 5'-DMT-2'-fluoro-L-uridine and 5'-DMT 2'-fluoro-N (Ac)-L-cytidin phosphoramidites (3 and 5) is depicted in FIGS. 15 to 17." Ex. 1020, Sheet 17, 16:38-40; 45:45-48. Accordingly, this further establishes that Compound 5 as disclosed in the '991 Patent is an ***L-configured*** nucleoside.

200. For illustrative purposes, the image below (to the right) shows an alternative depiction of Compound 5, after having been turned over from the left to the right (e.g., like a hamburger patty), with C1' located in the upper right of the sugar ring and C4' located in the upper left of the sugar ring (i.e., with the sugar ring orientated in the same fashion as the N2-acetyl 2'-F-deoxyguanosine of Claim 2), as discussed in more detail below.



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



Alternative Depiction of The '991 patent, Fig. 16 (#5)

201. In contrast, in my opinion, a POSA would have also understood that the compound claimed in Claim 2 of the '885 patent is a ***D-configured*** nucleoside. Even assuming N2-acetyl-protected guanine was identical to a N4-acetyl-protected cytosine, which it absolutely is not, a POSA would have understood that such compounds would have been enantiomers (i.e., non-superimposable mirror images) of each other (i.e., like a left hand is to a right hand).

202. The accompanying structure listed in Claim 2 (i.e., general formula 1, depicting a nucleoside drawn in a so-called Haworth projection), provides unequivocal information about the stereochemical configuration at each chirality center, i.e., C1', C2', C3' and C4'. The stereochemical configuration at C1', C2', C3' and C4' is critical in establishing a nucleoside's identity and distinguishing between D- and L-configured nucleosides and nucleotides.

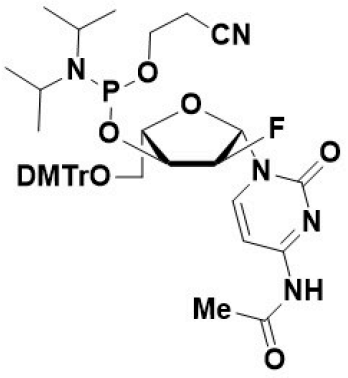
203. Thus, as a matter of undergraduate textbook chemistry, a POSA would understand, that each of the C1', C2', C3' and C4' atoms, has two atoms or groups that "point" in two specific directions (these being "up" or "down"). A POSA would also have understood that, for the compound claimed in Claim 2 of the ’885 patent, the nucleobase moiety ("B") at C1' to be pointing "up", "Z-W" at C2' to be pointing "down", "O-X" at C3' to be pointing "down", and the "$DMTOCH_2$“ group at C4' to be pointing "up". A POSA would have understood this to depict a D-configured nucleoside.

204. As a as matter of undergraduate textbook chemistry, a POSA would also understand that there is specific chemical meaning to the sugar ring of nucleosides to have been drawn with the four carbon atoms of the sugar ring proceeding C1'-C2'-C3'-C4' in a clockwise fashion (as in the general formula 1 of Claim 2 of the '885 patent) or in a counter-clockwise fashion (as in Figure 16 for compound #5 of the '991 patent). A POSA would have known that #5 of the '991 patent, alternatively, could be drawn with the sugar ring proceeding C1'-C2'-C3'-C4' in a clockwise fashion, and that this would invert the direction that the atoms or groups attached to C1'-C2'-C3'-C4' would point.

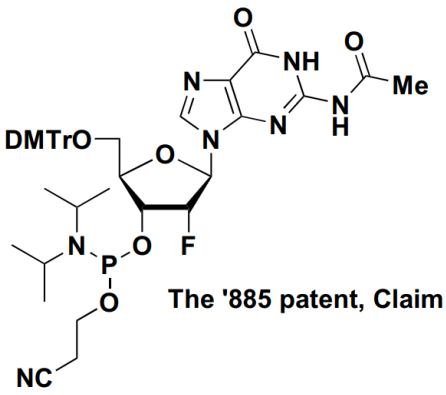
205. Thus, with the four carbon atoms of the sugar ring proceeding C1'-C2'-C3'-C4' in a clockwise fashion, a POSA would have understood that the nucleobase moiety at C1' would point "down", "F" at C2' would point "up", the phosphoramidite

group at C3' would be pointing "up", and the "DMTrO-CH_2" group at C4' to be pointing "down". A POSA would have understood that the original depiction of compound #5 in the '991 patent, and the alternative depiction of compound #5, are one and the same compound, i.e., they are identical molecules. Moreover, a POSA would have understood this to be a L-configured nucleoside.

206. When the L-configured Compound 5, depicted in this way, is then compared to the D-configured N2-acetyl 2'-F-deoxyguanosine of Claim 2 (below), a POSA would have seen how plainly different these molecules are.



Alternative Depiction of
The '991 patent, Fig. 16 (#5)



The '885 patent, Claim 2

207. Specifically, a POSA would have understood that these molecules were totally different, would have to be prepared completely differently, would have had opposite stereochemical configurations, would have required different starting materials for their synthesis (i.e., enantiomeric starting materials), and would have reacted completely differently during SPOS, and in any case were not "almost identical."

2. A POSA Would Not Have Selected Compound 5 of the ’991 Patent as a Lead Compound and, in Any Event, a POSA Would Not Have Selected Compound 5 as a Lead Compound

208. Petitioner and Dr. Baran again fail to provide any reasoning why a POSA would have selected Compound 5 as a lead compound other than the conclusory statement that a POSA would have viewed Compound 5 as a “building block” for a growing oligonucleotide chain. Pet., 40. Petitioner and Dr. Baran make no showing as to why a POSA would have selected Compound 5 as the most promising to modify in order to improve upon its activity and obtain a compound with better activity or why a POSA would have had a reason to select Compound 5 from the panoply of known oligonucleotide building block compounds in the prior art” or from the compounds described in the ’991 Patent. This again suggests hindsight reconstruction of the claimed compound.

209. Moreover, in my opinion, based on at least the drastic differences in compounds discussed above, a POSA would not have selected Compound 5 as a lead compound to synthesize Compound x.

3. A POSA Would Not Have Been Motivated by the ’991 Patent and Pitsch to Synthesize the N2-Acetyl-2’-F-2’-deoxyG Claimed in Claim 2

210. Petitioner argues that “[Compound 5] would have motivated a POSA to build the structurally analogous 2'-fluoro-guanosine phosphoramidite claimed in Claim 2, especially in view of Pitsch ….” Pet., 40-41.

211. The statements in the Petition are illogical and Petitioner provides no support, other than Dr. Baran's identical conclusory statements set forth in his declaration, for why Compound 5, a totally different L-configured compound with a cytosine base, would have motivated a POSA to build the structurally ***non-*** analogous D-configured N2-Acetyl-2'-F-2'-deoxyG claimed in Claim 2.

212. The statements in the Petition that Pitsch would have motivated a POSA to make the N2-Acetyl-2'-F-2'-deoxyG compound claimed in Claim 2 are also without merit for at least the reasons set forth above, including that the prior art taught away from using acetyl groups to protect 2'-deoxyguanosine. Ex. 2011, 221.

213. Furthermore, the teachings of the '991 Patent contradict the statements in the Petition that a POSA would have been motivated by it to make the claimed invention. For example, a POSA would have understood that the '991 Patent teaches that ***pyrimidine*** nucleotides were to be configured with F at the 2'-position:

> A particularly advantageous modification [to nucleic acids] in connection with the present invention constitutes configuring the inventive nucleic acid(s), in which at least one, preferably more and ***most preferably all pyrimidine nucleotides*** forming the nucleic acid have a 2′-fluoro group at the 2′ position of the ribose section of each nucleotide.

Ex. 1020, 12:33-40 (emphasis added). Here, a POSA would have known that the guanine base of Claim 2 of the '885 Patent is a ***purine***, not a ***pyrimidine*** base, and

therefore the ’991 Patent would not have motivated a POSA to synthesize a N2-Acetyl-2’-F-2’-deoxyG as claimed in Claim 2.

214. Moreover, the ’991 Patent would not have motivated a POSA in this way, since the ’991 Patent is directed to L-configured nucleic acids, not D-configured phosphoramidites (as in Claim 2), and, moreover, teaches instability of D-configured nucleic acids in aqueous solutions and biological systems.

> The L nucleic acids are enantiomers of the naturally occurring nucleic acids. ***The D nucleic acids however are not very stable*** in aqueous solutions and in particular in biological systems or biological samples as a result of the broad distribution of nucleases.

Ex. 1020, 12:3-7 (emphasis added). Therefore, a POSA reading the ’991 Patent would have been discouraged from pursuing D- over L-configured nucleic acids.

215. Accordingly, in my opinion, for at least these reasons, a POSA would not have been motivated by the ’991 Patent or Pitsch to make the N2-Acetyl-2’-F-2’-deoxyG phosphoramidite claimed in Claim 2.

4. A POSA Would Not Have Had a Reasonable Expectation of Successfully Synthesizing the Molecule in Claim 2 Based on the ’991 Patent

216. Petitioner relies solely on “Section VI.B.4” of its Petition to show a POSA would have had a reasonable expectation of success in synthesizing the molecule claimed in Claim 2 based on the ’991 Patent or Compound 5. Pet., 41. But, in my opinion, neither Section VI.B.4 of the Petition, nor anywhere else in the

Petition or Dr. Baran's Declaration, do Petitioner or Dr. Baran discuss or address reasonable expectation of success based on the '991 Patent or Compound 5.

217. Accordingly, in my opinion, Petitioner and Dr. Baran fail to provide any evidence or reasoning for reasonable expectation of success based on the '991 Patent or Compound 5 – a completely different molecule from Compound x from the '031 Patent and the molecules disclosed in Pitsch, Fan, Sivets (2007), Pitsch #2 (2001), and McBride (1983).

218. It is also my opinion, of course, that Petitioner's arguments also fail for at least the reasons stated in Sections VI.B. herein for Ground II.

