

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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SHANGHAI HONGENE BIOTECH CORPORATION,

Petitioner,

v.

CHEMGENES CORPORATION,

Patent Owner.

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

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

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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 and 2 of U.S. Patent No. 8,309,707 (“the ’707 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 bespoke nucleoside phosphoramidites, their use as reagents to make chemically modified oligonucleotides via machine-assisted 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. 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 and 2018, I served as a member, elected vice-chair, and elected chair of the Faculty Senate at the University of Idaho. Between 2018 and 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. In 2023, I received an Alumni Award for Excellence 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. The nucleoside phosphoramidites are then used as reagents in machine-assisted solid phase oligonucleotide synthesis.

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 applications, issued patents, and proceedings/abstracts 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 approximately 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 nucleosides, oligonucleotides, and nucleic acid sequencing technologies.

12. As reflected in my C.V., I have been involved as a subject matter expert 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);

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

(F) *Inter Partes* Review of U.S. Patent No. 9,884,885 IPR2023-00490 (representing ChemGenes Corporation); and

(G) *Inter Partes* Review of U.S. Patent No. 8,541,569 IPR2023-00862 (representing ChemGenes Corporation).

13. 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, knowledge, and experience in the relevant art of over 20 years, and considered the Petition, declaration submitted by Dr. Baran in support of the Petition, including all of its exhibits, Patent Owner's Motion to Amend Claims, as well as other literature referenced herein and listed in **Appendix B** and **Appendix C**.

**III. SUMMARY OF MY OPINIONS<sup>1</sup>**

16. Claim 1 of the '707 Patent, as Patent Owner has proposed it to be amended, claims compounds not anticipated over the cited prior art.

17. Claim 2 of the '707 Patent, as Patent Owner has proposed it to be amended, claims compounds not anticipated over the cited prior art.

**IV. LEGAL BASES FOR MY OPINIONS**

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<sup>1</sup> The summary of my opinions is in no way intended to be limiting, and I more completely discuss my opinions below.

18. I am not an attorney or a patent agent nor have I independently researched the law on patentability. ChemGenes' attorneys have explained the relevant legal standards to me that I have relied on in forming my opinions set forth in this declaration.

**A. Patent Claims in General**

19. 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.

20. 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 the independent claims of the '707 Patent are written in Markush format. I understand that the '707 Patent contains three independent claims (Claims 1-3) and no dependent claims. Petitioner has challenged only Claims 1 and 2.

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

21. 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 the 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.

22. 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**

23. 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.

24. 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 to 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.

25. 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.

26. 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. Anticipation**

27. 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.

28. 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.

29. 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.

**E. Priority and Prior Art**

30. 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.”

31. 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.

**V. THE '707 PATENT**

32. I have reviewed the '707 Patent, which was issued on November 13, 2012. Ex. 1001, 1. The cover of the '707 Patent indicates that the application that led to the issuance of the '707 Patent, U.S. Patent App. No. 12/584,625 (“the '625 Application”) (Ex. 1002, 5-71), was filed September 8, 2009 and claims priority to U.S. Provisional App. No. 61/191,065 (Ex. 2002) (“the '065 Provisional”), filed on September 6, 2008. *Id.*

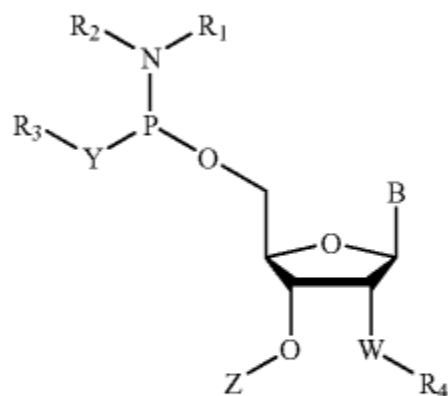
33. I have also reviewed the file history of the '707 Patent, Ex. 1002, and understand the background and exchanges between the United States Patent and Trademark Office ("U.S.P.T.O.") in the course of prosecuting the application that led to the issuance of the '707 Patent. *Id.*

34. Based on the cover of the '707 Patent, the '707 Patent is titled: "RNA synthesis-phosphoramidites for synthetic RNA in the reverse direction, and application in convenient introduction of ligands, chromophores and modifications of synthetic RNA at the 3'-end." *Id.*

35. The '707 Patent has 3 claims, all of which are independent claims. Independent Claims 1 and 2, which are relevant to the Petition, are reproduced from the published copy of the '707 Patent as follows (Ex. 1001, Cols. 33-36):



1. A phosphoramidite having formula (1),



Formula (1)

where,

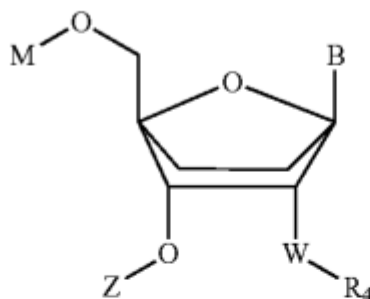
Y is an oxygen atom or a sulfur atom;

W is selected from the group consisting of an oxygen diradical, a N—H diradical and a fluorine radical, and R<sub>4</sub> is selected so that,

- if W is an oxygen diradical, then  $R_4$  is tert butyl dimethyl silyl (TBDMS) or triisopropylsilyloxymethylene (TOM);
- if W is a N—H diradical, then  $R_4$  is of the form  $R_5^x$  where x is selected from the group consisting of fluorenylmethyloxycarbonyl (Fmoc), trifluoroacetyl, acetyl, alkanoyl, and aroyl; and
- if W is a fluorine radical, then  $R_4$  is not present;
- B is selected from the group of nucleoside base radicals consisting of -9-( $N^6$ -benzoyladeninyl)-, 9-( $N^6$ -acetyladeninyl)-, 9-( $N^6$ -tert butyl phenoxyacetyladeninyl)-, 9-( $N^6$ -phenoxyacetyladeninyl)-, 9-( $N^6$ -isopropyl phenoxyacetyladeninyl)-, 1-( $N^4$ -benzoylcytosinyl)-, 1-( $N^4$ -acetylcytosinyl)-, 1-( $N^4$ —(N,N-dimethylformamidinyl)cytosinyl)-, 1-( $N^4$ -phenoxyacetylcytosinyl)-, 1-( $N^4$ -tertbutylphenoxyacetylcytosinyl)-, 1-( $N^4$ -isopropyl phenoxyacetylcytosinyl)-, 9-( $N^2$ -isobutyrylguaninyl)-, 9-( $N^2$ -tertbutylphenoxyacetylguaninyl)-, 9-( $N^2$ -isopropylphenoxyacetylguaninyl)- $N^4$ -phenoxyacetylcytosinyl)-, 1-( $N^4$ -tertbutylphenoxyacetylcytosinyl)-, 1-( $N^4$ -isopropyl phenoxyacetylcytosinyl)-, and 1-uracilyl-;
- or, B is a modified nucleoside base radical selected from the group consisting of 1-( $N^4$ -benzoyl-5-methylcytosinyl)-, 1-( $N^4$ —(N,N-dimethylformamidinyl)-5-methylcytosinyl)-, 1-( $N^4$ -acetyl-5-methylcytosinyl)-, 1-(5-methyl-uracilyl)-, -(5-fluoro-uracilyl)-, 1-( $N^4$ -benzoyl-5-fluorocytosinyl)-, 9-( $N^6$ -benzoyl-7-deazaadeninyl)-, 9-( $N^6$ —(N,N-dimethylformamidinyl)-7-deazaadeninyl)-, 9-( $N^2$ -isobutyryl-7-deazaguaninyl)-, and 9-( $N^2$ —(N,N dimethylformamidinyl)-7-deazaguaninyl)-;
- Z is a protecting group selected from the group consisting of dimethoxytriphenylmethyl (DMT), monomethoxytriphenylmethyl (MMT) and trimethoxytriphenylmethyl (TMT);
- $R_1$  is an alkyl or aryl radical;
- $R_2$  is an alkyl or aryl radical; and,
- $R_3$  is a cyanoethyl radical, alkyl radical or aryl radical.

2. A derivatized nucleoside having a structure of formula 2,

Formula (2)



where,

M is a hydrogen radical or a linker;

if M is a linker, then it is represented by the formula  
Y—C(O) and, optionally, connected to a solid support  
suitable for oligonucleotide synthesis, wherein

Y is a chain of between 2 and 20 carbons, selected from the  
group consisting of alkyl, alkenyl, cycloalkyl, aryl, and  
aralkyl, in a hydrocarbyldiradical moiety, optionally  
comprising intervening —O—, —S—, —S(O)<sub>2</sub>—,  
—C(O)—, and —NR<sub>6</sub>—, where R<sub>6</sub> is a hydrogen radi-  
cal, or a substituted C<sub>1</sub> to C<sub>20</sub> alkyl or a substituted  
aralkyl;

W is selected from the group consisting of an oxygen  
diradical, a N—H diradical and a fluorine radical, and R<sub>4</sub>  
is selected so that,

if W is an oxygen diradical, then  $R_4$  is tert butyl dimethyl silyl (TBDMS) or triisopropylsilyloxymethylene (TOM);

if W is a N—H diradical, then  $R_4$  is of the form  $R_5^x$  where x is selected from the group consisting of fluorenylmethyloxycarbonyl (Fmoc), trifluoroacetyl, acetyl, alkanoyl, and aroyl; and

if W is a fluorine radical, then  $R_4$  is not present;

B is selected from the group of nucleoside base radicals consisting of -9-( $N^6$ -benzoyladeniny)-, 9-( $N^6$ -acetyladeniny)-, 9-( $N^6$ -tert butyl phenoxyacetyladeniny)-, 9-( $N^6$ -phenoxyacetyladeniny)-, 9-( $N^6$ -isopropyl phenoxyacetyladeniny)-, 1-( $N^4$ -benzoylcytosiny)-, 1-( $N^4$ -acetylcytosiny)-, 1-( $N^4$ —(N,N-dimethylformamidiny)cytosiny)-, 1-( $N^4$ -phenoxyacetylcytosiny)-, 1-( $N^4$ -tertbutylphenoxyacetylcytosiny)-, 1-( $N^4$ -isopropyl phenoxyacetylcytosiny)-, 9-( $N^2$ -isobutyrylguaniny)-, 9-( $N^2$ -tertbutylphenoxyacetylguaniny)-, 9-( $N^2$ -isopropylphenoxyacetylguaniny)-,  $N^4$ -phenoxyacetylcytosiny)-, 1-( $N^4$ -tertbutylphenoxyacetylcytosiny)-, 1-( $N^4$ -isopropyl phenoxyacetylcytosiny)-, and 1-uracilyl-;

or B is selected from the group of modified nucleoside base radicals selected from the group consisting of

1-( $N^4$ -benzoyl-5-methylcytosiny)-, 1-( $N^4$ —(N,N-dimethylformamidiny)-5-methylcytosiny)-, 1-( $N^4$ -acetyl-5-methylcytosiny)-, 1-(5-methyl-uracilyl)-, -(5-fluoro-uracilyl)-, 1-( $N^4$ -benzoyl-5-fluorocytosiny)-, 9-( $N^6$ -benzoyl-7-deazaadeniny)-, 9-( $N^6$ —(N,N-dimethylformamidiny)-7-deazaadeniny)-, 9-( $N^2$ -isobutyryl-7-deazaguaniny)-, and 9-( $N^2$ —(N,N-dimethylformamidiny)-7-deazaguaniny)-; and,

Z is a protecting group selected from the group consisting of dimethoxytriphenylmethyl (DMT), monomethoxytriphenylmethyl (MMT) and trimethoxytriphenylmethyl (TMT).

