Filed On Behalf Of:

Alnylam Pharmaceuticals, Inc.

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ALNYLAM PHARMACEUTICALS, INC.,
Petitioner,
v.
SILENCE THERAPEUTICS GMBH,
Patent Owner.

Case No. Not Yet Assigned
U.S. Patent No. 9,758,784

PETITION FOR POST GRANT REVIEW OF U.S. PATENT NO. 9,758,784

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I. INTRODUCTION

U.S. Patent No. 9,758,784 ("the '784 patent") purports to cover an enormous, potentially unlimited, genus of structurally diverse small interfering RNA ("siRNA") molecules. Consequently, the scope of the '784 patent claims is far broader than any invention described in or enabled by the patent. The '784 patent claims are so broad, in fact, that they cover modifications and genetic targets that have yet to be discovered. By claiming broadly, Silence Therapeutics GmbH ("Patent Owner") attempts to draw a fence around a vast plot of land, which is permissible, ***if and only if***, the four corners of the patent provide support commensurate with the scope of the claimed genus. But here, there is no evidence that Patent Owner actually invented more than a tiny sliver of what it now claims.

Instead, it appears that, over a nearly 15-year period, Patent Owner used a series of continuation applications and claim amendments to obtain broad patent protection for subject matter not originally identified as the alleged invention. This ploy was designed to strategically (and improperly) cover the innovations of others, including those of Alnylam Pharmaceuticals, Inc., Petitioner in this matter. Such tactics directly contravene the fundamental purpose of the patent system and should not be permitted to create even a theoretical risk of blocking or delaying life-extending, disease-modifying technologies.

As explained in this Petition, the ’784 patent claims are unpatentable under 35 U.S.C. §§ 112 and 102. While the patent claims encompass a potentially unlimited genus of siRNA molecules, including molecules with any type of chemical modification, multiple end structures and varying double-stranded lengths, the patent and its underlying applications describe only a tiny subset of molecules encompassed by the claimed genus. Instead of providing representative species of the vast claimed genus, the patent only discloses species that are structurally similar. For example, the only siRNA molecules disclosed in the patent’s figures and examples that fall within the claimed genus comprise 2’-O-methyl modified ribonucleotides that alternate with unmodified ribonucleotides across the full stretch, are blunt ended on both ends and have a duplex length of 19 or 21 ribonucleotides. In addition, although the claimed genus of siRNA molecules can be directed against any nucleic acid target in the entire genome, Patent Owner has only shown that this small subset of siRNA molecules has RNA interference (“RNAi”) activity against three nucleic acid targets. Patent Owner also concedes that siRNA molecules encompassed by the broad claimed genus are not functional. As a result of the disconnect between the patent specification and its claims, as well as the unpredictability of the field of chemically modified siRNAs, it is clear the inventors did not possess what is now claimed, and a person of ordinary skill in

the art ("POSA") would be unable to make and use the full scope of the claims without undue experimentation.

Because the '784 patent is not entitled to a priority date earlier than its actual filing date of May 8, 2017, the patent claims are also invalid as anticipated under 35 U.S.C. § 102. In fact, the intervening art discloses multiple species encompassed by the broad claims of the '784 patent, thereby anticipating the genus.

For the foregoing reasons, and as explained in detail below, Petitioner requests post-grant review ("PGR") and cancellation of claims 1-24 of the '784 patent.

II. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

The real parties-in-interest are Petitioner Alnylam Pharmaceuticals, Inc. and its wholly owned subsidiary Alnylam U.S., Inc. (collectively, "Alnylam" or "Petitioner").

Sanofi Genzyme and The Medicines Company may also have an interest in this matter by virtue of holding licenses to certain Alnylam products.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

On March 29, 2018, Petitioner filed Case No. 1:18-cv-10613 in the United States District Court for the District of Massachusetts seeking declaratory judgment of non-infringement of five of Patent Owner's related patents.

On April 2, 2018, Petitioner filed PGR2018-00059 seeking review of related U.S. Patent No. 9,695,423 ("the '423 patent").

C. Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3))

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D. Service Information (37 C.F.R. § 42.8(b)(4))

Please address all correspondence to the lead and back-up counsel at the above addresses. Petitioner also consents to electronic service to AlnylamPTAB@fchs.com and to the email addresses above.

E. Payment of Fees (37 C.F.R. §§ 42.203(a) and 42.15(b))

Pursuant to 37 C.F.R. §§ 42.203(a) and 42.15(b), the required fees are submitted herewith. If additional fees are due during this proceeding, the Office is authorized to charge Deposit Account No. 50-3939.

F. Time for Filing Petition

The '784 patent issued on September 12, 2017 and the instant Petition was timely filed on or before the date that is nine months after the date of the grant of the patent. 35 U.S.C. § 321(c); 37 C.F.R. § 42.202.

G. Grounds for Standing (37 C.F.R. § 42.204(a))

Petitioner certifies under 37 C.F.R. § 42.204(a) that the ’784 patent is available for PGR, and that Petitioner is not barred or estopped from requesting PGR of the ’784 patent challenging the patent claims on the grounds identified in this petition. Petitioner further certifies that the prohibitions of 35 U.S.C. § 325(a) are inapplicable.

The ’784 patent is available for PGR pursuant to the America Invents Act (“AIA”), Pub. L. No. 112-29, § 3(n)(1), 125 Stat. 284, 293 (2011), because, as explained in Section VIII, at least one claim has an effective filing date on or after March 16, 2013.

H. Identification of Challenged Claims and Relief

Petitioner respectfully requests PGR of claims 1-24 of the ’784 patent and cancellation of claims 1-24 as unpatentable under 35 U.S.C. §§ 102 and/or 112. It is more likely than not that claims 1-24 are unpatentable in view of the following unpatentability grounds and prior art references:

Ground	Claims	Statutory Basis	Prior Art References
1	1-24	35 U.S.C. § 112(a) Lack of Written Description	
2	1-24	35 U.S.C. § 112(a) Lack of Enablement	
3	1-7, 9, 11-14, 17-20	35 U.S.C. § 102	Czauderna (Exh. 1028)
4	1-8, 11-13, 15-16, 21-24	35 U.S.C. § 102	Allerson (Exh. 1016)
5	1-7, 10-14, 18-20	35 U.S.C. § 102	Feinstein (Exh. 1017)

III. THE '784 PATENT

The '784 patent, entitled "Interfering RNA Molecules," allegedly "provides novel forms of interfering ribonucleic acid molecules having a double-stranded structure." (Exh. 1001 at 1:40-41; Exh. 1002[1] at ¶¶57-58; *see also id*. at ¶¶59-80.) The '784 patent teaches that "[o]ne of the problems previously encountered when using unmodified ribooligonucleotides [to accomplish RNAi] was the rapid degradation in cells or even in the serum-containing medium." (Exh. 1001 at 2:20-23, Exh. 1002 at ¶59.) The '784 patent purports to solve this problem by providing "synthetic interfering RNA molecules that are both stable and active in a biochemical environment such as a living cell." (Exh. 1001 at 2:29-31, Exh. 1002 at ¶59.) The '784 patent also asserts that "all of the ribonucleic acids of the present

[1] Exh. 1002 is the expert declaration of Dr. Jonathan K. Watts of the RNA Therapeutics Institute at the University of Massachusetts Medical School.

invention are suitable to cause or be[] involved in methods of RNA mediated interference." (Exh. 1001 at 12:41-43; Exh. 1002 at ¶62.)

The '784 patent claims recite an extremely broad, potentially unlimited genus of chemically modified siRNA molecules. (Exh. 1001 at Claims 1-24.) For instance, claim 1, the only independent claim, recites:

> 1. A double-stranded siRNA molecule against a target nucleic acid, wherein the double-stranded siRNA molecule comprises a first strand and a second strand,
>
> wherein the first strand comprises a first stretch that is complementary to the target nucleic acid,
>
> wherein the second strand comprises a second stretch that is complementary to the first stretch,
>
> wherein the first strand and the second strand form a double-stranded structure comprising the first and the second stretch,
>
> wherein the double-stranded siRNA molecule is blunt ended on at least one end, and
>
> wherein each stretch consists of at least 15 and fewer than 30 ribonucleotides and
>
> wherein the first stretch and the second stretch each comprises contiguous alternating modified ribonucleotides,
>
> wherein the alternating modified ribonucleotides alternate with unmodified or differently modified ribonucleotides.

(Exh. 1001 at Claim 1; Exh. 1002 at ¶¶81-82.)

The genus of chemically modified siRNA molecules encompassed by claim 1 comprises three generic modification patterns: (1) modified ribonucleotides that alternate within a stretch with unmodified ribonucleotides, (2) modified ribonucleotides that alternate within a stretch with differently modified ribonucleotides, and (3) modified ribonucleotides that alternate within a stretch with a mixed motif of unmodified ribonucleotides and differently modified ribonucleotides. These modification patterns are illustrated below.

Modification Patterns Encompassed by '784 Patent Claim 1		
. . .(M)(U)(M)(U). . .	. . .(M)(D_n)(M)(D_n) . . .	. . .(M)(U/D_n)(M)(U/D_n). . .

(M) – modified; (U) – unmodified; (D_n) – differently modified where n is any type of modification which can be the same or different for each differently modified ribonucleotides (Exh. 1002 at ¶¶160-61.)

Within these recited modification patterns, claim 1 encompasses a potentially unlimited number of siRNA molecules that include any modification to the:

- ribonucleotide sugar;
- ribonucleotide base;
- backbone; and
- ends of the molecules, so long as at least one end is blunt ended.

(*Id*. at ¶¶160-82.)

In addition to these variables, the siRNA molecules encompassed by claim 1 can also vary as to the:

- ribonucleotide position within the stretch, strand, or molecule that contains sugar modifications;
- ribonucleotide position within the stretch, strand, or molecule that contains the base modification;
- ribonucleotide position within the stretch, strand, or molecule that contains the backbone modification;
- location of any end modification;
- number of sugar-modified ribonucleotides within a stretch, strand, or molecule;
- number of base-modified ribonucleotides within a stretch, strand, or molecule;
- number of backbone-modified ribonucleotides within a stretch, strand, or molecule;
- length of each stretch, so long as it is between 15-30 ribonucleotides; and
- length of the strands.

(*Id.*)

In addition to these chemical and structural variables, the claimed siRNA molecules are not limited to targeting a particular gene or gene sequence. The '784 patent claims thereby encompass siRNA molecules that target every nucleic acid in the entire genome – an enormous number of possibilities. (*Id*. at ¶¶156-59.) For example, the siRNA sequence options for the approximately 17,700 human genes that had been identified as of 2003 would number almost 47.5 million. (*Id*. at ¶159.) As of 2017, the number of human genes identified has increased to about 20,000, bringing the number of siRNA sequence options to almost 53.6 million. (*Id.*)

The dependent claims recite additional limitations related to the location of the blunt end (Exh. 1001 at Claims 2-4); overall length of the stretches or strands (*id.* at Claims 5-10); particular chemical modifications (*id*. at Claims 11-16, 18-24); and location of the modified and unmodified or differently modified ribonucleotides on each strand (*id.* at Claims 17, 19, 22). Despite these limitations, the dependent claims still encompass an extremely broad, potentially unlimited number of diverse siRNA molecules, which, as explained above, must be "stable and active." (Exh. 1002 at ¶¶83-106; 155-82; *see also id*. at ¶59; Exh. 1001 at 2:29-31.)