5. Secondary Considerations of Non-Obviousness Further Establish that Claim 2 is Not Obvious

219. In my opinion, Claim 2 would also not have been obvious to a POSA for at least the reasons set forth for secondary considerations of non-obviousness for Ground II discussed in Section VI.B.5.

D. Ground IV: Claim 3 Would Not Have Been Obvious in View of the '031, Pitsch, Fan, and Scaringe

1. Claim 3 Should be Interpreted Such That "M" Should be "Ethyl" and Ground IV Should Fail Under any Interpretation

220. As discussed above, I agree with Dr. Baran that Claim 3 should be interpreted such that "M" should be "ethyl" and not "succinyl," and is not unpatentable based on that interpretation for the reasons stated herein.

221. Alternatively, if the Board does not construe Claim 3 in this manner (i.e., not correcting the error and instead requiring "M" to be succinyl and not ethyl), then Ground IV would fail because none of the prior art references cited in Ground IV (i.e., the '031 Patent, Pitsch, Fan, and Scaringe) discloses compounds where "M" is succinyl or any of the remaining compounds listed in the Claim 3 Markush group (i.e., where M is "oxalyl" or "hydroquinolynyl").

222. Accordingly, because all of the limitations of uncorrected Claim 3 are not taught by the prior art under this interpretation, and my understanding is that the missing element would not have been supplied by the knowledge of a person of ordinary skill in the art, Claim 3 would not be obvious.

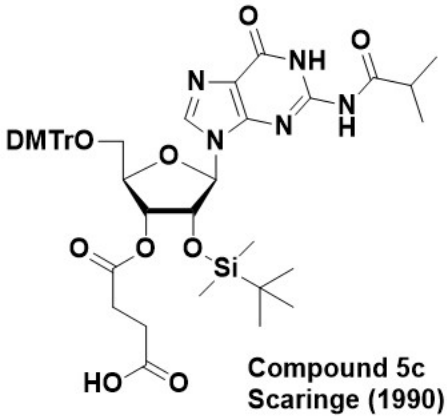
2. Petitioner's Arguments with Respect to Alleged Obviousness of Claim 3 Fail for at Least the Reasons its Arguments in Connection with Claim 2 Also Fail

223. In my opinion, the molecules in Claims 2 and 3 are identical except that Claim 2 has a "cyanoethyl dialkyl phosphoramidite" at the 3'-position and Claim 3 has succinyl, solid support and spacer groups at the 3'-position. Pet., 44. Petitioner mainly relies on the arguments it made in connection with Ground II relating to the molecule claimed in Claim 2 where "B" is guanine-N-acetyl and "Z" is ribo fluoro to support its arguments in this Ground IV. Pet., 45.

224. In my opinion, Petitioner's arguments for this ground fail for at least the reasons set forth in Section VI.B. (Ground II) above relating to Claim 2, i.e., (a)

Petitioner and Dr. Baran fail to provide a rationale as to why a POSA would have chosen Compound x as a lead compound; (b) neither Pitsch nor Fan would have motivated a POSA to modify Compound x to make the compounds claimed in Claim 2; (c) a POSA would not have had a reasonable expectation of success in synthesizing the compounds claimed in Claim 2; and (d) secondary indicia of non-obviousness further establish that Claim 2 (further discussed below) is not unpatentable.

225. Furthermore, in my opinion, the molecule disclosed in Scaringe ("Compound 5c"), shown below, is also different from the molecules covered by Claim 3 and the various molecules disclosed in the '031 Patent, Pitsch, and Fan (discussed in Section VI.B. above).



Compound 5c
Scaringe (1990)

226. As shown above, Scaringe does not disclose 2'-F groups and instead uses an O2'-TBDMS group and only teaches using an isobutyryl group to protect the N2-position of the above guanine nucleobase, does not teach using an acetyl group, and does not disclose deprotection rates. *See*, *e.g.*, Ex. 1022, 5434.

227. Accordingly, in my opinion, for at least these reasons, and the reasons provided in above, a POSA would not have been motivated by Scaringe to synthesize the succinate claimed in Claim 3 where "B" is guanine-N-acetyl and "Z" is ribo fluoro, with a reasonable expectation of success.

3. Secondary Considerations

228. In my opinion, the secondary considerations of non-obviousness discussed Claim 2 above further establish that Claim 3 would not have been obvious.

229. I have been advised about the legal standard for a nexus of long-felt need and unexpected results, and in my opinion, here the nexus between the claimed invention and secondary indicia including long-felt need and unexpected results is directly related to the core structure at issue (i.e., as Petitioner admits the claimed molecule in Claim 3 is the corresponding succinate of the phosphoramidite in Claim 2) and therefore the nexus should be presumed.

E. Ground V: Claim 4 Would Not Have Been Obvious in View of Scaringe, Pitsch, and Fan

1. Claim 4 Should be Interpreted Such That "M" Should be "Ethyl" and Ground V Should Fail Under any Interpretation

230. As discussed above, I agree with Dr. Baran that Claim 4 should be interpreted such that "M" should be "ethyl" and not "succinyl," and is not unpatentable based on that interpretation for the reasons stated herein.

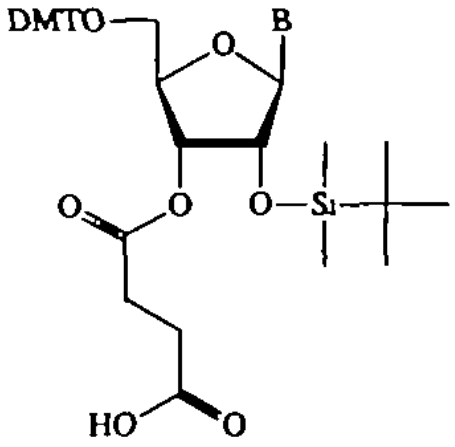
231. Alternatively, should the Board not construe Claim 4 in this manner (i.e., not correcting the error and instead requiring "M" to be succinyl and not ethyl), then Ground V fails because none of the prior art references cited in Ground V (i.e., the Scaringe, Pitsch, Fan) discloses compounds where "M" is succinyl or any of the remaining compounds listed in the Claim 4 Markush group (i.e., where M is "oxalyl" or "hydroquinolynyl").

232. Accordingly, because all of the limitations of uncorrected Claim 4 are not taught by the prior art under this interpretation, and my understanding is that the missing element would not have been supplied by the knowledge of a person of ordinary skill in the art, Claim 4 would not be obvious.

2. A POSA Would Not Have Selected Compound 5(c) of Scaringe as a Lead Compound and, in Any Event, a POSA Would Not Have Selected Compound 5(c) as a Lead Compound

233. Petitioner and Dr. Baran identified Compound 5(c) disclosed in Scaringe (1990) ("Compound 5(c)") as its primary reference for this Ground V.

a) B = N^6-Benzoyl adenine
b) = N^4-Benzoyl cytosine
c) = N^2-Isobutyryl guanine
d) = Uracil



5

Ex. 1022, 3, Fig. 1, #5; Pet., 48-52.

234. Petitioner makes ***no showing*** as to ***why*** a POSA would have selected compound 5(c) as a lead compound as the most promising to modify in order to improve upon its activity and obtain a compound with better activity or why a POSA "would have had a reason to selected Compound 5(c) from the panoply of known nucleoside building blocks in the prior art.

235. It is my opinion that a POSA would not have chosen Compound 5(c) as a lead compound. Scaringe reports the syntheses of oligoribonucleotides (RNA) via SPOS. During SPOS, the synthesis of the RNA strand proceeds in the 3' → 5' direction. A POSA would know that the nucleotide on the 3'-end was bound to a solid support (and thus made via the succinate) and the remaining nucleotides are sequentially added in coupling steps in a 3' → 5' fashion (i.e., added using phosphoramidites).

236. Scaringe discloses the synthesis of 4 RNA sequences as shown in Table 4 (the first four sequences shown below).

Table 4

Name	Sequence 5'-3'	Length
S	GCG CCG AAA CAC CGU GUC UCG AGC	24
R	GGC UCG ACU GAU GAG GCC C	18
μ-Helix	GGG GCU AUA GCU CUA GCU CCA CCA	24
m-Helix	GGG GCU AAG CGG UUC GAU CCC GCU UAG CUC CAC CA	35
1.	TTTTTrATTTT (2% 5'-2')	10
2.	TTTTTrATTTT	10
3.	TTTTTrGTTTT	10

Ex. 1022, 5436. In my opinion, none of those four sequences show a guanosine on the 3'-end, and they all instead show C, C, A, and A at their 3'-ends, and there is therefore no evidence of a solid support bound guanosine (or U) (via a succinate or otherwise) being used for the synthesis of these oligoribonucleotides. Ex. 2022, 5436. Thus, a POSA in reviewing Scaringe, would not have viewed Compound 5(c) as a lead compound and would have instead viewed Compounds 5(a) or 5(b) as leads because they were demonstrated as bound to a solid support used for RNA synthesis.

237. Accordingly, in my opinion, a POSA would not have selected Compound 5(c) as a lead compound.

3. A POSA Would Not Have Been Motivated by Pitsch and Fan to Install an Acetyl Protecting Group on Compound 5(c) of Scaringe and Petitioner Fails to Provide any Rationale as to How a POSA Would Have Done So with a Reasonable Expectation of Success

238. In my opinion, a POSA would have also known, as discussed above, that the prior art taught away from using acetyl groups to protect the N2-position of guanosine derivatives based on the demonstrated instability of acetyl group and that acetyl groups would have made guanosine derivatives less soluble in organic solvents than isobutyryl. Ex. 2013, 400. Accordingly, in my opinion, a POSA would not have been motivated by Pitsch and Fan to pursue a course antithetical to established teachings in the art. Pet., 51.