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

37. 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 1-2, Petitioner only challenged one compound per claim, i.e.,

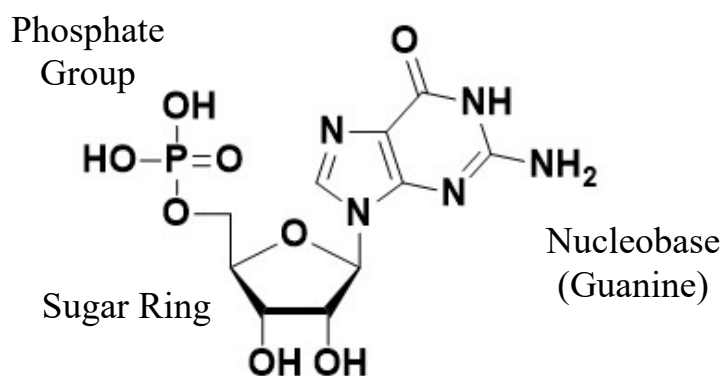
- a. “Y” is oxygen, “W” is a N—H diradical, “R<sub>4</sub>” is in the form of R<sub>5</sub><sup>x</sup> where x is trifluoroacetyl, “B” is 1-uracilyl, “Z” is dimethoxytriphenylmethyl, “R<sub>1</sub>” is an alkyl (i.e., isopropyl), “R<sub>2</sub>” is an alkyl (i.e., isopropyl), and “R<sub>3</sub>” is a cyanoethyl radical for Claim 1;
- b. “M” is a linker represented by the formula Y—C(O), “Y” is an alkyl chain of 2 carbons with an intervening —C(O)—, “W” is a N—H diradical, “R<sub>4</sub>” is in the form of R<sub>5</sub><sup>x</sup> where x is trifluoroacetyl, “B” is 1-uracilyl, and “Z” is dimethoxytriphenylmethyl for Claim 2;

Pet., 21-22, 28-30, 37-38.

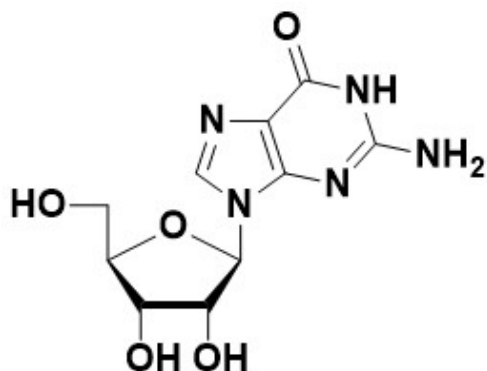
## VI. TECHNOLOGY BACKGROUND

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

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

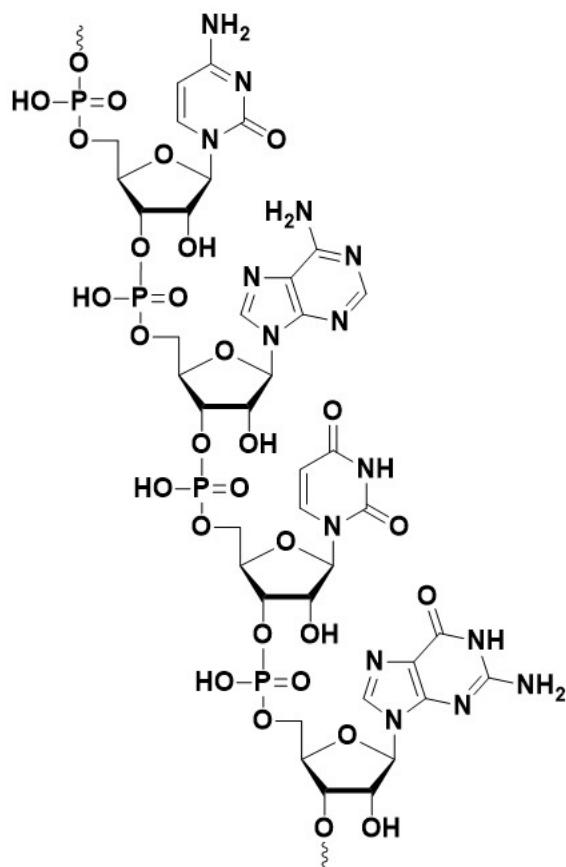


40. **Nucleosides.** Nucleosides are nucleotides without a phosphate group; an exemplary ribonucleoside having a guanine nucleobase, referred to as guanosine, is shown as follows:



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

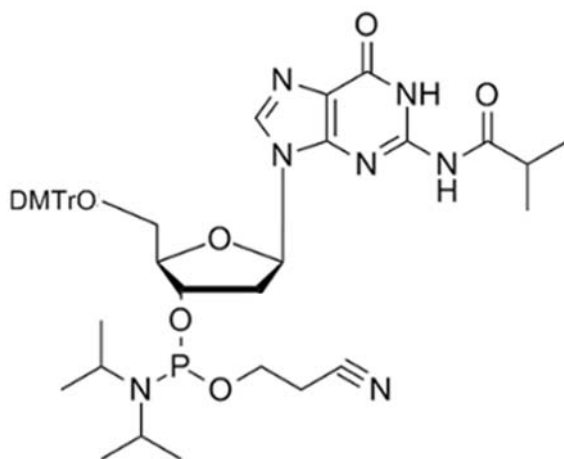
42. Oligonucleotides vary in length and sequences and can be comprised of a few, tens or hundreds of nucleotides, as compared to DNA and RNA that can comprise millions of 2'-deoxyribonucleotides and ribonucleotides, respectively. The following is a depiction of an exemplary oligoribonucleotide:



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

44. **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 2'-deoxyguanosine phosphoramidite is shown as follows:

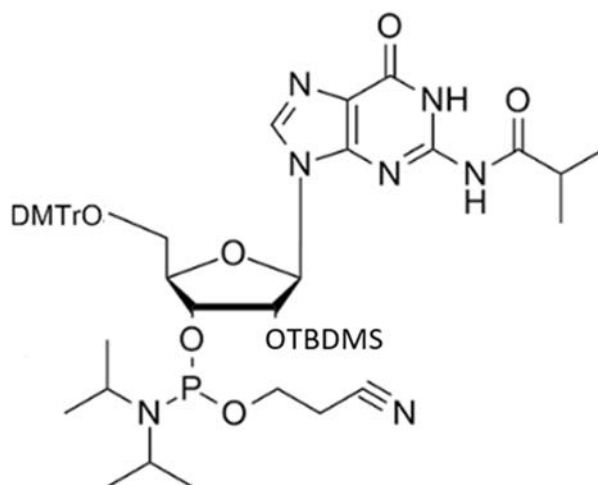




45. As shown above, a phosphoramidite is characterized by having the general structure  $(RO)_2PNR_2$ , i.e., a phosphorus atom in a P(III) oxidation state having one P-N bond and two P-O bonds, and of the two oxygen-containing functionalities, one is usually a protecting group (typically a  $\beta$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

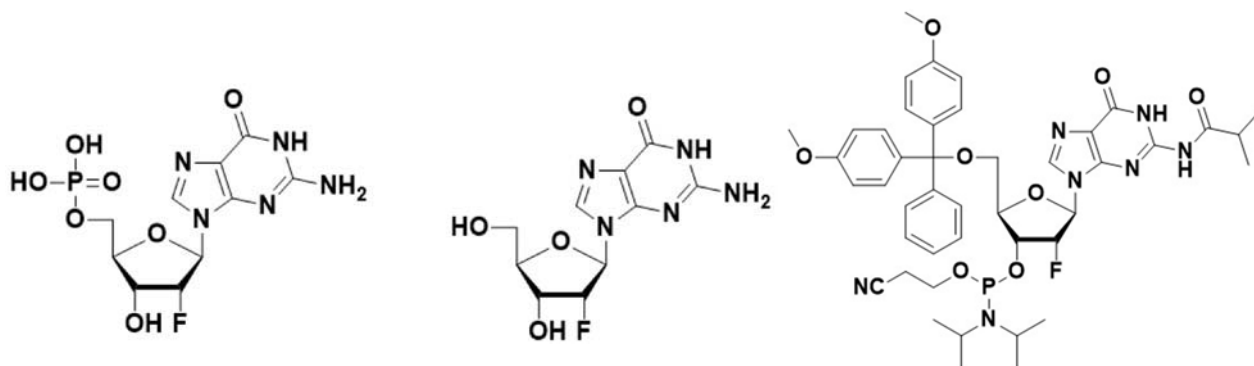
46. Phosphoramidites that are to be used in SPOS typically require additional protecting groups (in addition to the  $\beta$ -cyanoethyl group mentioned above), which shield reactive sites that would interfere with SPOS. Commonly, but not universally, phosphoramidites feature a 4,4-dimethoxytrityl (DMTr, also commonly referred to as DMT) group at the 5'-position (shown above and below). Typically, the exocyclic amines ( $-NH_2$ ) of most nucleobases (e.g., A, C, G) must also be protected (shown above and below as a N2-isobutyryl-protected guanine). For RNA synthesis, the hydroxyl group ( $-OH$ ) at the 2'-position of ribonucleoside phosphoramidites, also must be protected (most commonly, but not universally, as a