As discussed throughout this Petition, the '784 patent (including its original claims) and its underlying applications fail to describe or enable the full scope of

the genus of siRNA molecules claimed. (Exh. 1002 at ¶¶107-109, 119-233.) For example, while claims 1-13, 15-17 and 21-24 encompass siRNA molecules that contain modified ribonucleotides that alternate with ***differently modified ribonucleotides*** and/or siRNA molecules that contain modified ribonucleotides that alternate with a ***mixed motif*** of differently modified and unmodified ribonucleotides, neither the patent nor its underlying applications disclose ***even a single example*** of such siRNA molecules. (*Id*. at ¶¶128, 133, 183-86, 199; *see also id.* at ¶¶ 201, 210.) Further, while claims 1-13 and 15-23 place no limit on the type of chemical modifications for the modified or differently modified ribonucleotides, neither the patent nor its underlying applications disclose even a single siRNA molecule comprising any internal modification ***other than a 2'-O-methyl modification***. (*Id*. at ¶¶128, 133, 135-51, 182-86, 198-99; *see also id.* at ¶¶201, 210.) The patent and its underlying applications also fail to provide siRNA molecules with a double-stranded length greater than 21 ribonucleotides that meet the claim limitations, despite such molecules being encompassed by at least claims 1-7 and 10-24. (*See, e.g.*, Exh. 1001 at Examples 1-13; Exh. 1002 at ¶¶182, 192, 199, 201, 209-10.) And, nothing in the '784 patent or its underlying applications establishes that more than a sliver of siRNA molecules within the broadly claimed genus have any utility, let alone RNAi activity. (Exh. 1002 at ¶¶129, 134-151, 182, 198-201, 206-208, 210.) Indeed, while claims 1-7 and 11-24 encompass siRNA

molecules wherein the double-stranded region comprises 17 or fewer ribonucleotides, the ’784 patent and its underlying applications concede that such siRNA molecules are not functional. (*See, e.g.*, Exh. 1001 at 12:24-26, 24:55-62, 25:52-56; Exh. 1002 at ¶¶68, 72, 187-91, 199, 201, 208, 210; *see also id.* at ¶¶121, 135-36.)

IV. THE PRIORITY APPLICATIONS

The ’784 patent issued on September 12, 2017 from U.S. Application No. 15/589,971 (“’971 application,” Exh. 1004 at 32-109), which was filed on May 8, 2017. (Exh. 1001 at Cover.) The ’971 application is a continuation of a series of six patent applications and claims priority to European Patent Application No. 02017601, filed on August 5, 2002; U.S. Provisional Application No. 60/402,541, filed on August 12, 2002; and European Patent Application No. 03008383, filed on April 10, 2003, (collectively, “the priority applications”) as detailed in the following table:

Application	Filing Date	Exhibit
EP 02017601 ("EP1")	August 5, 2002	1006
Provisional App. No. 60/402,541 ("'541 provisional")	August 12, 2002	1007
EP 03008383 ("EP2")	April 10, 2003	1008
App. No. 10/633,630 (non-provisional) ("'630 application")	August 5, 2003	1009
App. No. 12/200,296 (continuation)	August 28, 2008	1010
App. No. 12/986,389 (continuation)	January 7, 2011	1011
App. No. 13/692,178 (continuation)	December 3, 2012	1012
App. No. 14/578,636 (continuation)	December 22, 2014	1013
App. No. 14/977,710 (continuation)	December 22, 2015	1005

(Exh. 1001 at Cover; *see also* Exh. 1002 at ¶57, ¶¶119-53.)

EP1 and the '541 provisional share identical specifications and were each filed with 16 figures, 13 examples and 55 claims that are substantially identical with only minor changes conforming certain claims to the U.S.P.T.O. and E.P.O. requirements. (Exhs. 1006-1007; Exh. 1002 at ¶¶121-24.)

Although EP1 and the '541 provisional provide a generic embodiment which may encompass siRNA molecules with contiguous alternating modified ribonucleotides and ***differently modified ribonucleotides*** and siRNA molecules with contiguous alternating modified ribonucleotides and a ***mixed motif*** of unmodified and differently modified ribonucleotides (Exhs. 1006-1007 at 4-5), there is no description of ***any*** of these molecules in the figures or examples. (Exh. 1002 at ¶¶125-28.) Instead, they disclose molecules having a modification pattern where modified ribonucleotides with the ***same modification*** alternate with

unmodified ribonucleotides across the full strand. (Exh. 1006; Exh. 1007; Exh. 1002 at ¶128.)

Further, nothing in EP1 or the ’541 provisional establishes that the full genus of claimed siRNA molecules have any utility, let alone are “suitable to cause or be[] involved in methods of RNA mediated interference” as recited in the patent specification. (Exh. 1001 at 12:41-43; Exh. 1006; Exh. 1007; Exh. 1002 at ¶¶128-29.) While certain claims of EP1 and the ’541 provisional specify particular uses for the claimed ribonucleic acids, including inhibiting the expression of a target gene (*see*, *e.g.*, Exh. 1006 at Claims 48, 55; Exh. 1007 at Claims 48, 55), such claims do not establish that siRNA molecules having a modification pattern of modified ribonucleotides alternating with ***differently modified ribonucleotides***, or a modification pattern of modified ribonucleotides alternating with a ***mixed motif*** of differently modified and unmodified ribonucleotides, would have the recited utility. Thus, EP1 and the ’541 provisional fail to adequately support the full scope of the genus of molecules encompassed by at least claims 1-13, 15-17 and 21-24. (Exh. 1002 at ¶¶122-29.)

Furthermore, EP1 and the ’541 provisional concede that siRNA molecules comprising a double-stranded region of 17 ribonucleotides or fewer are not functional. (Exh. 1006 at 10, 31, 32; Exh. 1007 at 10, 31, 32.) And there is no data presented for siRNA molecules with a double-stranded length greater than 21

ribonucleotides. (Exh. 1006 at Examples; Exh. 1007 at Examples.) These are additional reasons the full scope of the genus of molecules encompassed by at least claims 1-7 and 10-24 is not adequately supported by EP1 and the ’541 provisional. (Exh. 1002 at ¶¶190, 192.)

The EP2 specification is substantially similar to the specifications of EP1 and the ’541 provisional and contains 19 figures, 13 examples, and 59 claims, along with 174 sequences. (Exh. 1008; Exh. 1002 at ¶¶130-31.) EP2 contains additional figures and new disclosures related to siRNA duplex length, mismatches and siRNA molecules with internal 2’-O-methyl modifications. (Exh. 1008; Exh. 1002 at ¶¶131-32, 135.) One such new disclosure in EP2 describes blunt ended siRNA molecules comprising alternating 2’-O-methyl modified ribonucleotides and unmodified ribonucleotides having a double-stranded length of 19 nucleotides (instead of 21 nucleotides as previously disclosed). (*See, e.g.*, Exh. 1008 at Figures 16A-C; Exh. 1002 at ¶¶133, 135, 192.) Furthermore, similar to EP1 and the ’541 provisional, EP2 includes a generic embodiment that may encompass siRNA molecules with contiguous alternating modified ribonucleotides and differently modified ribonucleotides and siRNA molecules with contiguous alternating modified ribonucleotides and a mixed motif of unmodified and differently modified ribonucleotides. (Exh. 1008 at 4-5.) Nevertheless, there is no description of molecules comprising such modification patterns in the figures or examples.

(Exh. 1002 at ¶133.) Rather, just like in EP1 and the ’541 provisional, those disclosures in EP2 are directed to siRNA molecules having a modification pattern of alternating unmodified and modified ribonucleotides ***with the same modification*** throughout the strand. (Exh. 1008; Exh. 1002 at ¶133.)

Similar to EP1 and the ’541 provisional, certain claims of EP2 specify particular uses for the claimed ribonucleic acids, including inhibiting the expression of a target gene, but those claims do not establish that siRNA molecules across the full scope of the genus claimed, including those with a modification pattern of modified ribonucleotides alternating with ***differently modified ribonucleotides*** and those with a modification pattern of modified ribonucleotides alternating with a ***mixed motif*** of unmodified and differently modified ribonucleotides, would have the recited utility. (Exh. 1008 at Claims 52, 59; Exh. 1002 at ¶133-34.) Thus, EP2, like EP1 and the ’541 provisional, fails to adequately support the full scope of the genus of molecules encompassed by at least claims 1-13, 15-17 and 21-24. (*Id*.) Furthermore, EP2, like EP1 and the ’541 provisional, concedes that siRNA molecules comprising a double-stranded region of 17 ribonucleotides or less are not functional. (Exh. 1008 at 10-11, 35; Exh. 1002 at ¶190.) Likewise, EP2 fails to provide any data for siRNA molecules comprising a double-stranded region greater than 21 ribonucleotides. (Exh. 1008 at Examples; Exh. 1002 at ¶192.)

EP2 is substantially similar to the subsequent continuation applications, which share a common specification with the ’784 patent. (Exhs. 1005, 1008-1013; Exh. 1001; Exh. 1002 at ¶¶135-36.) The continuation applications add limited new disclosures, but none relate to siRNA molecules comprising alternating modified ribonucleotides and ***differently modified ribonucleotides***, or siRNA molecules comprising alternating modified ribonucleotides and a ***mixed motif*** of differently modified and unmodified ribonucleotides.

Like EP1, the ’541 provisional and EP2, certain claims of the continuation applications include generic language that may encompass additional siRNA molecules that fall within the scope of the ’784 patent claims. (*See, e.g.*, Exh. 1009 at Claims 11-18; Exh. 1010 at Claims 11-18; Exh. 1011 at 1-11; Exh. 1012 at Claims 11-12; Exh. 1002 at ¶¶135-50.) Further, the original claims of the ’971 application, directly underlying the ’784 patent, are identical to the issued claims. (Exh. 1004 at Claims 1-24; Exh. 1002 at ¶¶232-33.) However, those claims alone do not demonstrate that the inventors possessed or enabled those siRNA molecules. *Ariad Pharm., Inc. v. Eli Lilly & Co*., 598 F.3d 1336, 1350 (Fed. Cir. 2010) (en banc) (“[G]eneric claim language appearing in *ipsis verbis* in the original specification does not satisfy the written description requirement if it fails to support the scope of the genus claimed.”)

Additionally, the continuation applications, like EP1, the ’541 provisional, EP2, and the ’784 patent itself, concede that siRNA molecules comprising a double-stranded region of 17 ribonucleotides or fewer are not functional, despite being claimed. (*See, e.g.*, Exh. 1006 at 10, 31; Exh. 1007 at 10, 31; Exh. 1008 at 11, 35, 36; Exh. 1002 at ¶¶72, 187-91, 199, 201, 208, 210; *see also id.* at ¶¶121, 135-36.) Likewise, the continuation applications fail to provide any data for siRNA molecules comprising a double-stranded region of greater than 21 ribonucleotides, despite also being claimed. (Exh. 1002 at ¶192.)

V. THE PROSECUTION HISTORY

The ’971 application was examined under the pre-AIA first to invent provisions. (*See, e.g.*, Exh. 1004 at 376.) However, the legitimacy of the Applicant’s priority claims was never evaluated during prosecution and, as discussed in Section VIII, none of the ’784 patent claims are entitled to an effective filing date earlier than May 8, 2017 – the actual filing date of the ’971 application.

The ’971 application contained 24 claims, including one independent claim and 23 dependent claims. The original claims are identical to the issued claims.

The Examiner issued a single non-final rejection finding claims 1-14, 17-20 and 22-23 anticipated under 35 U.S.C. § 102(e) by U.S. Patent Pub. No. 2003/0190635 (“McSwiggen,” Exh. 1014), claims 1-24 obvious under 35 U.S.C. § 103 over McSwiggen in combination with other prior art, and claims 1-24

unpatentable on the ground of nonstatutory obviousness-type double patenting ("OTDP") as being unpatentable over six issued patents in the patent family. (Exh. 1004 at 374-86.) The Examiner found McSwiggen disclosed a ribonucleic acid molecule comprising a double-stranded structure wherein each strand comprises contiguous alternating modified ribonucleotides that alternate with unmodified or differently modified ribonucleotides. (*Id*. at 377.) The Examiner also found that McSwiggen taught the double-stranded nucleic acids of the invention could optionally comprise overhang regions on one or both strands and thus taught a structure that is blunt ended on one or both ends. (*Id*.)