239. Petitioner and Dr. Baran also state that a "POSA would have recognized that the substitution of the protecting group on the exocyclic NH_2 group of the guanine base ***would not be affected by*** the O2'-TBDMS protecting group, which had been commonly used to shield the 2'-OH." Pet., 51 (citing Ex. 1007). But Petitioner's and Dr. Baran's reliance on Beaucage (Ex. 1007) is misplaced because that reference does not disclose the use of an acetyl group on the N2-position of guanosine derivatives in conjunction with O2'-TBDMS protecting groups, never mind providing evidence that the substitution "would not be affected by the O2'-TBDMS protecting group." *Id.*

240. Similarly, Petitioner and Dr. Baran fail to provide any rationale as to how a POSA would have synthesized the "5'-O-DMT-2'-O-TBDMS N2-acetyl guanosine 3'-O-succinate" molecule, and fail to provide any evidence or argument for reasonable expectation of success for that molecule. Therefore, The statements in the Petition on these points rely solely on the conclusory testimony of Dr. Baran.

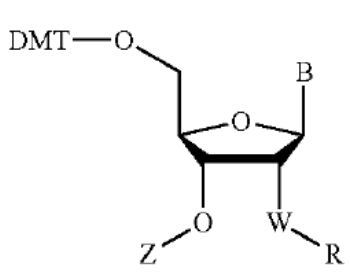
241. Accordingly, in my opinion, and based on the legal standards that I have been advised of, Claim 4 would not have been obvious to a POSA for this reason alone.

i. Ground VI: The Compounds of Substitute Claim 7 are Not Disclosed by the Prior Art.

242. As discussed above, I agree with Petitioner's and Dr. Baran's contention that Claim 5 should be interpreted such that "M" should be "ethyl" and not "succinyl." I also agree that Claim 5 should be interpreted such that the last clause in Claim 5 should read "and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1-C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy."

243. In my opinion, this interpretation should apply in connection with the merits of the Motion to Amend being filed contemporaneously with Patent Owner's Response, which seeks to remove "B" as "cytosine-N-isobutyryl" and "cytosine-N-acetyl" from Claim 5's Markush group, based upon Gaur. It is my further opinion that the amended claims are not disclosed in the prior art for the reasons stated below.

244. In my opinion, substitute Claim 7 is directed to derivatized nucleosides, succinates and solid supports of general formula 2,



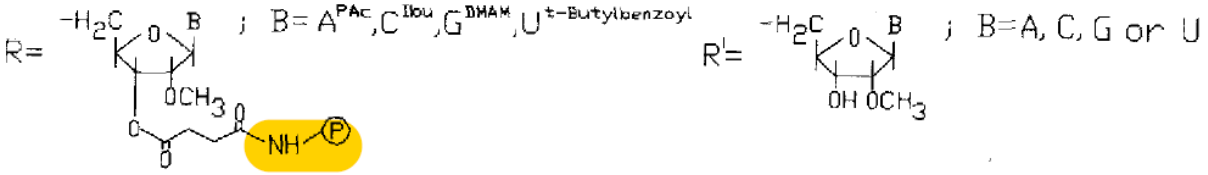
(Formula 2)

wherein B is selected from the group consisting of Guanine-N-acetyl, adenine-N-acetyl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl; W is Oxygen and R is methyl; and Z is C(O)-M-C(O)-NH, where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1-C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy. Petitioner's cited references do not disclose these limitations.

245. Petitioner and Dr. Baran references Gaur (1992) (Ex. 1024), as anticipating claim 5 because Gaur discloses a succinate molecule where the substituent group at the C1'-position (corresponding to "B" in Substitute Claim 7) is cytosine-N-isobutyryl. Substitute Claim 7 limits "B" such that it excludes cytosine-N-isobutyryl group from the group "consisting of Guanine-N-acetyl, adenine-N-acetyl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl." Gaur does

not disclose a succinate group with any of the "B" species recited in Substitute Claim 7 and therefore does not anticipate Substitute Claim 7.

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



Scheme 1. Reagents and conditions: (i), 3% TCA in CH_2Cl_2; (ii), salicyl phosphorochloridite; (iii), 0.5 M bis-tri-n-butylammonium pyrophosphate in DMF and tri-n-butylamine; (iv), sulphur; (v), dioxan-water; (vi) & (viii), 25% aq. ammonia; (vii), Iodine-water-pyridine-THF; PAc=phenoxyacetyl; Ibu=isobutyryl; DMAM=dimethyl-aminomethylidene, P=polymer support, DMT=4,4'-dimethoxytrityl.

(Ex. 1024, 3303).

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

248. Alternatively, should Claim 5 not be construed to correct the error and instead require "M" to be succinyl and not ethyl), then Ground VI fails because the reference that Petitioner and Dr. Baran rely on for this Ground VI (i.e., Gaur (1992) (Ex. 1024)), does not disclose a compound where "Z" is C(O)-M-C(O)-NH where "M" is succinyl or any of the remaining compounds listed in Claim 5's Markush group (i.e., where M is "oxalyl" or "hydroquinolynyl"). Accordingly, in my opinion, because all of the limitations of uncorrected Claim 5 are not taught by Gaur (1992) under this interpretation, then, based on the legal standards that I have been advised of, there is no anticipation under this Ground VI.

X. CONCLUSION

249. For the reasons stated above, and based on the legal standards that I have been advised of, it is my opinion that Claims 1-5 of the '885 Patent, as issued and amended, are not unpatentable.

I hereby declare under penalty of perjury under the laws of the United States that the foregoing is true and correct to the best of my knowledge, information, and belief.



Dated: 10/17/2023

Patrick J. Hrdlicka, Ph.D.

APPENDIX A

CURRICULUM VITAE

University of Idaho

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RANK: Professor

DEPARTMENT: Chemistry

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DATE OF TENURE: July 2011

IMMIGRATION STATUS: Permanent resident (green card holder)

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2006 Ph.D (Chemistry), Univ. Southern Denmark, Odense, Denmark (supervisor: Jesper Wengel)
2004 M.Sc (Chemistry), Univ. Southern Denmark, Odense, Denmark (supervisor: Jesper Wengel)
2000 B.Sc (Chemistry), Univ. Southern Denmark, Odense, Denmark (supervisor: JJL Iversen, deceased)

EXPERIENCE:

2017- Professor, Dept. Chemistry, Univ. Idaho
2011-2017 Associate Professor, Dept. Chemistry, Univ. Idaho
2006-2011 Assistant Professor, Dept. Chemistry, Univ. Idaho

2018-2019 Special Assistant to the Provost's Office, Univ. Idaho
2013-2016 Affiliate Faculty, Dept. Biological Sciences, Univ. Idaho
2011-2014 Adjunct Faculty, Dept. Chemistry, Washington State University
2006-2013 Affiliate Faculty, Neuroscience Graduate Program, Univ. Idaho

2023- Subject matter expert on a litigation pertaining to nucleoside/oligonucleotide chemistry
2022-2023 Subject matter expert on a litigation pertaining to DNA sequencing technology
2021 Subject matter expert on a litigation pertaining to nucleoside/nucleotide chemistry
2016-2020 Subject matter expert on two litigations pertaining to DNA sequencing technologies
2016-2017 Subject matter expert on a litigation pertaining to siRNA
2011-2015 Consultant for Minitube of America (now MOFA Global)
2011-2012 Consultant for ISIS Pharmaceuticals Inc (now Ionis Pharmaceuticals)

SCHOLARSHIP ACCOMPLISHMENTS:

Publications:
72 peer-reviewed articles and reviews (according to Google Scholar: >1,900 citations, h-index = 26 (underlined), i10-index = 56); eight patent applications (three issued); two book chapters; 36 published conference proceedings/abstracts; one published book review.

Peer Reviewed Journal Articles and Reviews:

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License Agreement:
Technology for use in diagnostic assays in animal reproduction technology was licensed to an undisclosed US company. Agreement was executed in November 1st 2011 and terminated in January 2019.

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[CP26] D. C. Julien, A. Giri, M. Papasani, G. Murdoch, P. Hrdlicka and R. A. Hill. Anti-K-Ras siRNA to treat pancreatic cancer. Nanotech Conference & Expo 2010: An Interdisciplinary Integrative Forum on Nanotechnology, Biotechnology and Microtechnology (Anaheim, CA), 401-404.

[CP25] M. R. Papasani, D. Pokharel, A. Giri, V. V. R. Sai, P. Hrdlicka and R. A. Hill. Oligoethylene glycol mediates knockdown effect of small interfering RNAs conjugated goldnanoparticles. Nanotech Conference & Expo 2010: An Interdisciplinary Integrative Forum on Nanotechnology, Biotechnology and Microtechnology (Anaheim, CA), 358-360.

[CP24] G. Wang, M. R. Papasani, P. J. Hrdlicka and R. A. Hill. Role of serum proteins in the cellular uptake of gold-peptide nanoconjugates. Nanotech Conference & Expo 2010: An Interdisciplinary Integrative Forum on Nanotechnology, Biotechnology and Microtechnology (Anaheim, CA), 304-307 (featured on Nano Science and Technology Institute webpage January 2011).

[CP23] P. Cheguru, M. Ostergaard, M. R. Papasani, V. V. R. Sai, J. Wengel, P. J. Hrdlicka and R. A. Hill. Novel nanoprobes to detect mRNA in situ, directed against mouse pyruvate dehydrogenase. Nanotech Conference & Expo 2010: An Interdisciplinary Integrative Forum on Nanotechnology, Biotechnology and Microtechnology (Anaheim, CA), 300-303.

[CP22] V. V. R. Sai, D. Gangaden, I. Niraula, G. Corti, D. N. McIlroy, D. E. Aston, J. Branen and P. J. Hrdlicka. Characterization of Au and Ag nanoparticle coated silica nanosprings - toward SERS based diagnostic applications. Nanotech Conference & Expo 2010: An Interdisciplinary Integrative Forum on Nanotechnology, Biotechnology and Microtechnology (Anaheim, CA), 19-22.

[CP21] S. Gibbon, J.R Branen, M. Frederickson and P. J. Hrdlicka. Identification of important food pathogens using LNA (Locked Nucleic Acid) probes. 2010 Joint 65th Northwest and 22nd Rocky Mountain Regional Meeting of the American Chemical Society (Pullman, WA), NWRM-207.