*tert*-butyldimethylsilyl “TBDMS” group) to shield its reactivity during SPOS (shown below):



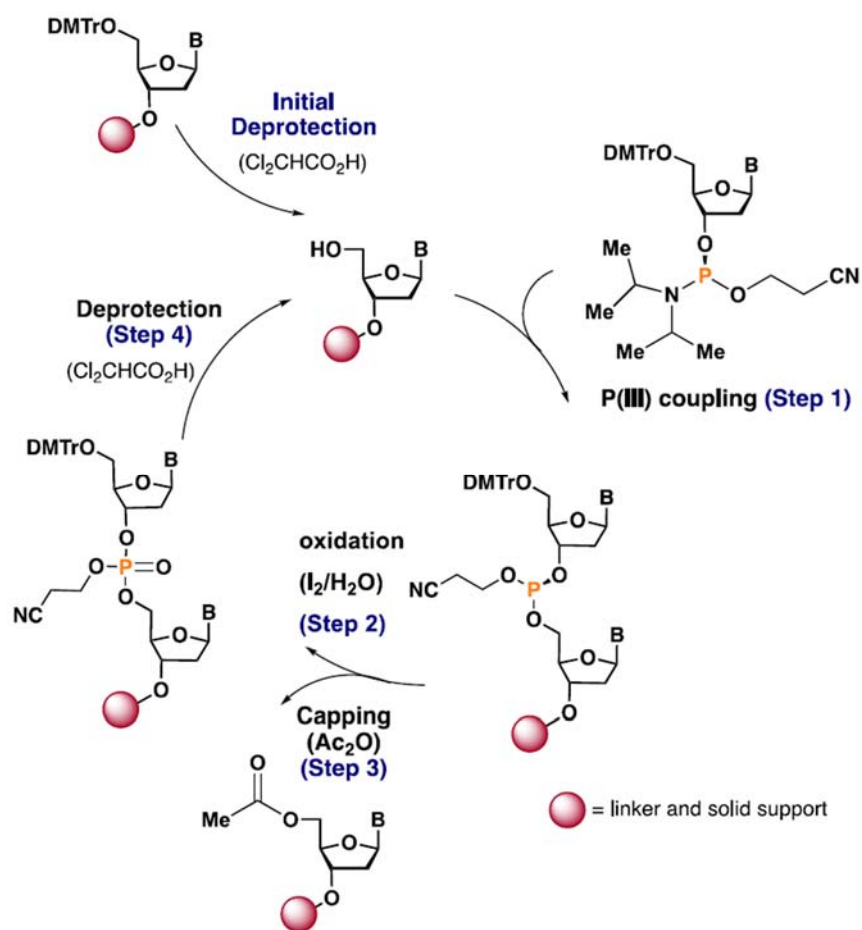
**47. Chemically Modified Nucleosides, Nucleotides, and Phosphoramidites.** Virtually every position on the sugar ring of a nucleoside, nucleotide, and phosphoramidite can be chemically modified, such as the 2'-position which can have, e.g., a halo atom (such as a fluoro). Nucleosides, nucleotides, and phosphoramidites can also feature non-canonical nucleobases and chemically modified nucleobases such as 5-methylcytosine. Examples of chemically modified nucleosides, nucleotides, and/or phosphoramidites include 2'-fluoro-2'-deoxyribonucleosides, 2'-fluoro-2'-deoxyribonucleotides, and 2'-fluoro-2'-deoxyribonucleoside phosphoramidites where a downward pointing fluoro (-F) is at the 2'-position. A modified oligoribonucleotide (i.e., RNA-based oligonucleotide) can feature one or more chemically modified nucleotides, such as 2'-fluoro-2'-

deoxyribonucleotides (2'-fluoro-2'-deoxyguanosine nucleotide shown on the left, 2'-fluoro-2'-deoxyguanosine nucleoside shown in the middle, and a 2'-fluoro-2'-deoxyguanosine phosphoramidite shown to the right):



48. 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 as of the date of the '707 Patent's inventions.

49. **Conventional DNA SPOS.** The synthesis of oligodeoxyribonucleotides (DNA) via SPOS in the traditional 3' → 5' direction, uses conventional 2'-deoxyribonucleoside phosphoramidites and is well-established. *See* Ex. 1010, 193-197. As shown below, and as previously presented in Dr. Baran's Declaration, the traditional 3' → 5' SPOS cycle for DNA synthesis (i.e., canonical SPOS cycle), begins with deprotection of the 5'-DMTr group of the support-bound 2'-deoxyribonucleoside, which reveals a 5'-hydroxyl group ("OH") at the 5' position. *Id.*, 194, 196.



In the presence of a suitable coupling reagent, the 5'-OH group then reacts with the phosphorus ("P") of the phosphoramidite group of the incoming 2'-deoxyribonucleoside, which displaces the amine (i.e., diisopropylamino) and results in coupling of the incoming 2'-deoxyribonucleoside with the support-bound 2'-deoxyribonucleoside. *Id.* The next step involves oxidation of the phosphorus from its P(III) state to the P(V) state (i.e., the oxidation state of the phosphorus in DNA and RNA). *Id.* This step is typically accomplished by adding a mixture of iodine in water (i.e.  $\text{I}_2/\text{H}_2\text{O}$ ), resulting in the formation of a stable phosphotriester linkage

between the two coupled nucleosides. *Id.* The next step is typically a capping step, which protects (and thereby inactivates) 5'-OH groups of any unreacted support-bound nucleosides, and thereby prevents undesirable elongation, which would lead to formation of shorter-than-desired oligonucleotides. *Id.* Next, the DMTr protecting group at the 5'-position of the support-bound dinucleotide is removed, exposing the 5'-hydroxyl group (as in step 1), and setting the stage for the cycle to repeat. *Id.* The process repeats to add a 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, etc., nucleoside to produce a support-bound oligonucleotide. *Id.* Once the desired oligonucleotide has been synthesized, the oligonucleotide is cleaved from the solid support and all protecting groups are removed. *Id.*, 196.

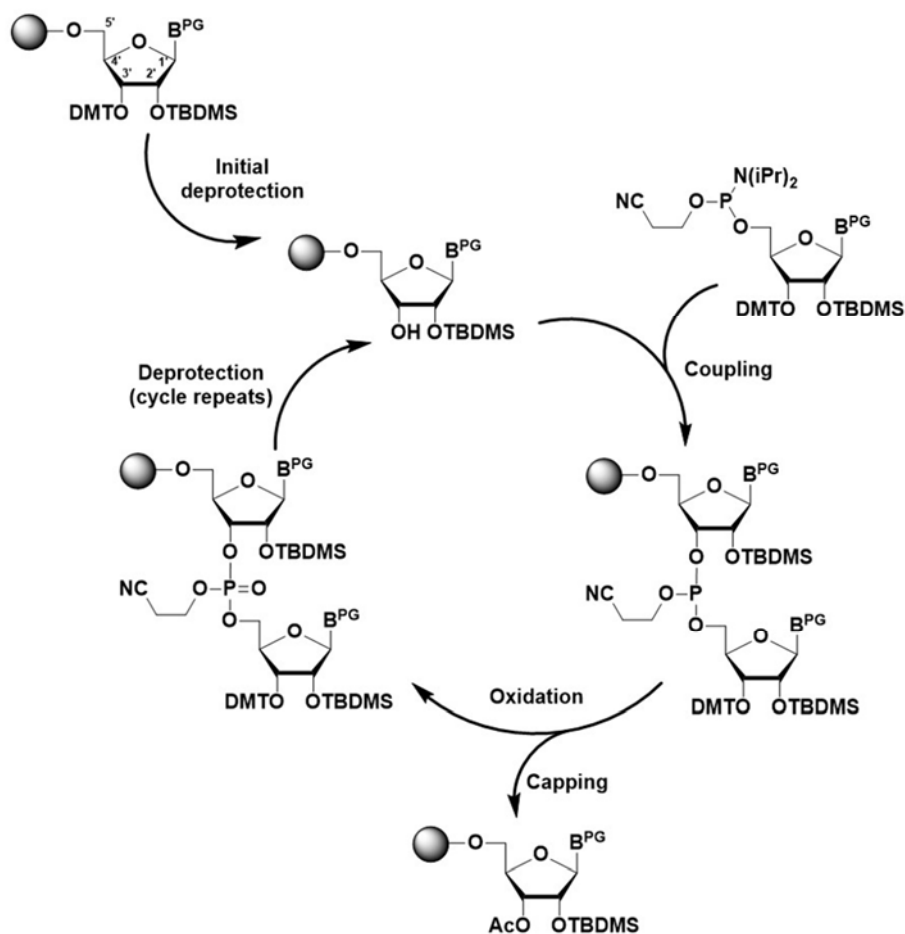
50. **Conventional RNA SPOS.** Development of canonical RNA SPOS proved far more challenging than canonical DNA SPOS, as it required development of suitable protecting groups for the 2'-OH group, alternative coupling reagents and deprotection protocols, and the use of longer coupling times and nuclease-free conditions. *See* Ex. 1009, 3862-3864. At the time of the '707 Patent's inventions, however, synthesis of oligoribonucleotides via SPOS in the traditional 3' → 5' direction and using conventional ribonucleoside phosphoramidites was established (though not routine or predictable) for the synthesis and development of a vast variety of therapeutic grade RNA molecules. Ex. 1001, 1:35-39. As described above, the ribonucleoside phosphoramidites require suitable protecting groups on the

nucleobase (typically acyl groups such as, e.g., N2-isobutyryl for G), the 5'-OH position (typically DMTr), the 2'-OH position (typically TBDMS), and the 3'-phosphoramidite (typically a  $\beta$ -cyanoethyl group). *See* Ex. 1009, 3859, 3864. Fundamentally, the steps of the 3'  $\rightarrow$  5' RNA SPOS cycle are similar to the 3'  $\rightarrow$  5' DNA SPOS cycle. *See id.*, 3864.

51. Modification of the 3'-end of RNA with certain chemical entities is desirable for certain applications. The synthesis of RNA modified at the 3'-end with lipophilic, long chain ligands or chromophores using the 3'  $\rightarrow$  5' synthesis methodology, is challenging and generally results in low coupling efficiency and purity of the final oligonucleotide. Ex. 1001, 8:25-32. Thus, additional purification steps are needed. Therefore, at the time of the '707 Patent's inventions, new synthetic methodologies were needed to efficiently synthesize RNA molecules quickly and in a manner that allowed for straightforward modification at the 3'-end of the oligonucleotide. *Id.*, 8:21-24, 34-39.