Following the Examiner's non-final rejection, the Applicant filed a declaration under 37 C.F.R. § 1.131 ("131 Declaration") as "clear evidence of actual reduction to practice prior to the reference date of McSwiggen and overcomes McSwiggen." (*Id*. at 421; *see also id.* 404-11.) The Applicant argued that the 131 Declaration showed the "inventors have synthesized an exemplary siRNA molecule as recited in claim 1, and demonstrated inhibition of PTEN expression by the siRNA molecule." (*Id.* at 421.) The 131 declaration emphasized the exemplary siRNA molecule's ability to "inhibit expression of PTEN," and its effectiveness "at reducing PTEN mRNA expression in cells." (*Id*. at 405.) The Applicant also filed terminal disclaimers in response to the OTDP rejections. (*Id*. at 412-13, 423-24.)

The Examiner found the 131 declaration "sufficient to overcome the McSwiggen reference" and allowed the claims. (*Id*. at 436.)

VI. A PERSON OF ORDINARY SKILL IN THE ART

The '784 patent is directed at small interfering RNA molecules which inhibit the expression of a target gene. (*See, e.g.*, Exh. 1001 at 1:40-50.) Therefore, a POSA would have (a) a Ph.D. in chemistry, medicinal chemistry, biochemistry, molecular biology, molecular pharmacology, or a closely related discipline, (b) an M.S. degree in chemistry, medicinal chemistry, biochemistry, molecular biology, molecular pharmacology, or a closely related discipline, with at least two years of practical experience in the field of RNAi, or (c) a bachelor's degree in chemistry, biochemistry, or a closely related discipline, with post-graduate work relating to RNAi. (Exh. 1002 at ¶¶37-38.)

VII. CLAIM CONSTRUCTION

The following claim terms require construction and should be given the constructions proposed below. The remaining claim terms should be given their broadest reasonable interpretation in light of the specification. *Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016).

A. "double-stranded siRNA molecule" and "double-stranded siRNA molecule against a target nucleic acid"

The terms "double-stranded siRNA molecule" and "double-stranded siRNA molecule against a target nucleic acid" appear in all of the '784 patent claims

expressly or via dependency. (Exh. 1001 at Claims 1-24.) The term "double-stranded siRNA molecule against a target nucleic acid" is recited in the introductory words of the claim and provides antecedent basis for the term "double-stranded siRNA molecule," which is recited in the body of the claim. *Novatek, Inc. v. Sollami Co*., 559 F. App'x. 1011, 1015 (Fed. Cir. 2014) ("[L]imitations in the body of the claim that rely upon and derive antecedent basis from the preamble may render the preamble a necessary component of the claimed invention; and therefore, a limitation on the claims.") (citing *NTP, Inc. v. Research in Motion, Ltd*, 418 F.3d 1282, 1306 (Fed. Cir. 2005)). As a result, a POSA would have understood the two terms to have the same meaning, which "can be resolved only on review of the entirety of the patent to gain an understanding of what the inventors actually invented and intended to encompass by the claim." *Corning Glass Works v. Sumitomo Elec., U.S.A., Inc.*, 868 F.2d 1251, 1257 (Fed. Cir. 1989). Specifically, a POSA would have understood the terms to convey a requirement that the claimed siRNA molecules interfere with gene expression, *i.e.*, exhibit RNAi activity. (Exh. 1002 at ¶¶113-18.) Petitioner's construction is supported by the claim language, the patent specification, and the prosecution history of the '784 patent and related patents, and is consistent with the meaning of the term "siRNA" as it is used in the field of RNAi.[2] (*Id*. at ¶¶113-18.)

[2] Petitioner's proposed construction would be same even if based only on the '784

First, the claim language emphasizes that the claimed molecules must be "siRNA molecule[s] ***against a target nucleic acid***." (Exh. 1001 at Claim 1.) The specification relates target nucleic acids to the "mode of action of interfering ribonucleic acids" (*Id*. at 12:5-8) and indicates that interfering ribonucleic acids act, for instance, by "inhibiting expression of a target gene" (*Id*. at 1:46-48), effecting "gene silencing" (*Id*. at 1:53-56) and/or "knockdown or knockout of any desired coding nucleotide such as an mRNA." (*Id*. at 19:63-67). Each of these actions requires RNAi activity and thus would be expected of the "siRNA molecule[s] against a target nucleic acid" claimed in the '784 patent. (Exh. 1002 at ¶¶114, 116; *see also id.* at ¶¶62-62.)

Furthermore, the '784 patent's stated problem to be solved is to provide siRNA molecules "that are both stable and active in a biochemical environment." (Exh. 1001 at 2:29-31.) And, the patent specification repeatedly emphasizes that the siRNA molecules are "suitable to cause or be[] involved in methods of RNA mediated interference." (*Id*. at 12:41-43; *see also id.* at 2:29-31, 11:19-23 (emphasizing activity and stability as advantages of the siRNA molecules of the invention); 1:46-57, 6:60-67 (identifying "inhibiting the expression of a target gene" as one of the uses for the siRNA molecules of the invention); 6:27-30,

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patent claims and specification.

19:67-20:8 (identifying "target validation" as one of the uses for the siRNA molecules of the invention); 6:31-42, 20:29-52 (identifying "medicaments and pharmaceutical compositions" as one of the uses for the siRNA molecules of the invention); 19:63-67 (identifying "knockdown or knockout of any desired coding nucleotide" as one of the uses for the siRNA molecules of the invention); Exh. 1002 at ¶116-117; *see also id*. at ¶¶62-64.)

Likewise, all but one of the patent examples relate to the impact of various siRNA modifications on RNAi activity. (Exh. 1001 at Example 1 (investigating the impact of NH_2 end protection groups on activity), Example 2 (investigating the impact of overhangs on activity), Example 3 (investigating the impact of duplex length on activity), Example 4 (investigating the homology between target mRNA and siRNA required for activity), Example 6 (investigating the impact of end groups on sense strand on activity), Example 7 (investigating the impact of 2'-O-methyl modifications on activity), Example 8 (investigating the impact of blocks of internal 2'-O-methyl modifications on activity), Example 9 (investigating the impact of alternating internal 2'-O-methyl modifications on, *inter alia*, activity), Example 10 (investigating the impact of internal 2'-O-methyl modifications on activity), Example 11 (investigating the impact of alternating 2'-O-methyl modifications on activity), Example 12 (investigating the impact of loop structures

on activity), Example 13 (investigating the impact of loop structures on activity); Exh. 1002 at ¶117; *see also id*. at ¶¶70-73; 75-79).

Additionally, as discussed in Section V, in order to overcome a rejection during prosecution, Patent Owner emphasized the activity of "an exemplary siRNA molecule as recited in claim 1" as "clear evidence of actual reduction to practice." (Exh. 1004 at 421.) Similarly, even when describing its claimed molecules more generally, Patent Owner has advocated they have activity. For instance, during the prosecution of the related '630 application, Patent Owner argued that claims directed to "nucleic acid molecules" were not rendered obvious by the prior art because "[t]here was [] no reasonable expectation that the [structural] modifications recited in the claims would provide a nucleic acid that would either retain RNAi activity or increase stability, let alone both increase stability and maintain activity." (Exh. 1018 at 28; *see also id*. at 24, 29-38, 41-42.) In fact, in that prosecution, Patent Owner submitted an expert declaration, which described the claimed "nucleic acid molecule[s]" as being "highly resistant to degradation by nucleases whilst maintaining potent activity in gene silencing." (*Id*. at 55 (¶4).)

Thus, Patent Owner has repeatedly and consistently described its claimed siRNA molecules as having, at minimum, RNAi activity, which should operate as a claim limitation. *VirnetX, Inc. v. Cisco Sys., Inc.*, 767 F.3d 1308, 1318 (Fed. Cir. 2014) ("The fact that [a particular feature] is 'repeatedly and consistently' used to

characterize the invention strongly suggests that it should be read as a part of the claim.") (citation omitted).

Additionally, Petitioner's construction is consistent with a POSA's understanding of the term "siRNA" as used in the field of RNAi. (Exh. 1002 at ¶118.)

Moreover, even if "against a target nucleic acid" is considered part of the claim preamble, as discussed above, it nevertheless defines the subject matter of the claimed invention (*i.e.*, "siRNA molecule") and, therefore, limits the scope of the claim. *See, e.g.*, *Aristocrat Techs. Austl. Pty Ltd. v. Int'l Game Tech*., 709 F.3d 1348, 1355 (Fed. Cir. 2013) ("A claim's preamble may limit the claim when the claim drafter uses the preamble to define the subject matter of the claim."); *Derman v. PC Guardian*, 37 U.S.P.Q.2D (BNA) 1733, 1734 (Fed. Cir. 1995) ("A claim preamble has the import that the claim as a whole suggests for it. In other words, when the claim drafter chooses to use ***both*** the preamble and the body to define the subject matter of the claimed invention, the invention so defined, and not some other, is the one the patent protects.") (emphasis in original) (citation omitted).

VIII. THE '784 PATENT IS ELIGIBLE FOR PGR AND NONE OF THE CLAIMS ARE ENTITLED TO A PRIORITY DATE EARLIER THAN MAY 8, 2017

A patent that issues from an application filed after March 16, 2013, that claims priority to an application filed before March 16, 2013, is available for PGR "if the patent contains . . . at least one claim that was not disclosed in compliance with the written description and enablement requirements of § 112(a) in the earlier application for which the benefit of an earlier filing date prior to March 16, 2013 was sought." *Inguran, LLC v. Premium Genetics (UK) Ltd.*, Case PGR2015-00017, Paper 8 at 11 (P.T.A.B. Dec. 22, 2015). Similarly, to be entitled to the priority benefit of a parent application, "Patent Owner must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, possession of the invention now claimed by describing the invention, ***with all its claimed limitations***." *Inguran, LLC v. Premium Genetics (UK) Ltd.*, Case PGR2015-00017, Paper 22 at 33-34 (P.T.A.B. Dec. 20, 2016) (emphasis in original). To meet the written description requirement of 35 U.S.C. § 112, the earlier application(s) must "reasonably convey[ ] to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (citation omitted). In essence, the specification must describe an invention in a manner "understandable to [a] skilled artisan and show that the inventor actually invented the invention claimed."

Id. Moreover, when a patent claims a genus using functional language to define a desired result, "the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant has invented species sufficient to support a claim to the functionally-defined genus." *Id*. at 1349.

To meet the enablement requirement of 35 U.S.C. § 112, the specification "must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation." *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1365 (Fed. Cir. 1997) (citations omitted). "Enablement serves the dual function in the patent system of ensuring adequate disclosure of the claimed invention and of preventing claims broader than the disclosed invention." *MagSil Corp. v. Hitachi Glob. Storage Techs., Inc.*, 687 F.3d 1377, 1380-81 (Fed. Cir. 2012). A specification that "provides a starting point from which one of skill in the art can perform further research in order to practice the claimed invention" does not fulfill the enablement requirement. *Nat'l Recovery Techs., Inc. v. Magnetic Separation Sys., Inc.*, 166 F.3d 1190, 1198 (Fed. Cir. 1999). Where functional limitations are involved, "the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility." *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991). Moreover, regardless of whether

the ’784 patent claims are properly construed to require activity, the enablement requirement “incorporates as a matter of law the requirement of 35 U.S.C. § 101 that the specification disclose as a matter of fact a practical utility for the invention.” *In re Fisher*, 421 F.3d 1365, 1378 (Fed. Cir. 2005) (citation omitted). Thus, to meet the “how to use” requirement, the specification must establish that the invention achieves its intended purpose. *See Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323 (Fed. Cir. 2005).