[CP20] V. V. R. Sai, D. Gangadean, I. Niraula, G. Corti, D. N. McIlroy, D. E. Aston, J. R. Branen and P. J. Hrdlicka. Au and Ag nanoparticle coated silica nanosprings: characterizarion of SERS-active materials and detection of DNA from biological threat agents. 2010 Joint 65th Northwest and 22nd Rocky Mountain Regional Meeting of the American Chemical Society (Pullman, WA), NWRM-206.

[CP19] B. A. Anderson, S. Karmakar, S. S. Iversen, R. L. Rathje, S. P. Sau and P. J. Hrdlicka. DNA targeting using next-generation invader LNAs. 2010 Joint 65th Northwest and 22nd Rocky Mountain Regional Meeting of the American Chemical Society (Pullman, WA), NWRM-53.

[CP18] S. P. Sau, S. S. Iversen, R. L. Rathje, B. A. Anderson, S. Karmakar, J. Onley, M. R. Papasani, R. A. Hill and P. J. Hrdlicka. Invader LNA - efficient targeting of iso-sequential double stranded DNA. 2010 Joint 65th Northwest and 22nd Rocky Mountain Regional Meeting of the American Chemical Society (Pullman, WA), NWRM-52.

[CP17] M. E. Østergaard, P. Kumar, B. Baral, D. C. Guenther, F. M. Ytreberg and P. J. Hrdlicka. Pyrene-functionalized oligonucleotides as probes in nucleic acid diagnostics. 2010 Joint 65th Northwest and 22nd Rocky

Mountain Regional Meeting of the American Chemical Society (Pullman, WA), NWRM-51.

[CP16] M. E. Østergaard, S. P. Sau, P. Kumar, B. A. Anderson, B. Baral, D. C. Guenther, M. Kaura and P. J. Hrdlicka. Optimized nucleic acid targeting using C5-functionalized LNA (Locked Nucleic Acid). 2010 Joint 65th Northwest and 22nd Rocky Mountain Regional Meeting of the American Chemical Society (Pullman, WA), NWRM-50.

[CP15] M. E. Østergaard, B. Baral and P. J. Hrdlicka. Discrimination of single nucleotide polymorphisms (SNPs) using brightly fluorescent C5-functionalized Locked Nucleic Acid (LNA) probes. 2010 Abstracts of Papers, 239th ACS National Meeting (San Francisco, CA), PHYS-671.

[CP14] M. E. Østergaard, S. P. Sau, P. Kumar, B. A. Anderson, B. Baral, D. C. Guenther and P. J. Hrdlicka. Optimized nucleic acid targeting using C5-functionalized LNA (Locked Nucleic Acid). 2010 Abstracts of Papers, 239th ACS National Meeting (San Francisco, CA), ORGN-429.

[CP13] S. P. Sau and P. J. Hrdlicka. Invader LNA: Efficient targeting of short double stranded DNA. 2010 Abstracts of Papers, 239th ACS National Meeting (San Francisco, CA), ORGN-323.

[CP12] B. A. Anderson, R. L. Rathje and P. J. Hrdlicka. DNA targeting using invader nucleic acids. 2010 Abstracts of Papers, 239th ACS National Meeting (San Francisco, CA), ORGN-305.

[CP11] S. Gibbon, M. E. Østergaard, J.R Branen and P. J. Hrdlicka. Identification of important food pathogens using LNA (Locked Nucleic Acid) probes. 2010 Abstracts of Papers, 239th ACS National Meeting (San Francisco, CA), AGFD-173.

[CP10] T. S. Kumar, A. S. Madsen, J. Wengel and P. J. Hrdlicka. N2′-Functionalized 2′-amino-alfa-L-LNA: A novel class of locked nucleic acids as emerging tools for nucleic acid therapeutics and diagnostics. 2008 Abstracts of papers, 235th ACS National Meeting (New Orleans, LA), CARB-009.

[CP9] M. E. Østergaard, J. Maity, J. Wengel and P. J. Hrdlicka. 2′-N-(Pyren-1-yl)carbonyl-2′-amino-LNA (locked nucleic acid): A versatile label for nucleic acid detection. 2008 Abstracts of papers, 235th ACS National Meeting (New Orleans, LA), BIOL-032.

[CP8] N. K. Andersen, J. Wengel and P. J. Hrdlicka. N2′-functionalized 2′-amino-α-L-LNA adenine derivatives - Efficient targeting of single stranded DNA. *Nucleosides Nucleotides Nucleic Acids* **2007**, *26*, 1415-1417.

[CP7] T. S. Kumar, J. Wengel and P. J. Hrdlicka. Pyrene-functionalized 2′-amino-α-L-LNA as potential diagnostic probes. *Nucleosides Nucleotides Nucleic Acids* **2007**, *26*, 1407-1409.

[CP6] T. S. Kumar, A. S. Madsen, J. Wengel and P. J. Hrdlicka. Synthesis and biophysical studies of N2′-functionalized 2′-amino-α-L-LNA. *Nucleosides Nucleotides Nucleic Acids* **2007**, *26*, 1403-1405.

[CP5] T. Umemoto, P. J. Hrdlicka, B. R. Babu and J. Wengel. Dual-probe system using pyrenylmethyl-modified amino-LNA for sensitive SNP genotyping in a homogeneous fluorescence assay. *Nucleosides Nucleotides Nucleic Acids* **2007**, *26*, 1261-1263.

[CP4] P. J. Hrdlicka, T. S. Kumar and J. Wengel. Synthesis of a 2′-amino-α-L-LNA-T phosphoramidite. *Nucleosides Nucleotides Nucleic Acids* **2005**, *24*, 1101-1104.

[CP3] P. J. Hrdlicka, J. S. Jepsen and J. Wengel. Synthesis and biological evaluation of conformationally restricted and nucleobase-modified analogs of the anticancer compound 3′-*C*-ethynylcytidine (ECyd). *Nucleosides Nucleotides Nucleic Acids* **2005**, *24*, 397-400.

[CP2] B. R. Babu, Raunak, M. D. Sørensen, P. J. Hrdlicka, S Trikha, A. K. Prasad, V. S. Parmar and J. Wengel. Novel nucleic acid architectures involving LNA (Locked Nucleic Acid) and pyrene residues – Results from an

Indo-Danish collaboration. *Pure Appl. Chem.* **2005**, *77*, 319-326.

[CP1] P. J. Hrdlicka, B. R. Babu, M. D. Sørensen, N. Harrit and J. Wengel. Ångström-scale chemical engineering: Multilabeled 2′-amino-LNA probes for nucleic acid detection in homogenous fluorescence assays. In: *Collection Symposium Series* (M. Hocek, Ed.), *7 (Chemistry of Nucleic Acid Components)*, 27-28, Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic, Prague **2005**.

Published Book Review:

[BR1] P. J. Hrdlicka. "Modified nucleosides in biochemistry, biotechnology and medicine" from Wiley, edited by Piet Herdewijn, *ChemBioChem,* **2009**, *10*, 378-379.

Presentations:
Delivered ~20 invited presentations, ~15 contributed talks and >25 posters at external venues, along with numerous internal contributions.

Invited Presentations:

2023: Idaho INBRE Research Conference (Moscow, ID).

2021: Post Fall High School (Post Falls, ID)

2020: Boise State University, Department of Chemistry (Boise, ID)

2017: Washington State University, School of Molecular Bioscience.

2016: University of Colorado (Denver, CO); University of Southern Denmark (Odense, Denmark); Idaho INBRE Research Conference (Moscow, ID).

2015: Alnylam Pharmaceuticals (Cambridge, MA); Gordon Conference on "Nucleosides, Nucleotides and Oligonucleotides" (Newport, RI); Alios BioPharma (South San Francisco, CA).

2014: Nucleic Acid Summit 2014 (San Diego, CA); 69th Northwest Regional Meeting of the American Chemical Society (Missoula, MT); 248th American Chemical Society Meeting (San Francisco, CA); Binghamton University (Binghamton, NY).

2012: 67th Northwest Regional Meeting of the American Chemical Society (Boise, ID); University at Albany (Albany, NY).

2011: University of Aarhus (Aarhus, Denmark); Carnegie Mellon University (Pittsburgh, PA); University of Copenhagen (Copenhagen, Denmark); Nucleic Acid Center Mini-symposium on "Nucleic Acid Chemical Biology" (Odense, Denmark).

2010: ISIS Pharmaceuticals (Carlsbad, CA); Minitube of America (Mt. Horeb, WI); Washington State University (Pullman, WA).

2008: University Southern Denmark (Odense, Denmark).

2007: Washington State University (Pullman, WA); Gordon Conference on "Nucleosides, Nucleotides and Oligonucleotides" (Newport, RI).

Contributed Talks:

2016: Eastern Washington University; University of Alaska, Fairbanks.

2014: 247th American Chemical Society National Meeting (Dallas, TX); Weber State University; Utah State University; Utah Valley University; Central Washington University; Brigham Young University (main campus); University of Utah; Brigham Young University (Idaho campus); Idaho State University.

2013: University of Montana; Eastern Washington University; Eastern Oregon University.

2012: 243th American Chemical Society National Meeting (San Diego, CA) – two presentations.

2010: 65th Northwest / 22nd Rocky Mountain Regional Meeting of the American Chemical Society (Pullman, WA); 239th American Chemical Society Conference (San Francisco, CA).

2008: 235th American Chemical Society National Meeting (New Orleans, LA).

2007: AAAS Pacific Division, 88th Annual Meeting of the Pacific Division Meeting & 62nd Annual Meeting of the Northwest Region, American Chemical Society (Boise, ID); Gonzaga University.

Student Presentations:

2022: Idaho INBRE Research Conference (Moscow, ID) - student presented a poster.

2021: 17th Annual Meeting of the Oligonucleotide Therapeutics Society (virtual) – student presented a video poster; Idaho INBRE Research Conference (Moscow, ID) - student presented a poster.