52. **Reverse RNA SPOS.** Reverse RNA SPOS is an innovative approach to synthesize oligoribonucleotides in the 5'  $\rightarrow$  3' direction (i.e., the opposite direction of the traditional approach). The use of reverse RNA nucleosides, phosphoramidites, and supports, like those claimed in the '707 Patent, allows for synthesis of high purity oligoribonucleotides and introduction of various modifications at the 3'-end. Ex. 1001, 4:1-4, 8:34-39. The use of reverse RNA amidites, like those disclosed in

the '707 Patent, in machine-assisted reverse SPOS leads to higher coupling efficiency per step, resulting in a greater ability to produce very long oligoribonucleotides of high purity. *Id.* An illustration I drew of the reverse 5' → 3' SPOS cycle is shown below<sup>2</sup>:



The reverse RNA SPOS cycle begins with deprotection of the 3'-DMTr group of the support-bound ribonucleoside, which reveals a 3'-hydroxyl group (“-OH”) at the 3'

<sup>2</sup> The following description of the reverse RNA SPOS cycle is exemplary and not limiting.

position. *See* Ex. 2004, 26:5-33, 122:55-123:13. In the presence of a suitable coupling reagent, the 3'-OH group then reacts with the phosphorus ("P") of the phosphoramidite group of the incoming reverse ribonucleoside phosphoramidite, which displaces the amine (i.e., diisopropylamino) and results in coupling of the incoming ribonucleoside with the support-bound ribonucleoside. *See id.*, 26:35-65, 123:15-61. The next step typically involves oxidation of the phosphorus from its P(III) state to the P(V) state (i.e., the oxidation state of the phosphorus in DNA and RNA). *See id.*, 27:3-22, 123:65-124:15. This step is typically accomplished by adding a mixture of iodine in water (i.e.  $I_2/H_2O$ ), resulting in the formation of a stable phosphotriester linkage between the two coupled nucleosides. *See id.* The next step is typically a capping step, which protects (and thereby inactivates) 3'-OH groups of any unreacted support-bound nucleosides, and thereby prevents undesirable elongation, which would lead to formation of shorter-than-desired oligonucleotides. *See id.*, 27:1-2, 123:64. Next, the DMTr protecting group at the 3'-position of the support-bound dinucleotide is removed, exposing the 3'-hydroxyl group (as in step 1), and setting the stage for the cycle to repeat. *See id.*, 27:24-45, 124:18-43. The process repeats to add a 3<sup>rd</sup>, 4<sup>th</sup>, 5<sup>th</sup>, etc., nucleoside to furnish a support-bound oligonucleotide. *See id.*, 27:50-28:51, 124:52-125:55. Once the desired oligonucleotide has been synthesized, the oligonucleotide is cleaved from the solid support and all protecting groups are removed. *See id.*



53. **Dr. Baran's Assertions Regarding the Background Art for Reverse SPOS.** I disagree with several characterizations in the Petition and in Dr. Baran's declaration concerning the disclosures of references regarding reverse oligonucleotide synthesis, i.e., 5' → 3' oligonucleotide synthesis. Without support, Dr. Baran states that "by the early 2000s, the advantages of oligonucleotide synthesis in the 5' → 3' or 'reverse' direction were well-recognized." Ex. 1003, ¶54; Pet., 14-15. He then lists several purportedly known advantages, such as "the ability to synthesize longer oligonucleotides" and the ability to "selectively remove[]" protective groups during synthesis to achieve higher purity. Ex. 1003, ¶55; Pet, 15. To the extent Dr. Baran is arguing that this was taught by the references discussed below, I disagree.

54. As support of the purportedly known advantages of 5' → 3' oligonucleotide synthesis, Dr. Baran cites to a paper by Wagner et al.<sup>3</sup>. Ex. 1003, ¶55; Pet, 15. The Wagner paper states that "very little is known in literature about the detailed specification of the synthesis of the appropriate 5'-phosphoramidites suitable for the built-up [*sic*] of oligonucleotides in the 5' → 3' direction." Ex. 1011,

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

2023. I understand that Dr. Baran agreed with the Wagner authors' assessment of the state of knowledge concerning 5' → 3' oligonucleotide synthesis during his deposition, and further agreed that much research was needed to understand how to synthesize oligonucleotides through SPOS in the reverse 5' → 3' direction. Ex. 2003, 142:18-143:22. I also note that the Wagner paper pertains to reverse DNA SPOS, and not reverse RNA SPOS as described and claimed in the '707 Patent.

55. Likewise, Dr. Baran cites a paper by Albert et al.<sup>4</sup> Ex. 1003, ¶55; Pet, 15. However, the discussion in Albert concerned synthesis of DNA (not RNA). *See* Ex. 1012, 1 (“DNA microarrays have revolutionized nucleic acid analysis”), 6 (“The cycle yields for DNA synthesis of DNA in the 5' → 3' direction were reported in a previous study for T and C (13). Our results with T were identical to that reported earlier.”). Thus, each of the Wagner and Albert references applies to reverse 5' → 3' synthesis for DNA, which is a different process than reverse 5' → 3' synthesis of RNA as described and claimed in the '707 Patent.

56. Further, I disagree that any references cited by Dr. Baran teach that an advantage of 5' → 3' oligonucleotide synthesis is “the ability to synthesize longer oligonucleotides” because in “the traditional 3' → 5' direction, the buildup of

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<sup>4</sup> T.J. Albert et al., *Light-directed 5'→3' synthesis of complex oligonucleotide microarrays*, Nucleic Acids Research (2003) Vol. 31, No. 7, 1-9 (Ex. 1012).

protecting groups needed to prevent unwanted side reactions may limit the length of oligonucleotides.” Ex. 1003, ¶55; Pet, 15. Dr. Baran cites to nothing in his declaration in support of these statements. In fact, the Albert paper states that “[s]tepwise yields are slightly lower on average than 3' → 5' synthesis.” Ex. 1012, 4. The Albert paper shows compelling data in Table 1 in support of this statement. *Id.*, 2. A POSA would have understood that the poorer coupling yields reported in Albert for oligonucleotide synthesis in the 5' → 3' direction, vis-à-vis synthesis in the 3' → 5' direction, would render synthesis of longer oligonucleotides less probable, not more probable, as even small decreases in coupling yields can have a significant impact on the overall yield of the desired oligonucleotide. Thus, to the extent Dr. Baran is arguing that Wagner and/or Albert teach that the synthesis of oligonucleotides in the 5' → 3' direction would produce longer oligonucleotides than in the 3' → 5' direction, I disagree.

57. Additionally, Dr. Baran, citing to Wagner, states that the “reverse 5' → 3' direction allows protecting groups to be selectively removed during synthesis to yield oligonucleotides of high purity, producing totally unprotected oligonucleotides that remain attached to the solid support.” Ex. 1003, ¶55; Pet, 15. In reading Wagner, a POSA would have readily understood that this purported advantage is not due to 5' → 3' oligonucleotide synthesis, but rather is due to the highly specialized nucleobase protecting groups being used in Wagner. *See* Ex. 1011, 2023

(“Application of the npe/npeoc strategy (npe = 2-(4-nitrophenyl)ethyl, npeoc = [2-(4-nitrophenyl)ethoxy]carbonyl) allows also the inverse (5' → 3')-directed built-up [*sic*] of oligonucleotides of high purity starting with the appropriately protected 5'-phosphoramidites. **By this strategy**, totally unprotected oligonucleotides still attached to the solid support are available ....” (emphasis added)).

58. Finally, citing Wagner, Dr. Baran stated that the advantages of reverse 5' → 3' “have enabled the development of oligonucleotide-based nanotechnology such as oligonucleotide microarrays (a/k/a DNA chips).” Ex. 1003, ¶55. Dr. Baran mischaracterizes the Wagner paper by insinuating that such technologies are predicated by reverse oligonucleotide synthesis. The Wagner paper lists oligonucleotide microarrays as an area of interest in the early 2000s, nothing more. There is nothing in Wagner tying oligonucleotide synthesis in the reverse (or any) direction to the development of oligonucleotide microarrays. *See* Ex. 1011 (“Beside the use of oligonucleotides in medicinal chemistry as potential antisense and antigene drugs, there is **increasing interest** in their use in oligonucleotide-chip technology, diagnostic tools, biological applications, and nanotechnology” (emphasis added)).

## VII. PETITIONER’S DEFINITION OF A POSA SHOULD BE MODIFIED

59. 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 2-3 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., 16 (emphasis added).

60. 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. 2003, 183:13-16; Ex. 2045, 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 in a related proceeding, is a fundamentally different synthesis platform than the P(III) chemistry at bar. Ex. 2045, 109:4-6 (“Q. But the focus of this paper [Ex. 2032] is on P(V)? A. The focus of this paper is awakening people to the difference between P(V) and P(III).”); Ex. 2030, 1 (Dr. Baran 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.”); *also see* Ex. 2032, 1268-69 (disclosing P(V)-based oligonucleotide synthesis not involving phosphoramidites, and instead using completely different “PSI” reagents in a “fundamentally” different process, such differences including different reagents, solid supports, nucleobase

protecting groups, coupling reagents, and no oxidation step as otherwise required by P(III) SPOS).

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

62. In my opinion, skilled artisans, as of the date of the '707 Patent's inventions, who developed synthesis schemes for, and who conducted or directed the syntheses of, nucleosides, phosphoramidites, and oligonucleotides in connection with P(III) chemistry, are those who would provide the most relevant viewpoints on aspects relating to whether the compounds claimed in the '707 Patent would have been anticipated or obvious, including knowledge, skills, motivations and reasonable expectations.

63. 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 conducting or directing the syntheses of, nucleosides, phosphoramidites or oligonucleotides pursuant to P(III) chemistry, are not as applicable to the central inquiries at bar, since the claims in the '707 Patent are directed to nucleosides,

phosphoramidites and solid supports for P(III) solid-phase synthesis of oligonucleotides and not the therapeutic and diagnostic uses of oligonucleotides.