Here, the ’971 application underlying the ’784 patent was filed on May 8, 2017 but, as detailed in Section IV, the patent claims priority to a series of continuation applications reaching back to August 5, 2003, as well as a provisional application filed on August 12, 2002 and two European applications filed on August 5, 2002 and April 10, 2003, respectively. (Exh. 1001 at Cover.) As detailed in Section IV, the disclosures in the priority applications are substantively the same except for their claims, in part, because the entire family of U.S. applications are continuations. Seven of the nine priority applications leading to the ’784 patent were filed before March 16, 2013. However, as discussed in detail below, the claims of the ’784 patent are not described or enabled by any of the priority applications or their original claims (or even the ’784 patent specification itself as discussed in Sections IX.A and IX.B). Accordingly, the ’784 patent is eligible for

PGR and none of the challenged claims are entitled to an effective filing date earlier than May 8, 2017 – the actual filing date of the ’784 patent.

A. The Applications Fail to Describe Representative siRNA Molecules Across the Full Scope of the Vast Genus Encompassed by Claims 1-24

As discussed in Section III, the ’784 patent claims recite an enormous, essentially unlimited, genus of diverse siRNA molecules, which may vary chemically, structurally and/or with respect to the particular gene or gene sequence being targeted. (Exh. 1002 at ¶¶107-109, 155-82, 192; *see also id*. at ¶¶204-205.)

As detailed in Section III, the dependent claims introduce additional structural limitations that narrow the scope of the claimed genus. (Exh. 1001 at Claims 2-24; Exh. 1002 at ¶¶172-73.) Nevertheless, the claimed genus of the dependent claims is still extremely broad and potentially unlimited. For example, claim 14, which specifies a genus of siRNA molecules that comprise contiguous alternating 2’-O-methyl modified ribonucleotides and unmodified ribonucleotides, encompasses molecules that may vary in terms of the:

- number of 2’-O-methyl ribonucleotides in each stretch, strand, or molecule;
- number of unmodified ribonucleotides in each stretch, strand, or molecule; and

- position of 2'-O-methyl and unmodified ribonucleotides within each stretch, strand, or molecule.

(Exh. 1002 at ¶¶160-82.)

The full scope of the genus of siRNA molecules of claim 14 also includes siRNA molecules with:

- modifications to ribonucleotide sugar in addition to 2'-O-methyl;
- modifications to the ribonucleotide base;
- modifications to the backbone;
- modifications to the ends, so long as at least one end is blunt ended; and
- stretch lengths between 15 and 30 ribonucleotides.

There is also no limit on the length of each strand or the siRNA target. (*Id*.)

Patent Owner has previously confirmed the broad scope of the genus of even narrowed claims like claim 14. During prosecution of the related '630 application (of which the '784 patent is a continuation), Patent Owner submitted a declaration by Dr. Jörg Kaufmann, an inventor on the '784 patent, that estimated a genus of siRNA molecules limited to a strand length of 23 nucleotides and comprising only various arrangements of a single type of 2'-modified nucleotides and unmodified nucleotides on each strand would encompass "7.0×10^{13} [70 trillion] possible

arrangements." (Exh. 1018 at 130-31 (¶¶2-5); *id*. at 36.) While Patent Owner may argue that the genus of the '784 patent claims is somehow narrower than the genus assessed in the '630 prosecution, Dr. Kaufmann's rudimentary assessment does not consider many of the variables contemplated by the '784 patent claims. In fact, Patent Owner admitted that if other possible types of 2'-modifications were included, "the number of possible arrangements becomes ***unimaginably high***." (*Id*. at 36 (emphasis added); *see also* Exh. 1002 at ¶181, n.22.) The same is true if other possible chemical modifications to ribonucleotide bases, strand lengths, stretch lengths, end modifications, backbone modifications, target genes, etc. are included. (Exh. 1002 at ¶¶181-82.)

In stark contrast to Patent Owner's admission, the disclosures of the underlying applications focus on a narrow sliver of structurally similar molecules. The only siRNA molecules disclosed in the figures and examples of the underlying applications that fall within that broad genus have a specific modification pattern (*i.e.*, modified/unmodified across the full strand), a single type of modification (*i.e.*, 2'-O-methyl only), only two double-stranded lengths (*i.e.*, 19 or 21 nucleotides), and a single end structure (*i.e.*, blunt ended on both ends). (*See, e.g.*, Exh. 1009 at Examples 7-11; Exh. 1002 at ¶¶76-79, 133, 135-36.)[3] The examples

[3] Certain examples describe siRNA molecules with different features (*e.g.*, different double-stranded lengths, overhang, etc.). However, such molecules are

fail to provide any siRNA molecules that comprise modified ribonucleotides that alternate with ***differently modified ribonucleotides*** or a ***mixed motif*** of differently modified and unmodified ribonucleotides as encompassed by at least claims 1-13, 15-17 and 21-24. (Exhs. 1005-1013 at Examples; Exh. 1002 at ¶¶70-79, 133, 135-36, 186, 199.) The examples also fail to disclose any siRNA molecules with a ***double-stranded length other than 19 or 21 ribonucleotides*** as encompassed by at least claims 1-7, and 10-24. (Exh. 1005-1013 at Examples; Exh. 1002 at ¶¶70-79, 133, 135-36, 186, 199.) Additionally, the examples fail to disclose any siRNA molecules with a ***2'-fluoro modification*** as encompassed by at least claims 11, 16 and 24. (Exh. 1005-1013 at Examples; Exh. 1002 at ¶¶70-79, 133, 135-36, 186, 199.) And, the examples fail to disclose any siRNA molecules with a 2'-O-alkyl modification ***other than 2'-O-methyl*** as encompassed by at least claims 11, 12, 18, 19, 21 and 22. (Exh. 1005-1013 at Examples; Exh. 1002 at ¶¶70-79, 133, 135-36, 186, 199.)

This sliver of structurally similar siRNA molecules is not representative of the full genus claimed and does not provide adequate written description. (Exh. 1002 at ¶186; *see also id*. at ¶¶121, 135-36.); *see, e.g., Abbvie Deutschland GmbH*

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not encompassed by the '784 patent claims because they are either completely unmodified or fully modified. (Exh. 1001 at Examples 2-5; Exh. 1002 at ¶185, n.23.)

& Co. v. Janssen Biotech, Inc., 759 F.3d 1285, 1300 (Fed. Cir. 2014) ("merely drawing a fence around a perceived genus is not a description of the genus;" "if the disclosed species only abide in a corner of the genus, one has not described the genus sufficiently to show that the inventor invented, or had possession of, the genus"); *Ariad Pharm.*, 598 F.3d at 1349 ("[A]n adequate written description of a claimed genus requires more than a generic statement of an invention's boundaries.") (citation omitted); *see also Boston Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1364-67 (Fed. Cir. 2011) (affirming summary judgment that claims to a broad genus were unsupported by general reference to subgenus and experiments that related to only a single species); *Centocor Ortho Biotech, Inc. v. Abbott Labs.*, 636 F.3d 1341, 1350-51 (Fed. Cir. 2011) (finding no adequate written description where "the patent broadly claims a class of antibodies that contain human variable regions [but] the specification does not describe a single antibody that satisfies the claim limitations."); *Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1125-26 (Fed. Cir. 2008) (affirming summary judgment of invalidity where claims to broad genus were unsupported by disclosure of single species).

Furthermore, to the extent the Board finds that the claimed siRNA molecules require RNAi activity – consistent with the express disclosure of the '784 patent (*see* Section VII.A) – Patent Owner's failure to provide adequate written

description of the full genus of siRNA molecules is even more compelling. As the Board has recognized, where there is a functionally-defined genus, "the specification must demonstrate that the applicant has made a generic invention that achieves the claimed result and do so by showing that the applicant ***has invented species sufficient to support a claim to the functionally-defined genus***." *US Endodontics, LLC v. Gold Standard Instruments, LLC*, Case PGR2015-00019, Paper 54 at 31 (P.T.A.B. Dec. 28, 2018 (emphasis in original) (quoting *Ariad Pharm.*, 598 F.3d at 1349); *see also Daiichi Sankyo Co., Ltd. v. Alethia Biotherapeutics, Inc.*, Case IPR2015-00291, Paper 75 at 16-19 (P.T.A.B. June 14, 2016) (finding a lack of adequate written description for claims directed to a genus of antibodies having inhibitory functions where there was no showing which antibodies would be inhibitory and which would not). The Federal Circuit has also recognized that the problem is "especially acute" when genus claims contain functional requirements. *Ariad Pharm.*, 598 F.3d at 1349; *see also Abbvie Deutschland GmbH & Co.*, 759 F.3d at 1301-302 (finding substantial evidence to support jury finding of lack of written description where patent claims attempt to cover every particular type of human antibody that would achieve a desired result but patent does not describe representative examples to support the full scope of the claims); *Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1350-51 (Fed. Cir. 2013) (affirming judgment as a matter of law of lack of written

description where patent application "[a]t best . . . describes a roadmap for producing candidate [ ] variants and then determining which might exhibit [the claimed functional characteristic]"); *Boston Sci. Corp.*, 647 F.3d at 1367 (affirming summary judgment of lack of written description where patent invites "other researchers to discover which of the thousands of [claimed compounds] could conceivably [meet the functional requirements of the claims]"); *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927 (Fed. Cir. 2004) (affirming summary judgment of lack of written description where, even though patent described a broad class of compounds, it did not describe "which" of those compounds "have the desired characteristic"); *Regents of Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997) (affirming finding of lack of written description where "the claimed genera of vertebrate and mammal cDNA are not described by the general language of the [patent at issue's] written description supported only by the specific nucleotide sequence of rat insulin").

Here, the figures and examples of the underlying applications – which are the only places Patent Owner provides activity data in any of its applications – provide data only for a narrow sliver of structurally similar siRNA molecules that fall within the claimed genus. These siRNA molecules all have a specific modification pattern (*i.e.*, modified and unmodified across the full strand), a single type of modification (*i.e.*, 2'-O-methyl), only two double-stranded lengths (*i.e.*, 19

or 21 ribonucleotides) and a single end structure (*i.e.*, blunt ended on both ends). (*See, e.g.*, Exh. 1009 at Examples 7-11; Exh. 1002 at ¶¶133, 135-36.) The RNAi activity data provided for these molecules is, likewise, limited to only three target genes (*i.e.*, PTEN, Akt and p110β). As explained above, this narrow disclosure of structurally similar molecules is not representative of the full genus being claimed. For instance, there is no disclosure of any active siRNA molecules having a modification pattern of modified ribonucleotides alternating with ***differently modified ribonucleotides***; any active molecules having a modification pattern of modified ribonucleotides alternating with a ***mixed motif*** of unmodified and differently modified ribonucleotides; or any active molecules comprising any modification other than a ***2'-O-methyl modification***. (*See, e.g.*, Exhs. 1005-1013 at Examples; Exh. 1004 at 60-76; *see also* Exh. 1002 at ¶¶133, 135-36.)