2020: 16th Annual Meeting of the Oligonucleotide Therapeutic Society meeting (virtual) - student presented a video poster.

2018: 14th Annual Meeting of the Oligonucleotide Therapeutic Society meeting (Seattle, WA) - student presented a poster.

2016: Idaho INBRE Research Conference (Moscow, ID) - student presented a poster.

2015: Idaho INBRE Research Conference (Moscow, ID) - student presented a poster.

2014: 10th Annual Oligonucleotide Therapeutics Society Meeting (San Diego, CA) – student presented poster and received the 2014 Dr. Alan M. Gewirtz Memorial Scholarship; Idaho INBRE Research Conference (Boise, ID) - student presented a poster; Nucleic Acid Summit (San Diego, CA) – student gave presentation and presented poster; 56th Idaho Academy of Science Conference (Moscow, ID) – student gave presentation; 247th ACS National Meeting (Dallas, TX) – students presented two posters.

2013: Idaho INBRE Research Conference (Moscow, ID) - student presented a poster.

2012: XX International Round Table on Nucleosides Nucleotides and Nucleic Acids (Montreal, Quebec, Canada) - students presented two posters; Idaho INBRE Research Conference (Moscow, ID) - student presented a poster (3rd place poster competition, faculty/staff choice category); Drug and Diagnostic Development Conference (San Francisco, CA) – postdoc presented a poster; 67th Northwest Regional Meeting of the American Chemical Society (Boise, ID) - student delivered a contributed talk; American Chemical Society Conference (San Diego, CA) - student presented a poster.

2011: Idaho-INBRE Research Conference (Moscow, ID) - student presented a poster; TIDES – Oligonucleotide and Peptide: Research Technology and Product Development (Boston, MA) – PI presented a poster; NW Regional Conference of the Society for Developmental Biology, Friday Harbor Laboratories (San Juan Island, WA) - collaborators presented a poster.

2010: 6th Annual Oligonucleotide Therapeutics Society Meeting (Dana Point, CA) – PI presented two posters; Pacific Northwest Undergraduate Research Symposium on Organic Chemistry & Chemical Biology - students delivered a contributed talk and a poster (winner of poster award); Bio Nanotech Conference and Expo (Anaheim, CA) - students and collaborators gave four contributed talks; 65th Northwest / 22nd Rocky Mountain Regional Meeting of the American Chemical Society (Pullman, WA) - students presented three contributed talks and two posters; American Chemical Society Conference (San Francisco, CA) - students presented a contributed talk and three posters.

2009: Sigma XI, Annual Meeting and Student Research Conference (Houston, TX) - students presented two posters; Donald S. Matteson Symposium (Washington State University) - students presented two posters (winner of poster award); Idea Network for Biomedical Research Excellence (INBRE) Conference (Pocatello, ID) - student presented a poster (winner of poster award).

2008: Sigma XI, Annual Meeting and Student Research Conference (Washington, DC) - students presented a poster; 17th Regional Conference on Undergraduate Research of the Murdock College Science Research Program (University of Puget Sound) - student presented a poster; Idea Network for Biomedical Research Excellence (INBRE) Conference (Boise, ID) - student presented a poster; American Chemical Society Conference (New Orleans, LA) - student presented a poster.
2007: Sigma XI, Annual Meeting and Student Research Conference (Washington, DC) - students presented a poster.

2006: XVII International Round Table, "Nucleosides, Nucleotides and Nucleic Acids" (Berne, Switzerland). – students and collaborators presented five posters (winner of poster award).

Local PI and Student Presentations*:*

2023: College of Science 20th Anniversary Seminar (Moscow, ID) – PI delivered a presentation

2021: 17th College of Science Student Research Expo (Moscow, ID) – student presented a poster.

2020: Department of Chemistry – PI delivered a presentation on Covid-19; 16th College of Science Student Research Expo (Moscow, ID) – student presented a poster.

2019: 15th College of Science Student Research Expo (Moscow, ID) – students presented two posters.

2018: 14th College of Science Student Research Expo (Moscow, ID) – students presented three posters.

2017: Department of Physics – PI delivered a presentation; 13th College of Science Student Research Expo (Moscow, ID) – student presented a poster.

2016: UI Undergraduate Research Symposium – student presented a poster.

2014: 10th College of Science Student Research Expo (Moscow, ID) – student presented a poster.

2013: Annual College of Science Student Research Exposition - students presented two posters (winner of Sigma Xi Scientific Research Society Award).

2012: Annual College of Science Student Research Exposition - students presented two posters.

2010: Annual College of Science Student Research Exposition - students presented four posters; Dept. Chemistry – PI delivered an oral presentation; Dept. of Microbiology, Molecular Biology and Biochemistry – PI delivered an oral presentation.

2009: Annual College of Science Student Research Exposition - students presented five posters; External review board meeting (IBEST/COBRE center) – PI presented two posters; IBEST Center – PI delivered an oral presentation; Neuroscience REU Poster Presentations - students presented two posters; BANTech Center – PI delivered an oral presentation.

2008: Annual College of Science Student Research Exposition - students presented five posters; Neuroscience REU Poster Presentations - students presented a poster.

2007: BANTech Center – PI delivered an oral presentation; IBEST Center – PI delivered an oral presentation; CAMBR Center – PI delivered an oral presentation.

2006: BANTech Center – PI delivered an oral presentation.

Grants and Contracts Awarded
Involved in securing seven external grants (total >$2M) and several internal grants (~$200k). Received unrestricted gifts totaling ~$50k from a US company.

External Grants Awarded:

2014-2016 Murdock Charitable Trust. Acquisition of a 500 MHz Nuclear Magnetic Resonance spectrometer ($681,866). Role: co-PI (PI: RV Williams, Univ. Idaho)

2014 Higher Education Research Council, Idaho State Board of Education (IGEM-004). Acquisition of a fluorescence microscope to support development of DNA diagnostics for use in the animal reproduction industry ($81,100). Role: PI.

2013-2014 Higher Education Research Council, Idaho State Board of Education (IF14-012). Production of gender-sorted sperm for applications in the animal reproduction industry using the Invader technology ($50,000). Role: PI.

2012-2013 Higher Education Research Council, Idaho State Board of Education (IF13-001). Development of diagnostic kits for gender determination of animal embryos ($50,000). Role: PI.

2010-2014 Department of Defense, Office of Naval Research (N00014-10-1-0282): Functionalized nanospring mats for detection of explosive materials (total $899,616). Role: PI of UI subcontract (PD: V Dobrohoktov, W. Kentucky Univ.; co-PI: DR McIlroy, Univ. Idaho).

2010-2011 INBRE-WSU Spokane – Institute of Translational Health Sciences (ITHS) Collaborative Translational Seed Grant: Invader LNAs to treat autosomal dominant retinal dystrophies ($40,000). Role: co-PI (PI: DR Stenkamp, Univ. Idaho; co-PI: M Neitz, Univ. Washington).

2009-2013 National Institute of Health, EUREKA (Exceptional, Unconventional Research Enabling Knowledge Acceleration), NIGMS (R01GM088697): Invader LNAs as novel gene specific therapeutics ($523,940). Role: PI (co-PIs: RA Hill, MR Papasani, Univ. Idaho).

Internal Grants Awarded:

2023 INBRE Pilot Grant. Silencing of gene expression using chemically modified DNA-targeting oligonucleotides ($50,000 direct). Role PI.

2016 Replacement of an ABI Expedite 8909 DNA Synthesizer, FY2016 One-Time Lab/Scientific/Test Equipment Funding Request ($22,000). Role: PI.

2015 Idaho INBRE: Submit your manuscript ($10,000). Role: PI.

2011 Idaho INBRE Graduate Student Grant: Application to support Ms. Brooke Anderson (~$25.000).

2010 Idaho INBRE Graduate Student Grant: Application to support Ms. Brooke Anderson (~$25.000).

2010 Idaho INBRE Travel grant: Attendance to 6th annual meeting of the oligonucleotide therapeutics society ($1,500). Role: PI.

2008 Univ. Idaho Research Office and Research Council Seed Grant: Functionalized Locked Nucleic Acid probes in enzymatic bio-nanotransduction systems for ultrasensitive biological threat detection platforms ($9,000). Role: PI, co-PIs: AL Branen and JR Branen (Univ. Idaho).

2008 Univ. Idaho, IBEST Pilot Grant Program: Intercalator-modified nucleic acid probes for targeting of double stranded DNA ($19,400). Role: PI.

2007 Idaho NSF EPSCoR Research Infrastructure Improvement (RII) – Startup Augmentation: Synthesis

of isotopically labeled nucleotide building blocks for characterization studies ($11,585). Role: PI.

2007 Idaho NSF EPSCoR Research Infrastructure Improvement (RII) – Instrumentation: Karl-Fischer titrator for water content determination in moisture-sensitive reactions ($8,000). Role: PI.

2007 Univ. of Idaho Research Office and Research Council Seed Grant: Easily accessible functionalized nucleic acids for targeting of dsDNA ($9,000). Role: PI.

2007 Univ. of Idaho EPSCoR Travel Grant: Travel to AAAS Pacific Division/ACS NW Regional Meeting ($900).

Funded participant on USDA CSREES Federal Appropriations proposals (PIs: DN McIlroy, DE Aston).

Funded member of BANTech Center, Univ. of Idaho (PD: DN McIlroy).

Gifts Received:

2012-2013 Unrestricted gifts ($50,000) from an undisclosed US company.

2012 Equipment donation (laminar flow hood, autoclave, thermal cyclers, incubators, -80 °C freezer, lyophilizer, microplate readers, centrifuges, etc) from Prof. Larry Branen (Univ. Idaho).

Honors and Awards:

2022 College of Science, Advisory Board Faculty Fellowship, Univ. Idaho

2013 Excellence in Research and Creative Activity Award, Univ. Idaho

2012 President's Inaugural Mid-Career Faculty Award, Univ. Idaho

2010 College of Science, Early Career Faculty Award, Univ. Idaho

TEACHING ACCOMPLISHMENTS:

Areas of Specialization: organic chemistry, medicinal chemistry, nucleic acid chemistry and biology.