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

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

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

Alternatively, someone with a Bachelor’s or Master’s degree in organic chemistry who had at least 5 years of extensive work experience in these fields, and who had gained a thorough understanding of the syntheses ~~development~~ of nucleic acid-based materials pursuant to P(III) chemistry, would also have qualified as a

POSA ~~with a Bachelor's or Master's degree in organic chemistry or medicinal chemistry.~~

65. This definition, in my opinion, would not exclude medicinal or other chemists so long as the chemist in question met the above requirements. Further, I understand that Dr. Baran testified during his deposition that there are “exceptions” to his proposed definition of a POSA, that his definition was “malleable,” and that he has “no problem” with other POSA definitions that have been proposed. Ex. 2003, 177:17-178:1. My opinions set forth in this declaration remain the same under either Petitioner’s definition or the definition that I provided above for the level of skill of a POSA.

### **VIII. THE '696 PATENT**

66. I understand that Petitioner has proffered U.S. Patent No. 5,869,696 (Ex. 1014) (the “’696 Patent”) as an anticipatory reference. The ’696 Patent is not directed to synthesis of oligonucleotides (or RNA) in the 5' → 3' direction. As shown on the face of the ’696 Patent, the ’696 Patent is directed to “[u]niversal solid support oligonucleotide synthesis processes, and reagents for cleaving oligonucleotides from solid supports.” Ex. 1014, Abstract. Universal supports are solid supports that allow a practitioner to synthesize oligonucleotides using a common solid support. *See Id.*, 1014, 4:31-36.



67. SPOS in the traditional 3' → 5' direction typically requires the use of solid supports attached to the 3'-position of the first nucleotide in the chain of nucleotides comprising the subject oligonucleotide. *See* Ex. 1014, 1:19-21; Ex. 2003, 156:13-18 (“Q: And you agree that in solid phase oligonucleotide synthesis in the traditional 3 prime to 5 prime direction, typically requires the use of solid supports that have the 3 prime most nucleotide attached to it? A: Yeah, that’s how it works.”). For instance, if an oligonucleotide sequence has a 2'-deoxyA (i.e., DNA-A) at its 3'-end, SPOS typically initiates with a solid support that is linked to a 2'-deoxyA nucleoside, from which the oligonucleotide sequence will proceed via a stepwise addition of phosphoramidites in the 3' → 5' direction. *See* Ex. 1014, 1:22-26. Similarly, if an oligonucleotide sequence has an rG (i.e., RNA-guanine) at its 3'-end, SPOS initiates with a support that is linked to an rG nucleoside, from which the oligonucleotide sequence will proceed via a stepwise addition of phosphoramidites in the 3' → 5' direction. *See id.*, 1:29-33. Universal supports allow practitioners to use one type of support for oligonucleotide syntheses and avoid stockpiling different types of solid supports. *See id.*, 1:34-43, 4:31-36. Dr. Baran agreed. *See* Ex. 2003, 155:10-18 (“Q: And it is your understanding that the teachings of this reference indicate that the use of the disclosed universal solid support allows a practitioner to avoid stockpiling different solid supports? A: By universal, the goal would be, you

know, to allow people to focus on using one for all their needs versus having, you know, multiple different types, so yeah.”).

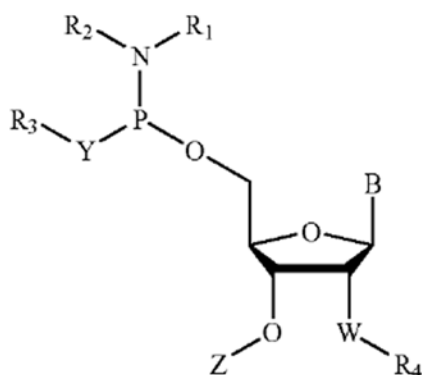
68. Specifically, the claims of the '696 Patent are directed towards oligonucleotide cleaving reagents, which Dr. Baran acknowledged. *See* Ex. 1014, 33:59-36:14; Ex. 2003, 157:5-7 (“Q: Looks like all these claims are directed to a cleaving reagent is that fair to say? A: Looks like it, mm-hmm, yeah.”). Cleaving reagents are useful for removing oligonucleotides from the solid support on which they are synthesized. Ex. 1014, 2:65-3:1; Ex. 2003, 157:8-11 (“Q: Is it fair to say that cleaving reagents are useful for [re]moving oligonucleotides from the solid support on which they are synthesized? A: Yeah.”). Thus, the claims are not directly directed to oligonucleotide synthesis in either the 5' → 3' or 3' → 5' direction. *See* Ex. 2003, 158:6-10 (“Q: [T]he claims aren’t directed to 5 prime to 3 prime or 3 prime to 5 prime synthesis, right? A: They could -- the claims don’t have that written in them, correct.”). The claims are also not directed to any nucleosides, phosphoramidites, supports or any compounds that are linked to supports. *See id.*, 158:11-21 (Dr. Baran admitting same).

## IX. OPINIONS

### A. Ground I: The Compounds of Substitute Claim 4 are Not Disclosed by the Cited Prior Art.

69. In my opinion, the Substitute Claim 4 as provided in Patent Owner's Motion to Amend, which removes an "N—H diradical" as an option for "W" from Claim 1's Markush group, is not disclosed by the cited prior art based on the reasons stated below.

70. Substitute Claim 4 is directed to a derivatized nucleoside having a structure of formula 1,

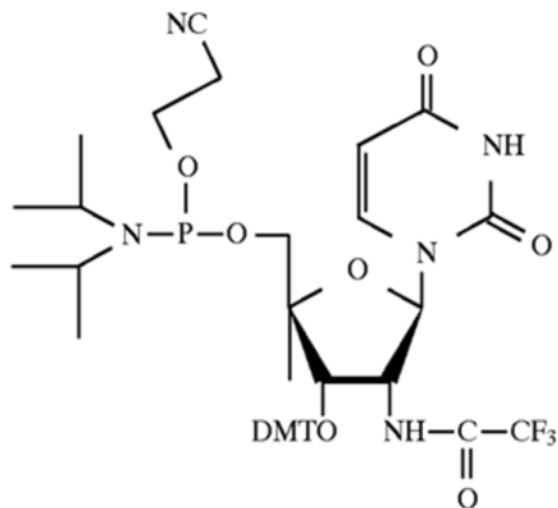


Formula (1)

where "Y" is an oxygen atom or a sulfur atom; "W" is selected from the group consisting of an oxygen diradical and a fluorine radical, R<sub>4</sub> is selected so that if W is an oxygen diradical, then R<sub>4</sub> is tert butyl dimethyl silyl (TBDMS) or triisopropylsilyloxymethylene (TOM), if W is fluorine radical, then R<sub>4</sub> is absent, B is selected from the recited group of nucleoside base radicals or a group of modified nucleoside base radicals, Z is a protecting group selected from the group consisting

of dimethoxytriphenylmethyl (DMT), monomethoxytriphenylmethyl (MMT) and trimethoxytriphenylmethyl (TMT),  $R_1$  and  $R_2$  are alkyl or aryl radicals, and  $R_3$  is a cyanoethyl radical, alkyl radical or aryl radical. The references cited in the Petition and Dr. Baran's Declaration do not disclose these limitations.

71. Petitioner and Dr. Baran cite to the '696 Patent (Ex. 1014) as anticipating Claim 1 because the '696 Patent discloses a compound in Example 3 where the substituent group at the "Y" position is oxygen, the substituent group at the 2' position ("W") is a N—H diradical, the substituent group at the "Z" position is a DMT protecting group, the substituent group at the 1' position ("B") is a 1-uracilyl nucleoside base radical, the substituent group at the "R<sub>4</sub>" position is trifluoroacetyl, the substituent group at the "R<sub>1</sub>" and "R<sub>2</sub>" positions is each an alkyl radical (specifically each an isopropyl radical), and the substituent group at the "R<sub>3</sub>" position is a cyanoethyl radical. Ex. 1014, 13:24-43. Example 3 from the '696 Patent is reproduced below:



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

72. The Institution Decision agreed with Petitioner that the '696 Patent's Example 3 compound discloses an identical compound recited by challenged Claim 1 in which "Y is an oxygen atom, W is a N—H diradical, R<sub>4</sub> is trifluoroacetyl, B is 1-uracilyl- nucleoside base radical, Z is a DMT protecting group, R<sub>1</sub> is an alkyl radical (specifically an isopropyl radical), R<sub>2</sub> is an alkyl radical (specifically an isopropyl radical), and R<sub>3</sub> is a cyanoethyl radical." Paper 6 at 7.

73. Substitute Claim 4 limits "W" such that it excludes "N—H diradical" from the group "consisting of an oxygen diradical and a fluorine radical." The '696 patent does not disclose a compound with any of the "W" and "R<sub>4</sub>" species recited in Substitute Claim 4 and therefore does not anticipate Substitute Claim 4.

74. Specifically, the '696 patent does not disclose or suggest any phosphoramidites having a group at "W" selected from the group consisting of an

oxygen diradical and a fluorine radical, where if W is an oxygen diradical, then R<sub>4</sub> is tert butyl dimethyl silyl (TBDMS) or triisopropylsilyloxymethylene (TOM); or if W is a fluorine radical, then R<sub>4</sub> is not present. The '696 patent also does not disclose the amended definition of “W” in combination with the other structural features of Claim 1.

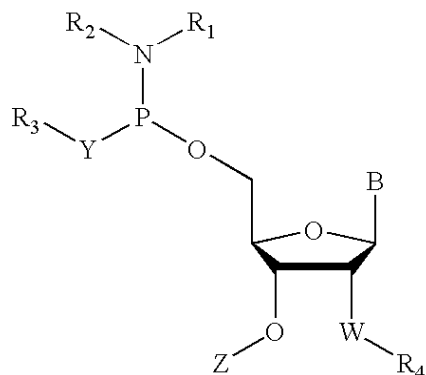
75. In my opinion, nothing in the '696 Patent alone or in combination with any of the other references of record in this IPR, which are encompassed by the materials that I have considered in preparing my opinions, would have provided a POSA with a reason or motivation to modify the N—H (at a position corresponding to “W” in Substitute Claim 4) and trifluoroacetyl (at a position corresponding to “R<sub>4</sub>” in Substitute Claim 4) of the '696 patent in such a way so as to arrive at the claimed compound with a reasonable expectation of success.