Patent Owner's failure to provide a representative number of active species is compounded by the unpredictability of the effect of different modifications on RNAi activity. *US Endodontics, LLC,* Case PGR2015-00019, Paper 54 at 35; (Exh. 1002 at ¶¶193-97.) Indeed, the field of RNAi was in its infancy in August 2002 – the time period to which Patent Owner claims priority. (Exh. 1002 at ¶211-24.) Patent Owner has also previously advocated this very lack of predictability. For instance, during the prosecution of the related '630 application, Patent Owner admitted "the effects of other types of potential 2'-modification[s] . . . are not

predictive . . . because various modifying groups differ in their chemical and physical properties." (Exh. 1018 at 59 (¶15).) Patent Owner also concluded "the effect of chemical modification of an siRNA molecule is ***highly unpredictable*** because it involves decreasing the ability of the nucleic acid to act as a substrate for one or more undesired nucleases present in cells and biological fluids whilst retaining its ability to act as a substrate for the desired endonuclease in the RISC complex." (*Id*. at 55 (¶7) (emphasis added).) And Patent Owner acknowledged that as of 2002, when the first priority applications were filed, "the level of unpredictability involved in achieving this desired outcome was even greater, because ***little or nothing was known*** about the nuclease or nucleases involved in the unwanted degradation of the double stranded siRNA . . . ***little was known*** about RISC . . . [a] ***further unknown*** was how tolerant RISC would be to 2'-O-methyl and other modifications." (*Id.* at 56 (¶8) (emphasis added).)

The lack of adequate written description is further evidenced by the fact that claims 1-7 and 11-24 of the '784 patent encompass siRNA molecules comprising a double-stranded region of 17 ribonucleotides or fewer, which the underlying applications (and the '784 patent itself) expressly teach "are not functional in mediating RNAi." (Exh. 1006 at 10, 31, 32; Exh. 1007 at 10, 31, 32; Exh. 1008 at 11, 35, 36; *e.g.*, Exh. 1009 at 16:25-28, 35:14-18, 36:25-28; *see also*, Exh. 1001 at 12:22-26, 24:55-60, 25:4-8, 25:52-53.) Therefore, the inventors were not in

possession of active siRNA molecules having a double-stranded region of 17 ribonucleotides or less. (Exh. 1002 at ¶¶187-92, 199; *see also id*. at ¶¶201-208, 210.); *see also Bamberg v. Dalvey*, 815 F.3d 793, 797-98 (Fed. Cir. 2016) (finding lack of possession and affirming finding of inadequate written description where patent specification described a claimed embodiment as inferior); *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1158-59 (Fed. Cir. 1998) (finding lack of possession and affirming finding of inadequate written description where patent specification "specifically distinguishes [an alleged embodiment of the invention] as inferior").

Although the underlying applications include generic embodiments or broad claims that arguably encompass additional siRNA molecules that fall within the claimed genus (as discussed in Section IV), the mere fact that the words appear does not reasonably suggest that Patent Owner was in possession of the full scope of the genus claimed. *Ariad Pharm.*, 598 F.3d at 1345.

For at least these reasons, none of the applications leading to the '784 patent application provide adequate written description for the full scope of the claimed genus of siRNA molecules. Therefore, none of the claims are entitled to an effective filing date earlier than May 8, 2017 and the '784 patent is PGR eligible.

B. The Applications Fail to Enable siRNA Molecules Across the Full Scope of the Vast Genus Encompassed by Claims 1-24

In addition to failing to provide adequate written description for claims 1-24, the priority applications also fail to enable the full scope of the claims without

undue experimentation. This is an additional and independent reason the ’784 patent is eligible for PGR and none of the claims are entitled to an effective filing date earlier than May 8, 2017.

As explained below, the highly speculative nature of the field of RNAi, the state of the prior art, the nature of the invention, the breadth of the claims, the lack of guidance in the applications, and the amount of experimentation necessary to make and use the claimed siRNA molecules confirm the claims of the ’784 patent are not enabled by the applications.

1. The Highly Speculative Nature of the Field of RNAi and the State of the Prior Art

In an unpredictable technology, “an enabling description in the specification must provide those skilled in the art with a specific and useful teaching.” *Genentech, Inc.*, 108 F.3d at 1367-68.

Here, the inventions claimed in the ’784 patent relate to chemically modified siRNA molecules. (Exh. 1002 at ¶¶57-80, 211.) As discussed in Section VII.A, the claim language, the patent specification and the prosecution history of the ’784 patent and related patents establish that the utility of the claimed siRNA molecules is that they possess RNAi activity.

The field of using chemically modified siRNA to knock-down gene activity in cells was in its infancy and poorly understood at the time of the filing of the earliest applications underlying the ’784 patent. (*Id*. at ¶¶212-24.)

The applications leading to the ’784 patent confirm the unpredictability of the field of RNAi. For instance, Examples 1 and 6 (which appear in all of the underlying applications and the ’784 patent itself) show that inclusion or exclusion of 3’-amino end caps can drastically impact function. (*Id*. at ¶¶70, 75, 121, 135-36; *see e.g.*, Exh. 1001 at Example 1, 6.) Additionally, Examples 7-11 (which in large part appear in all of the underlying applications and the ’784 patent itself) demonstrate that siRNA molecules with internal 2’-O-methyl modified and unmodified ribonucleotides can impact both the activity and stability of the siRNA molecules, and that not all 2’-O-methyl modified siRNA molecules retained activity or had improved stability. (Exh. 1002 at ¶¶76-79, 121, 135-36; *see, e.g.*, Exh. 1001 at Examples 7-11.) This unpredictability is further confirmed in the siRNA literature. For instance, a 2008 review article states:

> siRNA duplexes have been chemically modified in a wide variety of ways. ***Some of the results in the literature, however, seem to contradict one another, or to work on one system but not another. This field is still very young, and it will take time for the more robust and universal modifications to be recognized as such.*** In the meantime, it is useful to have many

> options so that at least one of the chemistries can be used to modify an siRNA without compromising its potency.

(Exh. 1027 at 843 (emphasis added); *see also* Exh. 1002 at ¶221.)

As noted in Section VIII.A, Patent Owner also stressed the unpredictability of the field during prosecution of related applications. (Exh. 1018 at 55-59 (¶¶7, 8, 15).)

In addition to the field of RNAi specifically, it is widely recognized that the fields of chemistry, biology and biotechnology are unpredictable. (Exh. 1002 at ¶¶193-97, 212-31); *see, e.g.*, *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001) (referring to "the unpredictable arts such as chemistry and biology") (citations omitted).

While the state of the art has evolved over the past 20 years, RNAi is still far from a settled technology. (Exh. 1002 at ¶¶224, 231; Exh. 1029 at 12.) Despite the emergence of some guiding principles to aid in designing synthetic siRNAs, a POSA still would not be able to reliably predict the impact of different modifications on RNAi across different gene targets. (Exh. 1002 at ¶¶224, 231.) The hurdles a POSA faces in the field of RNAi are further evidenced by the fact that a drug using this technology is only now – nearly 20 years after Patent Owner's alleged priority application filing – approaching market entry. (*Id*.)

The unpredictable nature of the field of RNAi supports a finding of lack of enablement.

2. The Nature of the Invention and the Wide Breadth of the Claims

"A patentee who chooses broad claim language must make sure the broad claims are fully enabled." *Sitrick v. Dreamworks, LLC*, 516 F.3d 993, 999 (Fed. Cir. 2008). And where claims require functional elements, such as activity, there must also be a "reasonable correlation" between the scope of the disclosure and the "scope of protection sought in the claims." *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1361 (Fed. Cir. 2007) (citation omitted).

Here, as discussed in Section VIII.A, the '784 patent claims encompass an enormous, potentially unlimited genus of structurally diverse chemically modified siRNA molecules directed to any genetic target. (Exh. 1002 at ¶¶155-82, 204-205.) The '784 patent claims are broad enough to cover structural modifications and genetic targets that have yet to be discovered. (*Id*. at ¶¶156, 174, 204-205.) Nevertheless, the underlying applications disclose only a sliver of structurally similar siRNA molecules encompassed by the claims that have any utility whatsoever. In fact, of the approximately 120 siRNA molecules disclosed in the '784 patent, less than about 50 have internal 2'-O-methyl modified ribonucleotides. (*Id*. at ¶185.) And, of those 50, only 25 are non-duplicative and less than ten are reported by Patent Owner as having RNAi. (*Id*. at ¶¶185, 206.) Further, each underlying application concedes that siRNA molecules encompassed by the claims, *i.e.*, those having a double-stranded length of 17 ribonucleotides or

less, are not active. (Exh. 1006 at 10, 31, 32; Exh. 1007 at 10, 31, 32; Exh. 1008 at 11, 35, 36; *e.g.*, Exh. 1009 at 16:25-28, 35:14-18, 36:25-28; *see e.g.*, Exh. 1001 at 12:22-26, 24:55-60, 25:52-53; Exh. 1002 at ¶¶190, 208; *see also id*. at ¶¶121, 135-36.)

The broad scope of the claimed genus, and the failure to disclose any practical utility for the vast majority of the claimed siRNA molecules, provides additional support for a finding of lack of enablement. (Exh. 1002 at ¶¶129, 134-51, 182, 198-99, 200-201, 206-208, 210; *see also id*. at ¶¶121, 135-36.)

3. The Lack of Guidance in the Underlying Applications and the Undue Experimentation Required to Practice the Alleged Invention

While "patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art . . . the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility." *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991). A patent specification that "provides only a starting point, a direction for further research . . . does not provide guidance to a person of ordinary skill in the art on how to make or use [a claimed invention]." *Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 1284 (Fed. Cir. 2007) (internal quotation marks omitted).

Here, as discussed in Section VIII.A, the applications underlying the ’784 patent disclose only a small sliver of the siRNA molecules that are encompassed by the broadly claimed genus. Moreover, the applications provide activity data only for a subset of this sliver. (Exh. 1002 at ¶¶129, 134-50.)

What is not disclosed, although claimed, is:

- any siRNA molecule that comprises modified ribonucleotides that alternate with differently modified ribonucleotides as encompassed by at least claims 1-13, 15-17 and 21-24;
- any siRNA molecule that comprises modified ribonucleotides that alternate with mixed motif of differently modified ribonucleotides and unmodified ribonucleotides as encompassed by at least claims 1-13;
- any siRNA molecule that comprises any modification other than 2’-O-methyl as encompassed by at least claims 1-13, 15-17 and 21-24;
- any siRNA molecule with a double-stranded length greater than 21 ribonucleotides as encompassed by at least claims 1-7 and 10-24;
- any siRNA molecule with a double-stranded length of 17 ribonucleotides or less as encompassed by at least claims 1-7 and 11-24;
- any siRNA molecule with a 2’-fluoro modification as encompassed by at least claims 1-13, 15-17, 21-24; and

- any siRNA molecule with a 2'-O-alkyl modification other than 2'-O-methyl as encompassed by at least claims 1-13 and 15-24.

(Exhs. 1005-1013 at Examples; Exh. 1002 at ¶¶128, 133, 135-50.)

The applications also fail to provide any rationale why the activity observed for only a few siRNA molecules, all of which had a specific modification pattern (*i.e.*, modified and unmodified across the full strand), a single type of modification (*i.e.*, 2'-O-methyl), only two double-stranded lengths (*i.e.*, 19 or 21 nucleotides) and a single end structure (*i.e.*, blunt ended on both ends) and target only three genes (*i.e.*, Akt, PTEN, p110β), would be expected to reasonably predict siRNA activity for the full scope of chemically and structurally diverse siRNA molecules that are directed to ***any*** gene. (Exh. 1002 at ¶¶129, 134-50; *see also id*. at ¶¶182, 200-201, 206-208, 210, 212-24.)

Moreover, as explained in Section VIII.A, the underlying applications concede that siRNA molecules comprising a double-stranded region of 17 nucleotides or fewer in length, as encompassed by at least claims 1-7 and 11-24, are not functional. (Exh. 1006 at 10, 31, 32; Exh. 1007 at 10, 31, 32; Exh. 1008 at 11, 35, 36; *e.g.*, Exh. 1009 at 16:25-28, 35:14-18, 36:25-28; *see e.g.*, Exh. 1001 at 12:22-26, 24:55-60, 25:52-53.) There is no information in the underlying applications as to how to use these non-functional siRNA molecules. (Exh. 1002 at ¶¶208; *see also id*. at ¶¶121, 135-36.)