Courses Taught and Developed

CHEM 277 Organic Chemistry I (Fall: 2009-2012, 2020-2023); 2010-2012 and 2021 classes averaged $58^{th}/65^{th}/60^{th}/38^{th}$ national percentile, respectively on standardized 1^{st} term ACS exams

CHEM 372 Organic Chemistry II (Spring: 2010, 2021-2023); 2010, 2022 and 2023 classes averaged $79^{th}/58^{th}/42^{nd}$ national percentile on standardized full-term ACS exam

CHEM 414/514 Applications of Nanomaterials in Biomedical Engineering (team taught, ~15% effort: Spring 2007/2008/2009/2010 – formerly CHEM404/504)

CHEM 472/572 Introduction to Medicinal Chemistry (Spring: 2008-2009, 2011, 2013-2015, 2017-2020, 2022-2023).

CHEM 571 Recent developments in Nucleic Acid Chemistry (Fall 2017)

CHEM 571 Nucleic Acids: Synthesis and Applications (Fall 2008/Spring 2012)

CHEM 571 Survey of DNA Targeting Technologies (Fall: 2013, 2015, 2019)

CHEM 571 Introduction to Nucleic Acid Chemistry (Fall: 2014, 2016)

Other Teaching Contributions:

CHEM 112H Principles of Chemistry II" (Spring 2007; guest lecturer); CHEM 299 Undergraduate Research (supervisor); CHEM 376 Organic Chemistry Lab II (Spring 2008; guest lecturer); CHEM 491 Undergraduate Research (supervisor); CHEM 500 Master's Research and Thesis (supervisor); CHEM 501 Seminar (Spring 2007-Spring 2008, coordinator); CHEM 502 Synthetic Nucleic Acid Chemistry (Spring 2008, supervisor); CHEM 502 Comprehensive Exam Organic Chemistry (Spring 2008, coordinator); CHEM 502 Advanced Nucleic Acid Chemistry (Spring 2009/2010, directed study); CHEM 502 Nucleobase-functionalized LNA (Fall 2016, Fall 2021); CHEM 502 Nucleic Acid Seminar (Spring 2018); CHEM 502 Survey of Invader technology (Fall 2019, directed study); CHEM 504 Frontiers in Nucleic Acids (Fall 2018, Spring 2020 and every semester onwards; CHEM590: Doctoral Research Proposal (supervisor); CHEM 600 Doctoral Research and Dissertation (supervisor); MMBB 404 Summer Research Seminar - Research Topics and Professional Development (Summer 2008/2009/2010/2011, supervisor); NEUR 508 Topics in Neuroscience (Spring 2007; guest lecturer); setting and grading cumulative and comprehensive exams.

Students Advised:

Undergraduate Students:

28 students have been supervised on research projects since 2006. UI students: Ryan Costa [fall 2022-spring 2023], Peter Wieber [summer 2022-present], Ibrahim Al Janabi [2021-2022], Allison Rowley [2014-2016], Hannah Kiser [2014], Philip Vukelich [2013-2015], Max Cowan [2013], Benjamin Denn [2011-2013], Mason Frederickson [2009-2011], Matt Womeldorff [2010-2011], Mitchell Odom [2010], David Love [2009-2010], Seth Gibbon [2009], Jared Rigoli [2008], Dusty van Hofwegen [2008], Pramod Yallamanchilli [2008], Kirsten Canady [2007], Michael Chavez [2007] and Sarah Doornbos [2007]; Visiting students: Macie-Grace Guthrie [2016, Brigham Young University - Idaho], Bradley Gibbons [2013, Brigham Young University - Idaho], Grace Anderson [2012, Montana Tech. Univ.], Tyler Horrocks [2012, Brigham Young University - Idaho], Jared Onley [2009, Whitworth University], Laurant Palmatier [2009, Univ. California San Diego], Daniel Raible [2008, Whitworth University], Joanna Hawryluk [2007, Simmons College] and Johanna Root [2007, Univ. Puget Sound].

I typically supervise 3-5 non-research undergraduates at any given time on curriculum and career matters, and typically write 5-10 recommendation letters per year for undergraduates seeking admission in graduate, medical or other professional schools.

Graduate Students:

Advised to completion of degree as major professor:

Summer 2021, Shiva P. Adhikari, PhD in Chemistry: "Optimizing Invader Probe Architectures for Sequence-Unrestricted Recognition of dsDNA Targets". Current occupation: Senior Scientist, Therapeutic Process Development, LGC Genomics (Bioresearch Technologies Inc.)

Summer 2020, Raymond G. Emehiser, PhD in Chemistry: "Exploring double-stranded DNA-targeting strategies". Current occupation: Senior Scientist, Abbott Laboratories (previous occupation: Scientist, Process Development, OliX).

Spring 2020, Caroline Shepard, MS in Chemistry: "Invader-mediated targeting of chromosomal DNA". Current occupation: Graduate student, University of Virginia Medical School.

Spring 2016, Eric Hall, MS in Chemistry (non-thesis option).
Current occupation: Graduate student, Idaho College of Osteopathic Medicine

Fall 2015, Dale C. Guenther, PhD in Chemistry: "Exploiting the Energy of Intercalation for Sequence-Specific Recognition of Double-Stranded DNA". Current occupation: Senior scientist, research analytics, Alnylam Pharmaceuticals, Cambridge, MA (previous: postdoctoral fellow at Alnylam Pharmaceuticals).

Spring 2015, Brooke A. Anderson, PhD in Chemistry: "Synthesis and Characterization of Energetically Activated Duplexes for Sequence-Unrestricted Recognition of Double-Stranded DNA". Current occupation: Senior scientist, oligonucleotide chemistry, Ionis Pharmaceuticals (previous: postdoctoral fellow with Ram Krishnamurthy, Scripps Research Institute).

Fall 2014, Mamta Kaura, Ph.D in Chemistry: "Synthesis and Characterization of Nucleobase Functionalized Locked Nucleic Acids (LNAs): Chemical Modifications for Therapeutics and Diagnostic Purposes".
Current occupation: Associate Scientist, Oligo Process Development section of Nitto Denko Avecia.

Fall 2013, Saswata Karmakar, Ph.D in Chemistry: "Synthesis and Biophysical Characterization of O2'-Intercalator-Functionalized Oligonucleotides for Mixed-Sequence Recognition of Double-Stranded DNA". Current occupation: Associate Director of Chemistry at Translate Bio (previous: postdoctoral fellow with Eric T. Kool, Stanford University).

Fall 2011, Sujay P. Sau, Ph.D in Chemistry: "Chemically modified oligonucleotides for targeting of DNA and RNA". Current occupation: Scientist with Aurigene Pharmaceutical Services Lmt. (previous occupation: postdoctoral fellow with John Chaput, UC Irvine).

Fall 2010, Michael E Østergaard, PhD in Chemistry: "Functionalized Locked Nucleic Acid for Therapeutic and Diagnostic Purposes". Current occupation: Research Fellow with Ionis Pharmaceuticals.

Spring 2010, Bharat Baral, MS in Chemistry: "Part I: Biophysical Characterization of C5-Functionalized Locked Nucleic Acids and Part II: Optimized Synthesis of [3-15N]-Labeled Uridine Phosphoramidites". Current occupation: Scientist with Janssen Pharmaceuticals.

Spring 2008, Todd Pankratz, MS in Chemistry (non-thesis option).
Current occupation: Director of Operations, Mary's Medicinals.

Visiting graduate students advised to completion of degree (as formal external supervisor):
Summer 2009, Sanne Iversen, M.Sc in Chemistry: "Intercalator modified RNA nucleosides" (co-supervisor: P Nielsen, Univ. Southern Denmark). Current occupation: Health Safety and Environment (HSE) Specialist at MHI Vestas Offshore Wind (Denmark)

Summer 2009, Rie L. Rathje, M.Sc in Chemistry: "DNA-targeting using N2'-functionalized 2'-methylamino DNA" (co-supervisor: P Nielsen, Univ. Southern Denmark). Present occupation: unknown.

Current advising of graduate students as major professor:
Michaela Brown (summer 2019-).
Ashikur Md. Rahman (fall 2021-)
Timo Dohm (fall 2022-)

Graduate committee member:
Daniel Julien (MS, major professor: Rod Hill, spring 2010)
Pallavi Cheguru (Ph.D, major professor: Rod Hill, spring 2011)
Niels Bomholt (Ph.D, major professor: Erik B. Pedersen, Univ. Southern Denmark, summer 2011)
Parameswara Subramanian (MS, major professor: Aaron Thomas, fall 2011)
Andrew Markelonis (MS, major professor: Chien Wai, fall 2011)
GuanKui Wang (Ph.D, major professor: Rod Hill, summer 2012)
Jamie Haas (Ph.D, major professor: David McIlroy, fall 2012)
Temple C. Warwick (Ph.D, major professor: Tom Bitterwolf, spring 2013)
Hugo Arajo (MS, major professor: Jakob Magolan, spring 2014)
Ebeneezer Jones-Mensah (PhD, major professor: Jakob Magolan, spring 2016)
Charlotte Reslow-Jacobsen (Ph.D, major professor: Poul Nielsen, Univ. Southern Denmark, summer 2016)
Dusty van Hofwegen (Ph.D, major professor: Sam Minnich, Fall 2016)
Tulsi Damase (Ph.D, major professor: Peter Allen, Fall 2018)
Abdulakeem Osumah (Ph.D, major professor: Kris Waynant, Summer 2020)
Moubani Chakraborty (Ph.D, major professor: Kris Waynant, Summer 2022)

Andrew Aring (Ph.D, major professor: Richard Williams, abandoned)

Postdoctoral fellows:
V.V.R. Sai (Mar 2009-Mar 2011). Current occupation: Associate Prof. Indian Institute of Technology, Madras

Shiva Rastogi (Dec 2010-Sep 2012). Current occupation: Lecturer, Texas State University

Visiting scientists:
Jianqin Liu (July 2013-Aug 2013: scientist at Minitube of America, Mt. Horeb, WI, USA)
Pawan Kumar (Jan 2008-Jan 2009 and March 2010-July 2010: Ph.D. student, Kurukshetra University, India)
T. Santhosh Kumar (Sep 2007-Dec 2007: Ph.D. student, Univ. Southern Denmark, Denmark)

Honors and Awards:

2022	Donald Crawford Graduate Faculty Mentoring Award, Univ. Idaho

SERVICE:

Professional Memberships

2008-2015	Member, American Chemical Society, carbohydrate section
2010-2011, 2018	Member, Oligonucleotide Therapeutics Society
2010-2011	Member, Institute of Translational Health Sciences (ITHS)

Professional Service

Referee on ~155 manuscripts submitted to Chemical Communications; Journal of Organic Chemistry; Journal of the American Chemical Society; Nucleic Acids Research; ChemBioChem; Organic and Biomolecular Chemistry; Chemistry – European Journal; Chemical Science; Angewandte Chemie; etc.