76. **Substitute Claim 4 is fully supported.** I understand that the '707 Patent issued from the '625 Application and claims priority to the '065 Provisional. I have reviewed Substitute Claim 4, and in my opinion, a POSA would have understood that Substitute Claim 4 is fully supported by the '625 Application and the '065 Provisional. I understand that Substitute Claim 4 is directed to:

**Substitute Claim 4**

A phosphoramidite having formula (1),

Formula (1)



where,

Y is an oxygen atom or a sulfur atom;

W is selected from the group consisting of an oxygen diradical and a fluorine radical, and R<sub>4</sub> is selected so that, if W is an oxygen diradical, then R<sub>4</sub> is tert butyl dimethyl silyl (TBDMS) or triisopropylsilyloxymethylene (TOM); and if W is a fluorine radical, then R<sub>4</sub> is not present;

B is selected from the group of nucleoside base radicals consisting of -9-(N<sup>6</sup>-benzoyladeninyl)-, 9-(N<sup>6</sup>-acetyladeninyl)-, 9-(N<sup>6</sup>-tert butyl phenoxyacetyladeninyl)-, 9-(N<sup>6</sup>-phenoxyacetyladeninyl)-, 1-(N<sup>4</sup>-benzoylcytosinyl)-, 1-(N<sup>4</sup>-acetylcytosinyl)-, 1-(N<sup>4</sup>-phenoxyacetylcytosinyl)-, 1-(N<sup>4</sup>-tertbutylphenoxyacetylcytosinyl)-, 9-(N<sup>2</sup>-isobutyrylguaninyl)-, 9-(N<sup>2</sup>-tertbutylphenoxyacetylguaninyl)-, and 1-uracilyl-;

or, B is a modified nucleoside base radical selected from the group consisting of 1-(5-methyl-uracilyl)-, and -(5-fluoro-uracilyl)-;
Z is a protecting group selected from the group consisting of dimethoxytriphenylmethyl (DMT), monomethoxytriphenylmethyl (MMT) and trimethoxytriphenylmethyl (TMT);
R <sub>1</sub> is an alkyl or aryl radical;
R <sub>2</sub> is an alkyl or aryl radical; and,
R <sub>3</sub> is a cyanoethyl radical, alkyl radical or aryl radical.

77. Each of the elements in Substitute Claim 4 is recited in original Claim 1 of the '707 Patent (Ex. 1001, 33:47-35:17), and is supported by at least pages 20:30-23:15, 37:11-38:9, 40:10-43:10, 45:4-23 (Claim 1) of the '625 Application. Ex. 1002, 23:30-26:15, 39:11-40:9, 42:10-45:10, 47:4-23 (Claim 1). Further, each of these elements is also supported by at least pages 14-16, 24, and 26-27 of the '065 Provisional. Ex. 2002, 21-23, 31, 33-34.

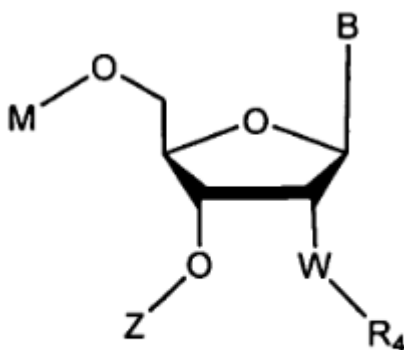
**B. Ground II: The Compounds of Substitute Claim 5 are Not Disclosed by the Cited Prior Art.**

78. In my opinion, the Substitute Claim 5 as provided in Patent Owner's Motion to Amend, that removes "W" as "N—H diradical" from Claim 2's Markush



group, based upon the '696 Patent, is not disclosed by the cited prior art based on the reasons stated below.

79. Substitute Claim 5 is directed to a derivatized nucleoside having a structure of formula 2,

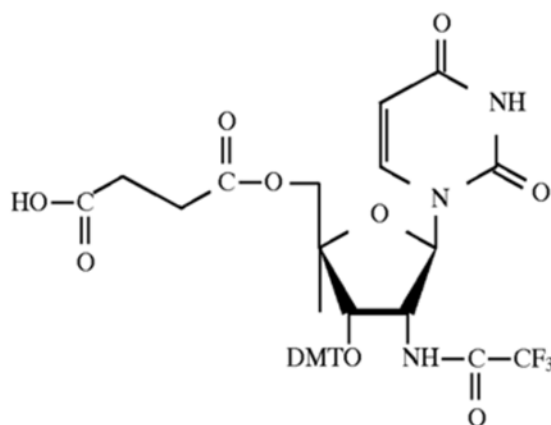


Formula (2)

where “M” is a hydrogen radical or a linker and if “M” is linker it is represented by the formula Y—C(O) and, optionally, connected to a solid support suitable for oligonucleotide synthesis, wherein “Y” is a chain of between 2 and 20 carbons selected from the group consisting of alkyl, alkenyl, cycloalkyl, aryl, and aralkyl, in a hydrocarbyldiradical moiety, optionally comprising intervening —O—, —S—, —S(O)<sub>2</sub>—, —C(O)—, and —NR<sub>6</sub>—, where “R<sub>6</sub>” is a hydrogen radical or a substituted C<sub>1</sub> to C<sub>20</sub> alkyl or a substituted aralkyl, where “W” is an oxygen diradical or a fluorine radical, where if “W” is an oxygen diradical then “R<sub>4</sub>” is TBDMS or TOM and if “W” is a fluorine radical then “R<sub>4</sub>” is absent, where “B” is selected from the recited group of nucleoside base radicals or a group of modified nucleoside base radicals,

and “Z” is a protecting group selected from the group consisting of DMT, MMT and TMT. The references cited in the Petition and Dr. Baran’s Declaration in this IPR do not disclose these limitations.

80. Petitioner and Dr. Baran cite to the ’696 Patent (Ex. 1014) as anticipating Claim 2 because the ’696 Patent discloses a compound in Example 2 where the substituent group at the “M” position is a succinate linker represented by the formula Y—C(O) in a hydrocarbyl diradical, the substituent group at the “Y” position is an alkyl chain having 2 carbons (i.e., ethyl) comprising an intervening —C(O)—, the substituent group at the “W” position is a N—H diradical, the substituent group at the “R<sub>4</sub>” position is trifluoroacetyl, , the substituent group at the “B” position is a 1-uracilyl- nucleoside base radical, and the substituent group at the “Z” position is a DMT protecting group. Ex. 1014, 12:1-17. Example 2 from the ’696 Patent is reproduced below:



**2'-Trifluoroacetamido-3'-O-(4,4'-dimethoxy-trityl)-2'-deoxyuridine-5'-succinate (hydroxyl/amino analog) (Ex. 1014, 12:1-13:19)**

81. The Institution Decision agreed with Petitioner that the '696 Patent's Example 2 compound discloses an identical compound recited by challenged Claim 2 in which "M is a succinate linker 'represented by the formula  $Y-C(O)$  in a hydrocarbyl diradical, wherein Y is an alkyl chain having 2 carbons, i.e., ethyl . . . and further comprises an intervening  $-C(O)-$ ,' W is a N—H diradical, R<sub>4</sub> is trifluoroacetyl, B is 1-uracilyl- nucleoside base radical, and Z is a DMT protecting group." Paper 6 at 10.

82. Substitute Claim 5 limits "W" such that it excludes "N—H diradical" from the group "consisting of an oxygen diradical and a fluorine radical." The '696 patent does not disclose or suggest any derivatized nucleosides of the general structure of Substitute Claim 5 having a group at "W" selected from the group consisting of an oxygen diradical, and a fluorine radical, and R<sub>4</sub> is selected so that, if W is an oxygen diradical, then R<sub>4</sub> is tert butyl dimethyl silyl (TBDMS) or triisopropylsilyloxymethylene (TOM); and if W is a fluorine radical, then R<sub>4</sub> is not present. The '696 patent also does not disclose the amended definition of "W" in combination with the other structural features of Substitute Claim 5.

83. In my opinion, nothing in the '696 patent alone or in combination with any other references of record in this IPR, 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 N—H (at a position corresponding to "W" in

Substitute Claim 5) and trifluoroacetyl (at a position corresponding to “R<sub>4</sub>” in Substitute Claim 5) of the '696 patent in such a way so as to arrive at the claimed compound with a reasonable expectation of success.

84. **Substitute Claim 5 is fully supported.** I have reviewed Substitute Claim 5, and in my opinion, a POSA would have understood that Substitute Claim 5 is fully supported by the '625 Application and the '065 Provisional. I understand that Substitute Claim 5 is directed to:

Substitute Claim 5
<p>A derivatized nucleoside having a structure of formula 2,</p> <div data-bbox="267 976 673 1323"> </div> <p>Formula (2)</p> <p>where,</p>
<p>M is a hydrogen radical or a linker;</p>
<p>if M is a linker, then it is represented by the formula Y—C(O) and, optionally, connected to a solid support suitable for oligonucleotide synthesis, wherein</p>

Y is a chain of between 2 and 20 carbons, selected from the group consisting of alkyl, alkenyl, cycloalkyl, aryl, and aralkyl, in a hydrocarbyldiradical moiety, optionally comprising intervening —O—, —S—, —S(O)<sub>2</sub>—, —C(O)—, and —NR<sub>6</sub>—, where R<sub>6</sub> is a hydrogen radical, or a substituted C<sub>1</sub> to C<sub>20</sub> alkyl or a substituted aralkyl;

W is selected from the group consisting of an oxygen diradical, and a fluorine radical, and R<sub>4</sub> is selected so that, if W is an oxygen diradical, then R<sub>4</sub> is tert butyl dimethyl silyl (TBDMS) or triisopropylsilyloxymethylene (TOM); and if W is a fluorine radical, then R<sub>4</sub> is not present;

B is selected from the group of nucleoside base radicals consisting of -9-(N<sup>6</sup>-benzoyladeninyl)-, 9-(N<sup>6</sup>-acetyladeninyl)-, 9-(N<sup>6</sup>-tert butyl phenoxyacetyladeninyl)-, 9-(N<sup>6</sup>-phenoxyacetyladeninyl)-, 1-(N<sup>4</sup>-benzoylcytosinyl)-, 1-(N<sup>4</sup>-acetylcytosinyl)-, 1-(N<sup>4</sup>-phenoxyacetylcytosinyl)-, 1-(N<sup>4</sup>-tertbutylphenoxyacetylcytosinyl)-, 9-(N<sup>2</sup>-isobutyrylguaninyl)-, 9-(N<sup>2</sup>tertbutylphenoxyacetylguaninyl)-, and 1-uracilyl-; or B is selected from the group of modified nucleoside base radicals selected from the group consisting of 1-(5-methyl-uracilyl)-, and -(5-fluoro-uracilyl)-; and,

Z is a protecting group selected from the group consisting of dimethoxytriphenylmethyl (DMT), monomethoxytriphenylmethyl (MMT) and trimethoxytriphenylmethyl (TMT).