Further, there is no guidance in any of the underlying applications as to how to practice the claimed invention without undue experimentation. (*Id*.) While the underlying applications disclose screening methods to determine whether an siRNA molecule has RNAi activity (*see, e.g.*, Exhs. 1005-1013 at Examples; Exh. 1004 at 60-76; Exh. 1001 at Examples; Exh. 1002 at ¶¶206-207), the Board has found that mere disclosure of testing methods "fails to provide sufficient guidance" and "would have required a person of ordinary skill in the art to engage in a complicated and lengthy screening process to practice the invention." *Daiichi Sankyo Co., Ltd. v. Alethia Biotherapeutics, Inc.*, Case IPR2015-00291, Paper 75 at 14-15 (P.T.A.B. June 14, 2016).

The lack of guidance in the underlying applications on how to use the claimed siRNA molecules would require a POSA to make a vast number of them and test them against a vast number of target genes without knowing which molecules may have any utility. (Exh. 1002 at ¶¶225-30; *see also id*. at ¶¶121, 135-36.) At minimum, for each siRNA molecule, a POSA would have to (1) select target nucleic acid or sequences, (2) select a duplex architecture for the siRNA molecules, (3) select a chemical modification strategy, (4) synthesize the siRNA molecule, and (5) test the siRNA molecule for activity. (*Id*. at ¶226; *see also id*. at ¶¶121, 135-36.) The need for iterative screening and testing is further complicated by the fact that the effectiveness of modifications is strongly sequence dependent

and does not provide predictability between and among sequences. (*Id*. at ¶¶227-28; *see also id*. at ¶¶121, 135-36.) Even the patent acknowledges that functionality is assay dependent. (Exh. 1001 at 8:46-49.)

This lack of guidance and required experimentation in order to use claimed molecules across the full scope of the genus further supports a finding of lack of enablement. *See Wyeth & Cordis Corp. v. Abbott Labs.*, 720 F.3d 1380, 1386 (Fed. Cir. 2013) (affirming finding of lack of enablement where "the specification . . . discloses only a starting point for further iterative research in an unpredictable and poorly understood field" and "one of ordinary skill would need to assay each of at least tens of thousands of candidates"); *ALZA Corp. v. Andrx Pharms., LLC*, 603 F.3d 935, 941 (Fed. Cir. 2010) (affirming finding of lack of enablement where POSA "would have been required to engage in an iterative, trial-and-error process to practice the claimed invention"); *see also Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1325 (Fed. Cir. 2005) ("If mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to 'inventions' consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses later proved true, the 'inventor' would be rewarded the spoils instead of the party who demonstrated that method actually worked.").

For at least these reasons, claims 1-24 are not enabled by the applications leading to the ’784 patent and none of the claims are entitled to an effective filing date earlier than May 8, 2017. Therefore, the ’784 patent is PGR eligible.

IX. THE CHALLENGED CLAIMS ARE UNPATENTABLE

As described below, the challenged claims of the ’784 patent are unpatentable.

A. Ground 1: Claims 1-24 Lack Written Description

As discussed in Section VIII.A, none of the applications leading to the ’784 patent provide adequate written description for the full scope of the ’784 patent claims. As noted in Section IV, the ’784 patent specification is identical or nearly identical to all the underlying applications and, therefore, also fails to provide adequate written description of the ’784 patent claims. Specifically, the ’784 patent, like the underlying applications, fails to demonstrate that the inventors were in possession of the full scope of the potentially unlimited number of structurally diverse chemically modified siRNA molecules, let alone molecules across the full scope of the claimed genus that have RNAi activity. (Exh. 1002 at ¶¶107-109, 154-99.) In addition, the patent specification teaches that siRNA molecules having a double-stranded region of 17 nucleotides or less as encompassed by at least claims 1-7, and 11-24, are not functional and, thus, not capable of RNAi, which further

evidences that the inventors were not in possession of the full scope of those claims. (*Id*. at ¶¶72, 187-92, 199.)

As discussed in Sections III and VIII.A, the ’784 patent claims encompass an enormous, potentially unlimited, number of chemically and structurally diverse siRNA molecules. (*Id*. at ¶154-82.) In addition, the ’784 patent claims are broad enough to encompass any of these chemically and structurally diverse siRNA molecules that are directed to any sequence of any target nucleic acid. (*Id*. at ¶¶156-59.) As also discussed in Section VIII.A, the additional limitations of the dependent claims do little to narrow the broad genus of siRNA molecules claimed.

Nevertheless, the ’784 patent specification focuses on the same narrow sliver of molecules within the broad genus claimed as the underlying applications. As in the underlying applications, the only siRNA molecules disclosed in the figures and examples of the ’784 patent specification that fall within the claimed genus have a ***specific modification pattern*** (*i.e.*, modified and unmodified across the full strand), ***a single type of modification*** (*i.e.*, 2’-O-methyl only), only two double-stranded lengths (*i.e.*, 19 or 21 nucleotides), ***a specific end structure*** (*i.e.*, blunt ended on both ends) and ***target only three genes*** (*i.e.*, Akt1, PTEN, p110β). (Exh. 1001 at Examples 7-11; Exh. 1002 at ¶¶183-97.) As discussed in Section VIII.A, this narrow disclosure is not representative of the full scope of the genus claimed.

Further, if the Board finds the '784 patent claims require the claimed siRNA molecules have RNAi activity, consistent with the express disclosure of the '784 patent (*see* Section VII.A), Patent Owner's written description problems are exacerbated. The '784 patent specification discloses activity data for fewer than ten non-duplicative siRNA molecules that fall within the claimed genus – all of which comprise alternating 2'-O-methyl modified and unmodified ribonucleotides, have a double stranded length of 19 or 21 nucleotides, are blunt ended on both sides and are used to target PTEN, Akt1 or p110β. (*See, e.g.*, Exh. 1001 at Examples 9-11; Exh. 1002 at ¶¶78-79, 198-99.) Furthermore, like the underlying applications, the '784 patent specification concedes that siRNA molecules comprising a double-stranded region of 17 ribonucleotides in length are "not functional." (Exh. 1001 at 12:22-26; *see also id*. at 24:55-60, 25:52-53; Exh. 1002 at ¶¶72, 187-92, 199.) Therefore, the inventors were not in possession of the claimed siRNA molecules having a double-stranded region of 17 ribonucleotides in length with RNAi activity. (Exh. 1002 at ¶191.)

For the foregoing reasons, and those discussed in Section VIII.A, claims 1-24 are unpatentable for failure to provide adequate written description for the full scope of the claims under 35 U.S.C. § 112.

B. Ground 2: Claims 1-24 Lack Enablement

As discussed in Section VIII.B, none of the applications underlying the '784 patent enable the broad scope of the '784 patent claims. As also discussed in Section IV, the '784 patent specification is identical or nearly identical to the underlying applications and, therefore, also fails to enable the full scope of the '784 patent claims. (*Id*. at ¶¶121, 124, 135-36, 200-31.) Specifically, claims 1-24 are unpatentable for lack of enablement because a POSA would be required to engage in undue experimentation to determine which of the claimed siRNA molecules within the extremely broad genus have utility. (*Id*. at ¶¶200-31.) Furthermore, because claims 1-7 and 11-24 encompass siRNA molecules comprising a double-stranded region of 17 ribonucleotides in length, which the '784 patent concedes are not functional, those claims are not enabled. (*Id*. at ¶¶72, 208, 210.)

As discussed here, and in Section VIII.B, the highly speculative nature of the field, the state of the prior art, the nature of the invention, the breadth of the claims, the lack of guidance in the applications and the patent specification, and the amount of experimentation necessary to make and use the claimed siRNA molecules all support Petitioner's position that undue experimentation would be required to practice the full scope of the claimed invention. Therefore, claims 1-24 are unpatentable for lack of enablement under 35 U.S.C. § 112(a). (*Id*. at ¶201.)

1. The Highly Speculative Nature of the Field of RNAi and the State of the Prior Art

As discussed in Section VIII.B.1, the ’784 patent relates to the field of RNAi technology and recites claims to chemically modified siRNA molecules. (*Id*. at ¶¶202-203.)

Unpredictability was, and remains, typical to the field of RNAi. (*Id*. at ¶¶211-31.) As discussed in Section VIII.B.1, the examples in the patent specification (Exh. 1001 at Example 1, 6-11), the siRNA literature (*e.g.*, Exh. 1027 at 843), admissions by the inventors (Exh.1028 at 2705; Exh. 1018 at 55-59 (¶¶7, 8, 15)) and the amount of time it has taken for a product using RNAi to become a clinical reality (Exh. 1029 at 12), are all evidence of this fact (Exh. 1002 at ¶¶211-31) – making the showing required for enablement all the more demanding. *See, e.g.*, *Genentech, Inc. v. Novo Nordisk A/S*, 108 F.3d 1361, 1367-68 (Fed. Cir. 1997). Moreover, despite the nearly 15-year gap between the filing of the earliest priority application and the filing of the application directly underlying the ’784 patent and the coincident evolution of the RNAi field, a POSA still would not be able to reliably predict the impact of different modifications on RNAi across different gene targets based on the ’784 patent specification. (Exh. 1002 at ¶¶223-24.)

2. The Nature of the Invention and the Wide Breadth of the Claims

As discussed in Sections III and VIII.B.2, the ’784 patent claims encompass an enormous, potentially unlimited, genus of structurally diverse chemically modified siRNA molecules directed to an unlimited genus of possible genetic targets. (*Id*. at ¶¶201, 204-205.) Furthermore, as required under 35 U.S.C. § 101, the siRNA molecules of the alleged invention must have a practical utility. As explained in Section VII, the claim language, the patent specification and the prosecution history of the ’784 patent and related patents establish that the practical utility of the claimed siRNA molecules is RNAi activity. (*Id*. at ¶¶58-64, 70-80, 129, 134-50; *see also id*. at ¶¶113-18.)

Nevertheless, the ’784 patent specification and its underlying applications report fewer than ten structurally similar siRNA molecules encompassed by the claims as having RNAi activity. (*Id*. at ¶¶185, 206.) This provides further support for a finding of lack of enablement. (*Id*.)

3. The Lack of Guidance in the Underlying Applications and the Experimentation Required to Practice the Alleged Invention

As discussed in Section VIII.B.3, the applications leading to the ’784 patent provide activity data for only a small sliver of siRNA molecules that fall within the broadly claimed structurally diverse genus of chemically modified siRNA molecules. The same is true for the ’784 patent specification. (*Id*. at ¶¶206-10.)

Further, as with the underlying applications, the '784 patent specification fails to explain why the activity observed for this small sliver of molecules would be predictive of RNAi for molecules across the full genus. (*Id.* at ¶207.) In fact, the patent specification, like the underlying applications, concedes that siRNA molecules encompassed by the broad genus, *i.e.*, those having a double-stranded region of 17 ribonucleotides or less, do not have utility. (*See, e.g.*, Exh. 1001 at 12:22-26, 24:55-60, 25:52-53.) There is no information in the patent specification or the underlying applications as to how to use such siRNA molecules. (Exh. 1002 at ¶¶225-30.)

Furthermore, the '784 patent specification, like the underlying applications, fails to provide any guidance on how to select siRNA molecules from the vast claimed genus that are active against genetic targets other than the three targets expressly disclosed, which leaves no guidance for the remainder of the claimed targets. (*Id*. at ¶¶206-10.)