Grant reviewer for National Science Foundation (NSF), Royal Society of Chemistry (UK), Czech Science Foundation, Biotechnology and Biological Science Research Council (UK), and Macquaire University (Australia). Pre-submission reviewer on NIH proposals from Univ. Nebraska.

Member of the Scientific Advisory Council of the Oligonucleotide Therapeutics Society (2013-present).

Member of the Scientific Advisory Board for OLIGOMED, an EU project (2021-present).

Guest Editor for special issue of the journal Chemosensors entitled “Nucleic Acid Probes” (2014-2015).

External reviewer, promotion and tenure committee, Colorado State University (2015) and Boise State University (2013).

Co-organizer, Medicinal Chemistry Section, ACS NORM-RMRM Meeting 2010.

Conducted and published book review for ChemBioChem (2009).

Committee Service:

University level:

2019-2020	Member, President Green's Sustainable Financial Model Working Group
2018-2019	Member, Promotion and Tenure Task Force (compensation)
2018	Member, University Finance Advisory Committee
2018	Member, PERSI/ORP workgroup
2018	Member, search committee, Manager for Faculty Operations
2017-2018	Member, search committee, Director for Confucius Institute
2017-2018	Member, 'Great Colleges to Work For' Cascading Plan workgroup
2017	Chair, nominating committee, Faculty Secretary search

2016-2017	Chair, Committee on Committees
2016-2018	Co-chair, Faculty Compensation Task Force
2016-2017	Member, University Budget and Finance Committee
2015-2018	Member, Faculty Senate (chair 2017-present; vice chair 2016-2017)
2015-2016	Member, Benefits Advisory Group
2015-2016	Member, Vandal Strategic Loan Fund Committee
2008-2011	Member, Faculty Affairs Committee

College level:

2023	Member, COS Budget Model Workgroup
2022-present	Member, COS Promotion and Tenure committee
2012-2014; 2015-2018	Member, Faculty and Staff Council
2012	Member, promotion committee (Animal Vet. Science)
2012	Member, search committee, interim and permanent Dean (College of Science)
2010	Faculty Marshal, commencement
2008-2011	Member, LeTourneau committee
Fall 2008	Member, 3rd year review committee (Dept. Physics)

Department level:

2022	Chair, promotion and tenure committee (Waynant)
2022	Member, 3rd year review committee (Andrasi)
2021-2022	Member, search committee, faculty position, Dept. Chemistry
2019, 2020	Chair, peer performance review committee
2017	Member, 3rd year review committee (Stoian)
2015	Member, promotion and tenure committee (Magolan)
2013-2018	Chair, graduate admissions and recruitment committee
2013	Member, promotion and tenure committee
2012	Member, 3rd year review committee (Magolan)
2010-2011; 2014-2015; 2017-2018; 2020	Member, chair's advisory committee
2009-2013	Member, graduate admissions committee (chair 2011-2012)
2009-2010	Member, search committee, Assistant Professor (Chemistry - organic)
2008-2011	Chair, graduate recruitment committee
2007	Member, exploratory committee, establishment of BS forensic chemistry degree
2006-2007	Member, committee for student-faculty relations
2006-2008	Faculty Secretary

Outreach:

2021	Helped design an experiment for a NASA-funded science project for Moscow cub scout pack 323 entitled "Plant Mars";
2021	Participated as a member of a faculty panel for the "Success in COS" program
2020	Interview in connection with a video entitled "Vandals Move Online Amid COVID19 Concerns"
2019	Contributed 1-page section to VandAlchemist, an alumni newsletter.
2018	Provided lab tour to Cub Scout Pack 323, Moscow, Idaho.
2017	Interview with the BLOT – a student magazine at the University of Idaho – concerning the Vandals Table Tennis Club.
2017	Interview with the Argonaut – the main student newspaper at the University of Idaho – concerning turnover of UI presidents.
2016	Interview with the Argonaut – the main student newspaper at the University of

	Idaho – concerning matters discussed at Faculty Senate.
2016	Participated in interview conducted by student working with the College of Science Student Ambassador program.
2015	Three interviews with the Argonaut – the main student newspaper at the University of Idaho – concerning matters discussed at Faculty Senate.
2013-present	Founder and editor of Departmental LinkedIn site.
2013	Extended Learning Internship Mentor for high school student (J. Cornwall, Moscow High School).
2013	Contributed article entitled "New study from Isis Pharmaceuticals on allele selective suppression of mutant Huntingtin in the central nervous system" to Oligonucleotide Therapeutics Society newsletter.
2013	Served as the formal university representative in discussions with Chairman Earl Sullivan from the Idaho Coalition for Innovation (The CORE).
2012	Interview with University Communications and Marketing Department in connection with development of new fundraising brochure.
2010	Interview articles with undergraduate researcher Mason Frederickson and Dr. Hrdlicka published on UI homepage.
2010	Interview articles with undergraduate researcher Mason Frederickson and Dr. Hrdlicka published in local newspaper, electronic news sites and UI media on the occasion of 2010 INBRE Conference.
2010	Article entitled "Nanomaterials for Biosensor Platforms Toward Increasing Safety and Shelf Life of Agricultural Commodities" (DE Aston, DN McIlroy, L Branen, S Rastogi, J Branen, G Corti, PJ Hrdlicka, K Noren and JJ Nagler) published in The World of Food Science.
2010	Interview articles published in UI Argonaut, UI Friday Letter, and regional newspapers and electronic news sites on the occasion of procuring the DoD award "Functionalized Nanospring mats for detection of explosive materials".
2009	Interview articles published in Vandal Science and regional newspapers and electronic news sites on the occasion of procuring the NIH award "Invader LNAs as novel Gene Specific Therapeutics".

Other Service:

Spring 2021	Participated in virtual undergraduate recruitment event at Post Falls High School
Fall 2016	Recruitment trips to Eastern Washington University and University of Alaska, Fairbanks
Summer 2016	Member, "Global Research Panel", Idaho INBRE Statewide Research Conference (Moscow, ID)
Fall 2014	Recruitment trips to Weber State University, Utah State University, Utah Valley University, Central Washington University, Brigham Young University (Idaho campus) and Idaho State University
Summer 2014	Recruiter at 69th Northwest Regional Meeting of the American Chemical Society (Missoula, MT)

Fall 2013	Recruitment trips to University of Montana, Eastern Washington University and Eastern Oregon University
Summers 2008-2016	Mentor, visiting undergraduates, INBRE REU program
Summers 2008-2011	Member, "Beyond Baccalaureate Discussion Panel", Idaho INBRE Seminar Series
Fall 2008	Co-host, ~15 potential transfer students from North Idaho College
Fall 2008	Participant, recruitment luncheon at Univ. Idaho for prospective graduate students from Brigham Young Univ
Spring 2008	Judge, UI Student Research Expo
Fall 2007	Recruitment trip, Gonzaga University
Summers 2007-2009	Mentor, visiting undergraduates, Neuroscience REU program
Fall 2007/2009/2010	Poster judge, Annual College of Science, Student Research Exposition, Univ. Idaho

Community Service:

2019	Hosted two table tennis practice sessions for Cub Scout Pack 323, Moscow, Idaho.
2008-present	Academic advisor and treasurer for the Vandals Table Tennis Club (2015-2019: secured ~$10,000 from the ASUI to purchase equipment; coordinated three student tournaments; maintains social media pages)

Honors and Awards:

2018	Recipient, Student Organization Advisor Award, Univ. Idaho

PROFESSIONAL DEVELOPMENT:

2020 Participant, webinar, I am afraid that my students are cheating, Univ. Idaho

2019 Participant, M.J. Murdock Trust Commercialization Initiation Program Info Session

2019 Participant, HERC IGEM Info Session

2019 Participant, webinar - Powerless to Powerful, Taking Control, Univ. Idaho

2019 Polyplexus Pilot 3 Proposers Day Webinar, Defense Science Office, DARPA

2018 Participant, mandatory training, IT Security Awareness, Univ. Idaho

2018 Participant, mandatory training, Creating a Respectful Community, Univ. Idaho

2018 Participant, mandatory training, Campus Security Authority Training, Univ. Idaho

2017 Participant, workshop – Center of Teaching Learning: Zoom Essentials, Univ. Idaho

2017 Participant, webinar – Strategic Thinking, Univ. Idaho

2016 Participant, workshop - Building Team Relationships

2016 Participant, webinar - Communicating Through Email: Top 10 Do's & Don'ts

2016 Participant, webinar - Public Speaking Without Fear, Univ. Idaho

2016 Participant, webinar - Defeating Negativity in the Workplace, Univ. Idaho

2016 Participant, webinar - How to Handle Emotions Under Pressure, Univ. Idaho

2016 Participant, mandatory training - Diversity & Inclusion at the University of Idaho

2016 Participant, mandatory training - IT Security

2016 Participant, mandatory training - Safety & Security Awareness

2015 Participant, mandatory training - University of Idaho Mission & Goals

2015 Participant, mandatory training - Performance Management

2015 Participant, mandatory training - Performance Evaluations

2015 Participant, mandatory training - Navigating the Employment Legal Landscape, Part 1

2015 Participant, mandatory training - Navigating the Employment Legal Landscape, Part 2

2015 Participant, mandatory training - Strategies for Selection & Hiring Success

2015 Participant, mandatory training - University of Idaho Stewardship of Resources & Ethical Conduct

2010 Participant, online course - Acuc101: Introduction to animal care and use, Univ. Idaho.

2010 Participant, "Write winning grants", Grant Writer's Seminar & Workshops, Idaho INBRE Program.

2010 Participant, annual retreat - Initiative for Bioinformatics and Evolutionary Studies (IBEST) Center.

2010 Participant, workshop - "So what ? who cares ? why you ?" hosted by Idaho TechConnect (Univ. Idaho), which presented commercialization success tools.