85. Each of the elements in Substitute Claim 5 is recited in original Claim 2 of the '707 Patent (Ex. 1001, 35:18-36:15), and is supported by at least pages 20:30-23:15, 38:11-26, 40:10-43:10, 45:25-46:15 (Claim 2) of the '625 Application. Ex. 1002, 23:30-26:15, 40:11-26, 42:10-45:10, 47:25-48:15 (Claim 2). Each of these elements is also supported by at least pages 15-16, 24, and 26-27 of the '065 Provisional. Ex. 2002, 22-23, 31, 33-34. The shading in the depicted chemical formula image in Substitute Claim 5 has been corrected as noted on pages 9-10 of the Institution Decision and is also supported by the cited support in the '625 Application and the '065 Provisional.

## **X. CONCLUSION**

86. For the reasons stated above, it is my opinion that Claims 1 and 2 of the '707 Patent, as 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: 2/5/2024

  
\_\_\_\_\_  
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 FIRST EMPLOYMENT AT UI:** August 2006

**DATE OF TENURE:** July 2011

**IMMIGRATION STATUS:** Permanent resident (green card holder)

#### PROFESSIONAL PREPARATION:

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 three litigations 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:**

[72] C. P. Shepard, R. G. Emehiser, S. Karmakar, and P. J. Hrdlicka\*. Factors impacting Invader-mediated recognition of double-stranded DNA. *Molecules* **2023**, 28, 127.

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J. Hrdlicka\*. C5-Functionalized LNA: Unparalleled hybridization properties and enzymatic stability. *ChemBioChem*, **2009**, 10, 2740-2743.

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[19] B. Baral, P. Kumar, B. A. Anderson, M. E. Østergaard, P. K. Sharma and P. J. Hrdlicka\*. Optimized synthesis of [3-<sup>15</sup>N]-labeled uridine phosphoramidites. *Tetrahedron Lett.*, **2009**, 50, 5850-5852.

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[17] J. W. Rigoli, M. E. Østergaard, K. M. Canady, D. C. Guenther and P. J. Hrdlicka\*. Selective deacylation of peracylated ribonucleosides. *Tetrahedron Lett.*, **2009**, 50, 1751-1753.

[16] T. S. Kumar, A. S. Madsen, M. E. Østergaard, S. P. Sau, J. Wengel and P. J. Hrdlicka\*. Functionalized 2'-amino- $\alpha$ -L-LNA - Directed positioning of intercalators for DNA targeting. *J. Org. Chem.* **2009**, 74, 1070-1081.

[15] T. S. Kumar, P. Kumar, P. K. Sharma and P. J. Hrdlicka\*. Optimized synthesis of LNA uracil nucleosides. *Tetrahedron Lett.*, **2008**, 49, 7168-7170.

[14] T. S. Kumar, A. S. Madsen, M. E. Østergaard, J. Wengel\* and P. J. Hrdlicka\*. Nucleic acid structural engineering using pyrene functionalized 2'-amino- $\alpha$ -L-LNA monomers and abasic sites. *J. Org. Chem.* **2008**, 73, 7060-7066.

[13] B. Vester, A. M. Boel, S. Lobedanz, B. R. Babu, M. Raunkjær, D. Lindegaard, Raunak, P. J. Hrdlicka, T. Højland, P. K. Sharma, T. S. Kumar, P. Nielsen and J. Wengel\*. Chemically modified oligonucleotides with retained



RNaseH response. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 2296-2300.

[12] T. Umemoto, P. J. Hrdlicka, B. R. Babu and J. Wengel\*. Sensitive SNP dual-probe assays based on pyrene-functionalized 2'-amino-LNA: Lessons to be learned. *ChemBioChem*, **2007**, *8*, 2240-2248.

[11] T. S. Kumar, J. Wengel and P. J. Hrdlicka\*. 2'-N-(pyren-1-yl)acetyl-2'-amino- $\alpha$ -L-LNA: Synthesis and detection of single nucleotide mismatches in DNA and RNA targets. *ChemBioChem*, **2007**, *8*, 1122-1125. (>50 citations).

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[9] T. S. Kumar, A. S. Madsen, J. Wengel and P. J. Hrdlicka\*. Synthesis and hybridization studies of 2'-amino- $\alpha$ -L-LNA and a tetracyclic 'Locked LNA'. *J. Org. Chem.* **2006**, *71*, 4188-4201 (>50 citations).

[8] P. J. Hrdlicka, T. S. Kumar and J. Wengel\*. Synthesis and thermal denaturation studies of conformationally restricted 3'-C-ethynyl-3'-O,4'-C-methylenel-ribonucleotides. *Eur. J. Org. Chem.* **2005**, 5184-5188.

[7] P. J. Hrdlicka, B. R. Babu, M. D. Sørensen, N. Harrit and J. Wengel\*. Multilabeled pyrene-functionalized 2'-amino-LNA probes for nucleic acid detection in homogenous fluorescence assays. *J. Am. Chem. Soc.* **2005**, *127*, 13293-13299 (>100 citations).

[6] P. J. Hrdlicka, T. S. Kumar and J. Wengel\*. Targeting of mixed sequence double-stranded DNA using pyrene-functionalized 2'-amino- $\alpha$ -L-LNA. *Chem. Commun.* **2005**, 4279-4281.

[5] B. R. Babu, P. J. Hrdlicka, C. J. McKenzie and J. Wengel\*. Optimized DNA targeting using *N,N*-bis(2-pyridylmethyl)- $\beta$ -alanyl 2'-Amino-LNA. *Chem. Commun.* **2005**, 1705-1707.

[4] P. J. Hrdlicka, N. K. Andersen, J. S. Jepsen, F. G. Hansen, K. F. Haselmann, C. Nielsen and J. Wengel\*. Synthesis and biological evaluation of branched and

conformationally restricted analogs of the anticancer compounds 3'-C-ethynyluridine (EUrd) and 3'-C-ethynylcytidine (ECyd). *Bioorg. Med. Chem.* **2005**, *13*, 2597-2621.

[3] P. J. Hrdlicka, J. S. Jepsen, C. Nielsen and J. Wengel\*. Synthesis and biological evaluation of nucleobase-modified analogs of the anticancer compounds 3'-C-ethynyluridine (EUrd) and 3'-C-ethynylcytidine (ECyd). *Bioorg. Med. Chem.* **2005**, *13*, 1249-1260.

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[1] P. J. Hrdlicka, A. B. Sørensen, B. R. Poulsen, G. J. G. Ruijter, J. Visser and J. J. L. Iversen\*. Characterization of nerolidol biotransformation based on indirect on-line estimation of biomass concentration and physiological state in batch cultures of *Aspergillus niger*. *Biotechnol. Prog.* **2004**, *20*, 368-376.

#### **Manuscripts Submitted for Review:**

N/A

#### **Refereed Book Chapters:**

[BC2] P. J. Hrdlicka\* and Michael E. Østergaard. Fluorophore-functionalized Locked Nucleic Acids (LNAs) in *DNA Conjugates and Sensors*, *RSC Biomolecular Science Series*, edited by K. R. Brown and T. Brown (RSC Publishing, 2012), Vol. 26, 1-33.

[BC1] D. Choi\*, D. McIlroy, J. Nagler, E. Aston, P. J. Hrdlicka, K. Gustin, R. Hill, D. Stenkamp and J. Branen. 1-Dimensional silica structures and their applications to the biological sciences in *Nanomaterials for the Life Sciences, Nanostructured Oxides*, edited by C. Kumar (Wiley, 2009), Vol. 2, 83-108.

#### **Patent Applications:**

[PA8] B. Didion, P. J. Hrdlicka and J. P. Verstegen. Gender-specific

identification of sperm cells and embryos using locked nucleic acids. 2013, PCT WO 2013103713A1.

**[PA7]** P. J. Hrdlicka. Embodiments of a probe and method for targeting nucleic acids. U.S. Patent No. 9,885,082 (**issued February 2018**).

**[PA6]** P. J. Hrdlicka and Sujay P. Sau. Universal DNA/RNA hybridization probes. Provisional patent application, Univ. Idaho, October 31, 2011.

**[PA5]** P. J. Hrdlicka. Embodiments of a probe and method for targeting nucleic acids. Provisional patent application, Univ. Idaho, September 30, 2011.

**[PA4]** P. J. Hrdlicka and S. Karmakar. Selective targeting of single-stranded DNA using intercalator-functionalized oligonucleotides for diagnostic and biotechnological applications. Provisional patent application, Univ. Idaho, July 19, 2011.

**[PA3]** P. J. Hrdlicka, P. Kumar and Michael E. Østergaard. Nucleobase-functionalized conformationally restricted nucleotides and oligonucleotides for targeting of nucleic acids. U.S. Patent No. 8,518,908 (**issued August 2013**). **Continuation issued on December 2014** as U.S. Patent No. 8,912,318).

**[PA2]** P. J. Hrdlicka, P. Kumar and Michael E. Østergaard. The use of oligonucleotides modified with conformationally restricted C5-functionalized pyrimidine nucleotide building blocks for targeting of nucleic acids. Provisional patent application, Univ. Idaho, Sep 4, 2009.

**[PA1]** P. J. Hrdlicka and P. Kumar, Synthesis and applications of C5-Functionalized Locked Nucleic Acid (LNA). Provisional patent application filed, Univ. Idaho, July 31, 2008.

**License Agreement:**

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

**Published Conference Proceedings/Abstracts:**

**[CP36]** P. J. Hrdlicka, S. Adhikari, R. Emehiser, D. C. Guenther, and S.

Karmakar. Detection of Mixed-Sequence dsDNA using Bulged Invader Probes. 14th Annual Meeting of the Oligonucleotide Therapeutics Society.

[CP35] P. J. Hrdlicka. Synthesis and biophysical properties of nucleobase-functionalized LNA (locked nucleic acid). 2014 247<sup>th</sup> American Chemical Society National Meeting (San Francisco, CA), CARB-38.

[CP34] P. J. Hrdlicka. Recognition of double-stranded DNA using energetically activated duplexes modified intercalator-functionalized nucleotides. 2014 69<sup>th</sup> Northwest Regional Meeting of the American Chemical Society (Missoula, MT), NORM-16.

[CP33] S. Andersen, B. A. Anderson, B. Denn, D. C. Guenther, S. Karmakar, R. L. Rathje, S. P. Sau and P. J. Hrdlicka. Invaders: Recognition of double-stranded DNA using energetically activated duplexes modified intercalator-functionalized nucleotides. 2014 247<sup>th</sup> American Chemical Society National Meeting (Dallas, TX), CARB-90.