It follows that to practice the claimed invention, a POSA would need to make and test a vast number of possible molecules against numerous target genes and numerous gene sequences without any guidance as to which may work. (*Id*. at ¶¶211-31; *see also id*. at ¶¶155-82.) This would involve, at least, (1) the selection of target nucleic acid or sequences, (2) the selection of a duplex architecture for the siRNA molecules, (3) the selection of a chemical modification strategy, (4) the

synthesis of the siRNA molecule, and (5) testing of the siRNA molecule for activity. (*Id*. at ¶226.) As noted above, there is little predictability between and among sequences, thereby necessitating a repetitive testing and screening process. (*Id*. at ¶¶225-31.) This is true between 2002 and 2017 despite advances in the field of RNAi. (*Id*.)

Like the applications leading to the '784 patent, the patent discloses screening methods to determine whether an siRNA molecule has RNAi. (*Id*.) However, as discussed in Section VIII.B.3, such a disclosure is not sufficient to avoid undue experimentation. (*Id*.); *see also Daiichi Sankyo Co., Ltd. v. Alethia Biotherapeutics, Inc.*, Case IPR2015-00291, Paper 75 at 14-15 (P.T.A.B. June 14, 2016).

For the foregoing reasons, and as discussed in Section VIII.B, claims 1-24 are unpatentable for lack of enablement under 35 U.S.C. § 112.

C. Ground 3: Claims 1-7, 9, 11-14 and 17-20 Are Anticipated by Czauderna

A claim is only invalid for anticipation if "a single prior art reference discloses each and every limitation of the claimed invention." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 958 (Fed. Cir. 2014) (citation omitted). "When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the

scope of the claim is known in the prior art." *Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001) (citation omitted).

Czauderna, et al., "Structural variations and stabilizing modifications of synthetic siRNAs in mammalian cells" ("Czauderna") was published on June 1, 2003.[4] (Exh. 1028; Exh. 1002 at ¶235.) Although this date is after the earliest possible priority date ("EPP") for the '784 patent, as explained in Section VIII, none of the challenged claims are entitled to an effective filing date earlier than May 8, 2017 – the actual filing date of the '784 patent. Therefore, Czauderna is prior art to the '784 patent under 35 U.S.C. § 102(a)(1). (Exh. 1002 at ¶236.) As explained below, Czauderna discloses several double-stranded siRNA molecules that anticipate claims 1-7, 9, 11-14 and 17-20. (*Id*. at ¶237-73.)

1. Claim 1

a. "A double-stranded siRNA molecule against a target nucleic acid"

Claim 1 of the '784 patent recites "a double-stranded siRNA molecule against a target nucleic acid." (Exh. 1001 at Claim 1.) As explained in Section VII,

[4] The named inventors of the '784 patent are co-authors of Czauderna. (Exh. 1028 at 2075.) Czauderna discloses only a subset of the sliver of siRNA molecules disclosed in the '784 patent and, therefore, provides even less written description and enabling disclosure than the patent itself. (Exh. 1002 at ¶¶214-15, 235-46.)

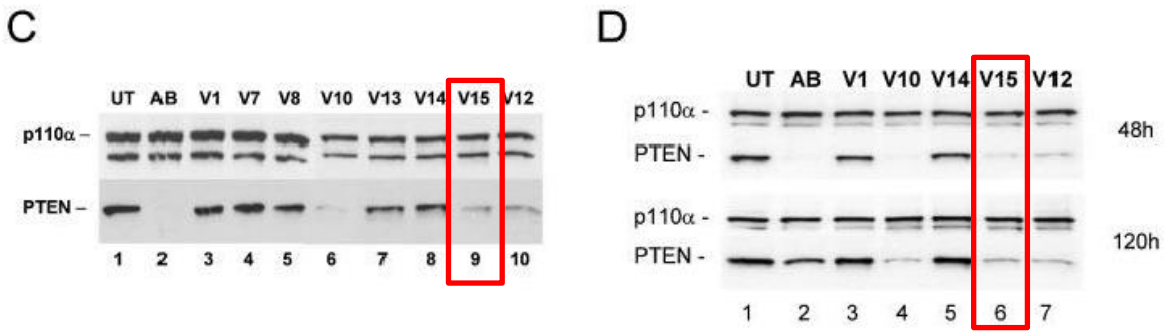
a POSA would have understood this term to require that the claimed "siRNA molecule" exhibits RNAi activity.

Czauderna discloses double-stranded siRNA molecule PTEN V15 (reproduced below, wherein the underlined and bold ribonucleotides comprise 2'-O-methyl modifications).

(Exh. 1028 at Figure 5B; Exh. 1002 at ¶¶240-41.)

Figures 5C and D (reproduced and annotated below) demonstrate that PTEN V15 inhibited PTEN protein expression and thus exhibits RNAi. (Exh. 1028 at Figure 5C, D; Exh. 1002 at ¶246.) PTEN V15, therefore, satisfies this limitation of claim 1.[5] (Exh. 1002 at ¶249.)

[5] Even if the patent claims are construed not to require RNAi, PTEN V15 still anticipates claims 1-7, 9, 11-14 and 18-20 because it meets all of the claims' structural requirements. (Exh. 1002 at ¶¶247-73.)



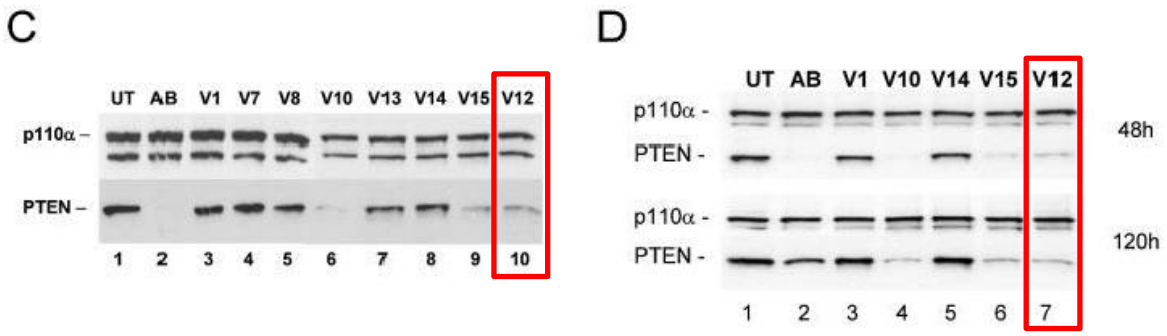
(Exh. 1028 at Figures 5C and D; Exh. 1002 at ¶246.)

Czauderna also discloses double-stranded siRNA molecule PTEN V12 (reproduced below, wherein the underlined and bold ribonucleotides comprise 2'-O-methyl modifications).

(Exh. 1028 at Figure 5B; Exh. 1002 at ¶¶240, 242.)

Figures 5C and D (reproduced and annotated below) demonstrate that PTEN V12 inhibited PTEN protein expression and thus exhibits RNAi. (Exh. 1028 at Figure 5C, D; Exh. 1002 at ¶246.) PTEN V12, therefore, satisfies this limitation of claim 1.[6] (Exh. 1002 at ¶249.)

[6] Even if the patent claims are construed not to require RNAi, PTEN V12 still anticipates claims 1 and 17 because it meets all of the claims' structural requirements. (Exh. 1002 at ¶¶247-73.)



(Exh. 1028 at Figures 5C and D; Exh. 1002 at ¶¶246.)

b. <u>"wherein the double-stranded siRNA molecule comprises a first strand and a second strand"</u>

Claim 1 of the '784 patent also recites "the double-stranded siRNA molecule comprises a first strand and a second strand." (Exh. 1001 at Claim 1.) As shown in reproduced Figure 5B, PTEN V15 and PTEN V12 are double-stranded and, therefore, satisfy this limitation of claim 1. (Exh. 1002 at ¶250.)

c. <u>"wherein the first strand comprises a first stretch that is complementary to the target nucleic acid"</u>

Claim 1 of the '784 patent also recites "the first strand comprises a first stretch that is complementary to the target nucleic acid." (Exh. 1001 at Claim 1.) PTEN V15 is "specific for the tumour suppressor PTEN." (Exh. 1028 at 2706; Exh. 1002 at ¶¶240, 251.) PTEN V15 and PTEN V12 are complementary to PTEN mRNA. (Exh. 1002 at ¶251; Exh. 1066 at 8.) PTEN V15 and PTEN V12, therefore, satisfy this limitation of claim 1. (Exh. 1002 at ¶251.)

d. <u>"wherein the second strand comprises a second stretch that is complementary to the first stretch"</u>

Claim 1 of the '784 patent also recites "the second strand comprises a second stretch that is complementary to the first stretch." (Exh. 1001 at Claim 1.) As shown in reproduced Figure 5B, the first and second strands of PTEN V15 are complementary to each other with each cytosine corresponding to guanine and each uracil corresponding to adenine. (Exh. 1002 at ¶252.) As also shown in reproduced Figure 5B, the first and second strands of PTEN V12 are complementary to each other. (*Id*.) Because the strands of PTEN V15 and PTEN V12 are complementary, so are the stretches in each strand. (*Id*.) PTEN V15 and PTEN V12, therefore, satisfy this limitation of claim 1. (*Id*.)

e. <u>"wherein the first strand and the second strand form a double-stranded structure comprising the first stretch and the second stretch"</u>

Claim 1 of the '784 patent also recites "the first strand and the second strand form a double-stranded structure comprising the first and the second stretch." (Exh. 1001 at Claim 1.) As shown in reproduced Figure 5B, PTEN V15 and PTEN V12 each comprise two stretches that form the double-stranded structure. (Exh. 1002 at ¶253.) PTEN V15 and PTEN V12, therefore, satisfy this limitation of claim 1. (*Id*.)

f. <u>"wherein the double-stranded siRNA molecule is blunt ended on at least one end, and"</u>

Claim 1 of the ’784 patent also recites “the double-stranded siRNA molecule is blunt ended on at least one end.” (Exh. 1001 at Claim 1.) As shown in reproduced Figure 5B, PTEN V15 and PTEN V12 are blunt ended on each (and therefore, also, at least one) end. (Exh. 1002 at ¶254.) PTEN V15 and PTEN V12, therefore, satisfy this limitation of claim 1. (*Id*.)

g. <u>“wherein each stretch consists of at least 15 and fewer than 30 ribonucleotides and”</u>

Claim 1 of the ’784 patent also recites “each stretch consists of at least 15 and fewer than 30 ribonucleotides.” (Exh. 1001 at Claim 1.) As shown in reproduced Figure 5B, PTEN V15 and PTEN V12 each have a double-stranded region of 21 ribonucleotides. (Exh. 1002 at ¶255.) Because PTEN V15 and PTEN V12 are blunt ended on both ends, their stretches are also each 21 ribonucleotides long, which falls within the claimed range. (*Id*.) PTEN V15 and PTEN V12, therefore, satisfy this limitation of claim 1. (*Id*.)

h. <u>“wherein the first stretch and the second stretch each comprises contiguous alternating modified ribonucleotides”</u>

Claim 1 of the ’784 patent also recites “the first and the second stretch each comprise contiguous alternating modified ribonucleotides.” (Exh. 1001 at Claim 1.) As shown in reproduced Figure 5B, both strands of PTEN V15 and of PTEN V12, and thus also both stretches of each, comprise contiguous alternating 2’-O-

methyl ribonucleotides and unmodified ribonucleotides. (Exh. 1002 at ¶256.) PTEN V15 and PTEN V12, therefore, satisfy this limitation of claim 1. (*Id*.)

i. "wherein the alternating modified ribonucleotides alternate with unmodified or differently modified ribonucleotides."