2008 Participant, annual retreat - Initiative for Bioinformatics and Evolutionary Studies (IBEST) Center.

2007 Participant, workshop - "NSF Days at WSU Spokane Riverpoint".

2007 Participant in three workshops on "Finding Funding/Responding to a Program Announcement", "Proposal Budget Development and Award Administration", and "Reviewer`s Perspective on Proposals" offered by Grant Development Specialists at Univ. Idaho.

Patrick J. Hrdlicka – Experience as subject matter expert.

Rendered expert analysis pertaining to a pending litigation between Alnylam Pharmaceuticals, Inc. v. Dicerna Pharmaceuticals, Inc. concerning trade secret misappropriation claims against Dicerna, and counterclaims asserted by Dicerna. A settlement was reached. Retained by: Choate Hall & Stewart LLP (Greta Fails) representing Alnylam Pharmaceuticals. Analyzed technical reports.

United States International Trade Commission involving "Certain single-molecule nucleic acid sequencing systems and reagents, consumables, and software for and use with same", 337-TA-1032. Retained by Baker Botts LLP (Puneet Kohli, Stephen Hash) representing Oxford Nanopore. Analyzed technical reports, prepared expert reports, and was deposed.

Prepared declaration in Support of Petition for *Inter Partes* Review of U.S. Patent No. 9,738,929; Oxford Nanopore Technologies, Inc. Petitioners v. Pacific Biosciences Of California, Inc. Patent Owner, IPR2018-01792, Patent 9,738,929. Retained by Baker Botts LLP (Puneet Kohli, Stephen Hash) representing Oxford Nanopore.
Pacific Biosciences of California, Inc., v. Oxford Nanopore Technologies, Inc. district court matters (C.A. No. 17-01353-LPS and C.A. No. 17-00275-LPS). Retained by Baker Botts LLP (Stephen Hash, Elizabeth Flannery, Samoneh Kadivar) representing Oxford Nanopore. Analyzed technical reports, prepared expert reports, was deposed, and testified in court.

CGI Matters Adverse To Illumina (Case No. 1:19-cv-00970-MN (D. Del.); Case No. 19-cv-03770-WHO (N.D. Cal.); Case No. 20-cv-01465-WHO (N.D. Cal.). Retained by Quinn Emanuel Urquhart & Sullivan, LLP (Margaret Shyr, David Blisker, Anne Toker) representing CGI. Analyzed technical reports, prepared expert report and was deposed.

Twinstrand Biosciences, inc., & University of Washington v. Guardant Health, Inc (Case No. 1:21-cv-01126-LPS (D. Del.). Retained by Sterne, Kessler, Goldstein & Fox P.L.L.C (Trey Powers) representing Twinstrand. Performed a preliminary analysis of a representative patent.

Providing expert opinions in connection with an *Inter Partes* Review (IPR2023-004490) of U.S. Patent No. 9,884,885. Retained by Rothwell, Figg, Ernst & Manbeck (Daniel Shores) (via Rubin Anders Scientific) representing ChemGenes.

Areas of expertise: Nucleic acids, DNA, RNA, oligonucleotides, antisense oligonucleotides, splice-switching oligonucleotides, small interfering RNA (siRNA), messenger RNA (mRNA), aptamers, duplexes, triplexes, nucleic acid structures, fluorescence in situ hybridization (FISH), imaging, nucleic acid therapeutics, nucleic acid diagnostics, DNA sequencing, gene editing, synthesis, carbohydrates, nucleosides, nucleotides, medicinal chemistry, protecting groups, organic chemistry, conformationally restricted nucleotides, chemically modified nucleosides, chemically modified oligonucleosides, Locked nucleic acid (LNA), Bridged nucleic acid (BNA), peptide nucleic acid (PNA), pyrene, intercalators.

APPENDIX B

Petitioner's Exhibits

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

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

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

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

EXHIBIT C

Patent Owner's Exhibits

Ex. No.	Description
2001	Y. Huang et al., *A P(V) platform for oligonucleotide synthesis*, SCIENCE 373(6560):1265-70 (Sept. 2021)
2002	D. Flood et al., *DNA Encoded Libraries: A Visitor's Guide*, ISRAEL J. CHEM 60(3):268-280 (Jan. 2020)
2003	D. Flood et al., *Expanding Reactivity in DNA-Encoded Library Synthesis via Reversible Binding of DNA to an Inert Quaternary Ammonium Support*, J. AM. CHEM. SOC. 141(25):9998-10006 (May 2019)
2004	Exhibit number not used
2005	Exhibit number not used
2006	R. Hogrefe et al., *Current Challenges in Nucleic Acid Synthesis*, ISRAEL J. CHEM 53(6):326-349 (Jun. 2013)
2007	Second Amended Complaint, *ChemGenes Corp. v. Hongene Biotech Corp.*, 1:22-cv-10290, D.I. 18 (D. Mass. May 27, 2022)
2008	Expert Declaration of Patrick Hrdlicka, Ph.D.
2009	Dr. Phil S. Baran Deposition Transcript
2010	K. Krouse et al., *Unlocking P(V): Reagents for chiral phosphorothioate synthesis*, SCIENCE 361(6408):1234-38 (Aug. 2018)
2011	H. Weber & H. Khorana, *Total synthesis of the structural gene for an alanine transfer ribonucleic acid from yeast. Chemical synthesis of an icosadeoxynucleotide corresponding to the nucleotide sequence 21 to 40*, J. MOL. BIOL. 72(2):219-249 (Dec. 1972)

2012	H. Schaller et al., *The Stepwise Synthesis of Specific Deoxyribopolynucleotides (4). Protected Derivatives of Deoxyribonucleosides and New Syntheses of Deoxyribonucleoside-3' Phosphates*, J. AM. CHEM. SOC. 85(23):3821-27 (Dec. 1963)
2013	J.C. Schulhof et al., *The final deprotection step in oligonucleotide synthesis is reduced to a mild and rapid ammonia treatment by using labile base-protecting groups*, NUCLEIC ACID RES. 15(2):397-416 (Jan. 1987)
2014	W. Guschlbauer & K. Jankowski, *Nucleoside conformation is determined by the electronegativity of the sugar substituent*, NUCLEIC ACID RES. 8(6):1421-33 (Mar. 1980)
2015	M. Ober et al., *Base Pairing and Replicative Processing of the Formamidopyrimidine-dG DNA Lesion*, J. AM. CHEM. SOC. 127(51):18143-49 (Dec. 2005)
2016	R. P. Iyer, *Nucleobase Protection of Deoxyribo- and Ribonucleosides*, CURRENT PROTOCOLS IN NUCLEIC ACID CHEMISTRY 2:2.1.1-2.1.17 (May 2001)
2017	H. Köster, *N-Acyl Protecting Groups for Deoxynucleosides*, TETRAHEDRON 37(2):363-69 (1981)
2018	N.D. Sinha, *Labile exocyclic amine protection of nucleosides in DNA, RNA and oligonucleotide analog synthesis facilitating N-deacylation, minimizing depuration and chain degradation*, BIOCHIMIE 75(1):13-23 (1993)
2019	S. Scaringe, *Preparation of 5'-Silyl-2'-Orthoester Ribonucleosides for Use in Oligoribonucleotide Synthesis*, CURRENT PROTOCOLS IN NUCLEIC ACID CHEMISTRY 2:2.10.1-2.10.16 (May 2004)
2020	H. Weber & H. Khorana, *Total synthesis of the structural gene for an alanine transfer ribonucleic acid from yeast. Chemical synthesis of an icosadeoxynucleotide corresponding to the nucleotide sequence 31 to 50*, J. MOL. BIOL. 72(2):251-288 (Dec. 1972)
2021	L. McBride et al, *Amidine Protecting Groups for Oligonucleotide Synthesis*, J. AM. CHEM. SOC. 108:2040-48 (1986)

2022	R. Iyer et al., *Nucleobase Protection of Deoxyribo-and Ribonucleosides,* CURRENT PROTOCOLS IN NUCLEIC ACID CHEMISTRY, 2.1.1-2.1.40 (2017)
2023	A. Culf et al., *Fast Deprotection of Synthetic Oligodeoxyribonucleotides Using Standard Reagents under Microwave Irradiation,* OLIGONUCLEOTIDES 18:81-92 (2008)
2024	GEORGE OKAFO ET AL., ANALYSIS OF OLIGONUCLEOTIDES AND THEIR RELATED SUBSTANCES (2013)
2025	A. Kawasaki et al., *Uniformly Modified 2'-Deoxy-2'-fluoro Phosphorothioate Oligonucleotides as Nuclease-Resistant Antisense Compounds with High Affinity and Specificity for RNA Targets*, J. MED. CHEM. 26:831-41 (1993)
2031	R. T. Pon, *Solid-Phase Supports for Oligonucleotide Synthesis*, CURRENT PROTOCOLS IN NUCLEIC ACID CHEMISTRY, 3.1.1-3.1.28 (2000)