[CP32] M. Kaura, P. Kumar and P. J. Hrdlicka. Synthesis and characterization of oligodeoxyribonucleotides modified with nucleobase-functionalized Locked Nucleic Acids (LNAs). 2014 247<sup>th</sup> American Chemical Society National Meeting (Dallas, TX), BIOL-94.

[CP31] S. Karmakar, B. A. Anderson, R. L. Rathje, S. Andersen and P. J. Hrdlicka. [High-affinity DNA targeting using simplified mimics of N2'-intercalator-functionalized 2'-amino- \$\alpha\$ -L-LNA](#). 2012 67<sup>th</sup> Northwest Regional Meeting of the American Chemical Society (Boise, ID), NORM-231.

[CP30] P. J. Hrdlicka. Sequence-unrestricted targeting of double stranded DNA (dsDNA): How to 'unlock' the dsDNA-targeting potential of Invader LNAs. 2012 67<sup>th</sup> Northwest Regional Meeting of the American Chemical Society (Boise, ID), NORM-129.

[CP29] P. J. Hrdlicka. Nucleobase-functionalized Locked Nucleic Acids (LNAs): Optimized probes for nucleic acid targeting. 2012 Abstracts of Papers, 243<sup>rd</sup> ACS National Meeting (San Diego, CA), ORGN-328.

[CP28] P. J. Hrdlicka. Sequence-unrestricted targeting of double stranded DNA (dsDNA): How to 'unlock' the dsDNA-targeting potential of Invader LNAs. 2012 Abstracts of Papers, 243<sup>rd</sup> ACS National Meeting (San Diego, CA),

CARB-55.

**[CP27]** D. C. Guenther, P. Kumar and P. J. Hrdlicka. C5-amino acid functionalized LNA: Synthesis, evaluation of biophysical properties, and potential for antisense therapeutics. 2012 Abstracts of Papers, 243<sup>rd</sup> ACS National Meeting (San Diego, CA), BIOL-152.

**[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 nanoprobe 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. Brannen 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. Brannen, M. Frederickson and P. J. Hrdlicka. Identification of important food pathogens using LNA (Locked Nucleic Acid)

probes. 2010 Joint 65<sup>th</sup> Northwest and 22<sup>nd</sup> 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: characterization of SERS-active materials and detection of DNA from biological threat agents. 2010 Joint 65<sup>th</sup> Northwest and 22<sup>nd</sup> 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 65<sup>th</sup> Northwest and 22<sup>nd</sup> 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 65<sup>th</sup> Northwest and 22<sup>nd</sup> 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 65<sup>th</sup> Northwest and 22<sup>nd</sup> 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 65<sup>th</sup> Northwest and 22<sup>nd</sup> 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, 239<sup>th</sup> 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, 239<sup>th</sup> 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, 239<sup>th</sup> 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, 239<sup>th</sup> 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, 239<sup>th</sup> 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- $\alpha$ -L-LNA: A novel class of locked nucleic acids as emerging tools for nucleic acid therapeutics and diagnostics. 2008 Abstracts of papers, 235<sup>th</sup> 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, 235<sup>th</sup> ACS National Meeting (New Orleans, LA), BIOL-032.

[CP8] N. K. Andersen, J. Wengel and P. J. Hrdlicka. N2'-functionalized 2'-amino- $\alpha$ -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- $\alpha$ -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- $\alpha$ -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- $\alpha$ -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); 69<sup>th</sup> Northwest Regional Meeting of the American Chemical Society (Missoula, MT); 248<sup>th</sup> American Chemical Society Meeting (San Francisco, CA); Binghamton University (Binghamton, NY).

2012: 67<sup>th</sup> 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: 247<sup>th</sup> 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: 243<sup>th</sup> American Chemical Society National Meeting (San Diego, CA) – two presentations.

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

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

2007: AAAS Pacific Division, 88<sup>th</sup> Annual Meeting of the Pacific Division Meeting & 62<sup>nd</sup> 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: 17<sup>th</sup> Annual Meeting of the Oligonucleotide Therapeutics Society (virtual) – student presented a video poster; Idaho INBRE Research Conference (Moscow, ID) - student presented a poster.

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

2018: 14<sup>th</sup> 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: 10<sup>th</sup> 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; 56<sup>th</sup> Idaho Academy of Science Conference (Moscow, ID) – student gave presentation; 247<sup>th</sup> 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 (3<sup>rd</sup> place poster competition, faculty/staff choice category); Drug and Diagnostic Development Conference (San Francisco, CA) – postdoc presented a poster; 67<sup>th</sup> 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: 6<sup>th</sup> 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; 65<sup>th</sup> Northwest / 22<sup>nd</sup> 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; 17<sup>th</sup> 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 20<sup>th</sup> Anniversary Seminar (Moscow, ID) – PI delivered a presentation

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

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

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

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

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

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

2014: 10<sup>th</sup> 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:**

2023      Alumni Awards for Excellence, Univ. Idaho (w/ Celeste Condie)

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, 2021 and 2023 classes averaged 58<sup>th</sup>/65<sup>th</sup>/60<sup>th</sup>/38<sup>th</sup>/58<sup>th</sup> national percentile, respectively on standardized 1<sup>st</sup> term ACS exams



- CHEM 372            Organic Chemistry II (Spring: 2010, 2021-2023); 2010, 2022 and 2023 classes averaged 79<sup>th</sup>/58<sup>th</sup>/42<sup>nd</sup> 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)  
Ebenezer 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, 3 <sup>rd</sup> year review committee (Dept. Physics)
Department level:	
2022	Chair, promotion and tenure committee (Waynant)
2022	Member, 3 <sup>rd</sup> year review committee (Andrasi)
2021-2022	Member, search committee, faculty position, Dept.
Chemistry	
2019, 2020	Chair, peer performance review committee
2017	Member, 3 <sup>rd</sup> 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, 3 <sup>rd</sup> 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 69<sup>th</sup> 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
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### 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 Idaho	Participant, webinar - Powerless to Powerful, Taking Control, Univ.
2019 DARPA	Polyplexus Pilot 3 Proposers Day Webinar, Defense Science Office,
2018	Participant, mandatory training, IT Security Awareness, Univ. Idaho
2018 Univ. Idaho	Participant, mandatory training, Creating a Respectful Community,
2018 Univ. Idaho	Participant, mandatory training, Campus Security Authority Training,
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 & Don'ts	Participant, webinar - Communicating Through Email: Top 10 Do's
2016	Participant, webinar - Public Speaking Without Fear, Univ. Idaho
2016 Idaho	Participant, webinar - Defeating Negativity in the Workplace, Univ.
2016 Univ. Idaho	Participant, webinar - How to Handle Emotions Under Pressure,
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.

## APPENDIX B

### Petitioner's Exhibits

Ex. No.	Title	Abbreviation
1001	U.S. Patent No. 8,309,707	the '707 Patent
1002	File History of U.S. Patent Appl. No. 12/584,625 (which issued as the '707 Patent)	the '707 File History
1003	Declaration of Phil S. Baran, Ph.D. in support of Petition for Inter Partes Review of the '707 Patent	Baran Decl.
1004	S.L. Beaucage & M.H. Caruthers, <i>Deoxynucleoside Phosphoramidites – A New Class of Key Intermediates for Deoxypolynucleotide Synthesis</i> , Tetrahedron Letters (1981) Vol. 22, No. 20, 1859- 1862	Beaucage (1981)
1005	M.D. Matteuci & M.H. Caruthers, <i>Synthesis of Deoxyoligonucleotides on a Polymer Support</i> , J. Am. Chem. Soc. (1981) 103, 3185-3191	Matteuci (1981)
1006	L.J. McBride & M.H. Caruthers, <i>An Investigation of Several Deoxynucleoside Phosphoramidites Useful for Synthesizing Deoxyoligonucleotides</i> , Tetrahedron Letters (1983) Vol. 24, No. 3, 245- 248	McBride (1983)
1007	S.L. Beaucage & R.P. Iyer, <i>Advances in the Synthesis of Oligonucleotides by the Phosphoramidite Approach</i> , 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)	Twist (2018)

1009	C.B. Reese, <i>Oligo- and poly-nucleotides: 50 years of chemical synthesis</i> , Org. Biomol. Chem. (2005) Vol. 3, 3851-68	Reese (2005)
1010	H.A. White, <i>Manual Oligonucleotide Synthesis Using the Phosphoramidite Method</i> , Methods in Molecular Biology Vol. 4 (1988), Ch. 14, 193-213	White (1988)
1011	T. Wagner & W. Pfliderer, <i>Synthesis of 2'-Deoxy-ribonucleoside 5'-Phosphoramidites: New Building Blocks for the Inverse (5'-3')-Oligonucleotide Approach</i> , Helvetica Chimica Acta – Vol. 83 (2000), 2023-2035	Wagner (2000)
1012	T.J. Albert et al., <i>Light-directed 5'→3' synthesis of complex oligonucleotide microarrays</i> , Nucleic Acids Research (2003) Vol. 31, No. 7, 1-9	Albert (2003)
1013	A.P. Guzaev & M. Manoharan, <i>A Conformationally Preorganized Universal Solid Support for Efficient Oligonucleotide Synthesis</i> , J. Amer. Chem. Soc. (2003) 125, 2380-2381	Guzaev (2003)
1014	U.S. Patent No. 5,869,696	the '696 Patent



## APPENDIX C

### Patent Owner's Exhibits

Ex. No.	Description
2002	U.S. Provisional Patent Application No. 61/191,065
2003	Deposition Transcript of Dr. Phil S. Baran (Jan. 22, 2024)
2004	U.S. Patent No. 8,541,569 (Ex. 1001 in IPR2023-00862)
2006-2029	Exhibit numbers not used
2030	Knouse et. al, <i>Unlocking P(V): Reagents for chiral phosphorothioate synthesis</i> , 361 SCIENCE 1234-1238 (2018)
2031	Exhibit number not used
2032	Huang et al., <i>A P(V) platform for oligonucleotide synthesis</i> , 373 SCIENCE 1265-1270 (2021)
2033-2039	Exhibit numbers not used
2042-2044	Exhibit numbers not used
2045	Dr. Phil S. Baran 9/13/2023 Deposition Transcript from IPR2023-00490 (Ex. 2009)