Claim 1 of the '784 patent also recites "the alternating modified ribonucleotides alternate with unmodified or differently modified ribonucleotides." (Exh. 1001 at Claim 1.) As shown in reproduced Figure 5B, both strands, and thus both stretches, of PTEN V15 and of PTEN V12 comprise contiguous alternating 2'-O-methyl ribonucleotides and unmodified ribonucleotides. (Exh. 1002 at ¶257.) PTEN V15 and PTEN V12, therefore, satisfy this limitation of claim 1. (*Id*.)

* * * * * * * * * * * *

As explained above, PTEN V15 and PTEN V12 contain each limitation of claim 1 of the '784 patent and are species encompassed by that claim. Therefore, they anticipate claim 1. (*Id*. at ¶258.)

2. Claims 2-4 and 6

Claims 2-4 and 6 depend from claim 1. Claim 2 additionally recites "the double-stranded siRNA molecule is blunt ended on the end defined by the 5' end of the first strand and the 3' end of the second strand." (Exh. 1001 at Claim 2; Exh. 1002 at ¶259.) Claim 3 additionally recites "the double-stranded siRNA molecule is blunt ended on the end defined by the 3' end of the first strand and the 5' end of

the second strand." (Exh. 1001 at Claim 3; Exh. 1002 at ¶259.) Claim 4 additionally recites "the double-stranded siRNA molecule is blunt ended on both ends." (Exh. 1001 at Claim 4; Exh. 1002 at ¶259.) Claim 6 additionally recites "the first and second stretch are the same length." (Exh. 1001 at Claim 6; Exh. 1002 at ¶259.)

As discussed in Section IX.C.1, PTEN V15 contains all of the features of claim 1 and is blunt ended on both ends. (Exh. 1002 at ¶260.) As an siRNA molecule that is blunt ended on both ends, each stretch is the same length. (*Id*.) Therefore, PTEN V15 is a species encompassed by claims 2-4 and 6 and anticipates those claims. (*Id*.)

3. Claims 5, 7 and 9

Claims 5, 7 and 9 depend from claim 1. Claim 5 additionally recites "the first and second strand consists of 17 to 30 ribonucleotides." (Exh. 1001 at Claim 5.) Claim 7 additionally recites "each of the first strand and the second strand is 17 to 23 nucleotides long." (*Id*. at Claim 7.) Claim 9 additionally recites "each of the first strand and the second strand is 21 nucleotides long." (*Id*. at Claim 9.) As discussed in Section IX.C.1, PTEN V15 contains all of the features of claim 1 and each strand of PTEN V15 is 21 ribonucleotides in length. (Exh. 1002 at ¶¶261-62.) Therefore, PTEN V15 is a species encompassed by claims 5, 7 and 9 and anticipates those claims. (*Id*.)

4. Claims 11 and 13

Claims 11 and 13 depend from claim 1. Claim 11 additionally recites "the modified ribonucleotides are selected from the group consisting of 2'-O-alkyl ribonucleotides, 2'-fluoro ribonucleotides and 2'-amino ribonucleotides." (Exh. 1001 at Claim 11.) Claim 13 additionally recites "the modified ribonucleotides are 2'-O-methyl ribonucleotides." (*Id*. at Claim 13.) As discussed in Section IX.C.1, PTEN V15 contains all of the features of claim 1 and comprises 2'-O-alkyl, specifically 2'-O-methyl, ribonucleotides. Therefore, PTEN V15 is a species encompassed by claims 11 and 13 and anticipates those claims. (Exh. 1002 at ¶¶263-64.)

5. Claims 12 and 14

Claims 12 and 14 depend from claims 11 and 13, respectively. Claim 12 specifies "the 2'-O-alkyl ribonucleotides are selected from the group consisting of 2'-O-methyl ribonucleotides and 2'-O-ethyl ribonucleotides." (Exh. 1001 at Claim 12.) Claim 14 recites "the 2'-O-methyl ribonucleotides alternate with the unmodified ribonucleotides." (*Id*. at Claim 14.) As discussed above, PTEN V15 contains all the features of claims 11 and 13. As shown in reproduced Figure 5B, PTEN V15 comprises 2'-O-methyl ribonucleotides and unmodified ribonucleotides. (Exh. 1002 at ¶¶265-66.) Therefore, PTEN V15 is a species encompassed by claims 12 and 14 and anticipates those claims. (*Id*.)

6. Claim 17

Claim 17 depends from claim 1. Claim 17 additionally recites "the alternating modified ribonucleotides of the first strand are shifted by at least one ribonucleotide relative to the unmodified or differently modified ribonucleotides of the second strand." (Exh. 1001 at Claim 17.) As discussed in Section IX.C.1, PTEN V12 contains all of the features of claim 1. As shown in reproduced Figure 5B, the alternating 2'-O-methyl modified ribonucleotides of the first strand of PTEN V12 are shifted by one ribonucleotide relative to the unmodified ribonucleotides of the second strand. (Exh. 1002 at ¶¶267-68.) Therefore, PTEN V12 is a species encompassed by claim 17 and anticipates that claim. (*Id*.)

7. Claim 18

Claim 18 depends from claim 1 and additionally recites "the first and the second stretch each comprises contiguous alternating single 2'-O-alkyl modified ribonucleotides, and wherein the single 2'-O-alkyl modified ribonucleotides alternate with the unmodified ribonucleotides." (Exh. 1001 at Claim 18.) As discussed in Section IX.C.1, PTEN V15 contains all of the features of claim 1. As shown in reproduced Figure 5B, both strands, and, therefore, also both stretches, of PTEN V15 comprise contiguous alternating single 2'-O-alkyl ribonucleotides, specifically 2'-O-methyl ribonucleotides, that alternate with unmodified

ribonucleotides. (Exh. 1002 at ¶¶269-70.) Therefore, PTEN V15 is a species encompassed by claim 18 and anticipates that claim. (*Id*.)

8. Claims 19 and 20

Claims 19 and 20 depend from claim 18. Claim 19 additionally recites "the single 2'-O-alkyl modified ribonucleotides of the first strand are shifted by one ribonucleotide relative to the single 2'-O-alkyl modified ribonucleotides of the second strand." (Exh. 1001 at Claim 19.) Claim 20 additionally recites "the single 2'-O-alkyl modified ribonucleotides are 2'-O-methyl ribonucleotides." (*Id*. at Claim 20.) As discussed above, PTEN V15 contains all the features of claim 18. As shown in reproduced Figure 5B, the single 2'-O-methyl modified ribonucleotides of the first strand of PTEN V15 are shifted by one ribonucleotide relative to the single 2'-O-methyl modified ribonucleotides of the second strand. (Exh. 1002 at ¶¶271-72.) Therefore, PTEN V15 is a species encompassed by claims 19 and 20 and anticipates those claims. (*Id*.)

D. Ground 4: Claims 1-8, 11-13, 15-16 and 21-24 Are Anticipated by Allerson

Allerson, et al., "Fully 2'-Modified Oligonucleotide Duplexes with Improved in Vitro Potency and Stability Compared to Unmodified Small Interfering RNA" ("Allerson") was published on January 20, 2005. (Exh. 1016 at 901; Exh. 1002 at ¶274.) Although this date is after the EPP for the '784 patent, as explained in Section VIII, none of the challenged claims are entitled to an effective

filing date earlier than May 8, 2017 – the actual filing date of the ’784 patent. Therefore, Allerson is prior art to the ’784 patent under 35 U.S.C. § 102(a)(1). (Exh. 1002 at ¶275.) As explained below, Allerson discloses a double-stranded siRNA molecule, duplex 8, that anticipates claims 1-8, 11-13, 15-16 and 21-24. (*Id*. at ¶¶276-318.)

1. Claim 1

a. “A double-stranded siRNA molecule against a target nucleic acid”

Claim 1 of the ’784 patent recites “a double-stranded siRNA molecule against a target nucleic acid.” (Exh. 1001 at Claim 1.) As explained in Section VII, a POSA would have understood this term to require that the claimed “siRNA molecule” exhibits RNAi activity.

Allerson discloses double-stranded siRNA molecules “consisting entirely of 2’-O-methyl and 2’-fluoro nucleotides, that display[] enhanced plasma stability and increased in vitro potency.” (Exh. 1016 at Abstract; Exh. 1002 at ¶¶276-79.) Allerson discloses duplex 8 (reproduced and illustrated below), which has the following structure:

N = 2'-OMe
N = 2'-F
P = 5'-phosphate

(Exh. 1016 at Figure 2A; Exh. 1002 at ¶¶282-83.)

Illustrated Duplex 8

Sense Strand 5′ P-aaguaaggaccagagacaa 3′

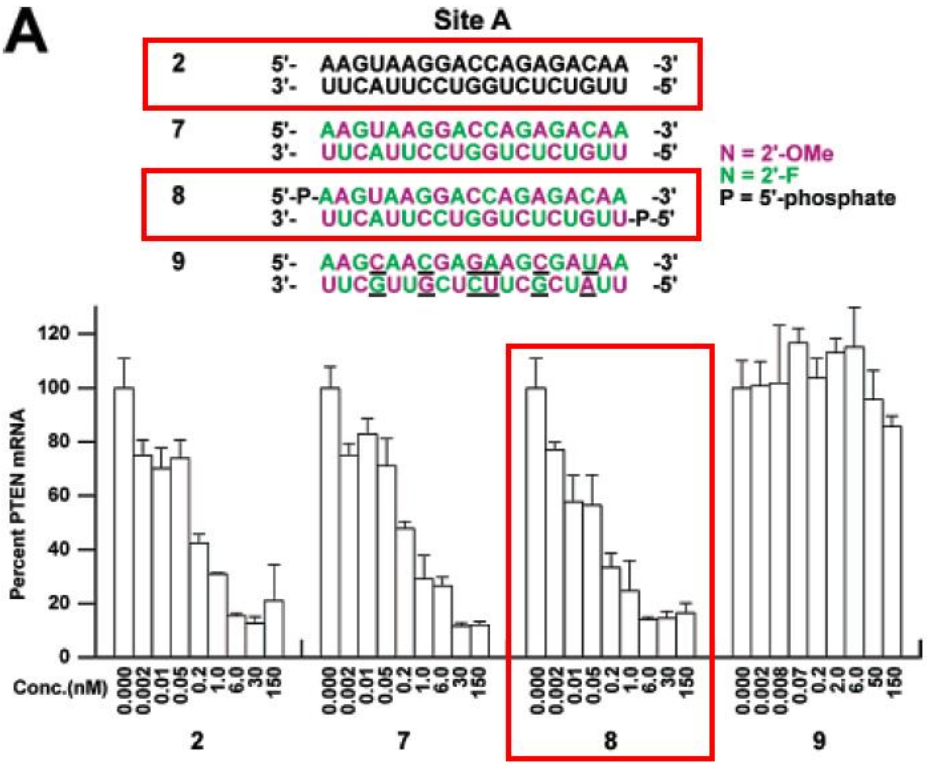
Antisense Strand 3′ uucauuccuggucucuguu-P 5′

Lower case = 2'-O-methyl ribonucleotide P = 5'-phosphate
Lower case = 2'-fluoro ribonucleotide

(Exh. 1006 at Figure 2A.)

Figure 2A of Allerson (reproduced and annotated below) provides RNAi activity data for duplex 8 demonstrating has RNAi activity. (Exh. 1002 at ¶¶286-89.) Duplex 8, therefore, satisfies this limitation of claim 1.[7] (*Id*. at ¶292.)

[7] Even if the patent claims are construed not to require RNAi activity, duplex 8 anticipates claims 1-8, 11-13, 15-16 and 21-24 of the '784 patent because it meets all of the claims' structural requirements. (Exh. 1002 at ¶¶290-318.)



(Exh. 1016 at Figure 2A.)

b. <u>"wherein the double-stranded siRNA molecule comprises a first strand and a second strand"</u>

Claim 1 of the '784 patent also recites "the double-stranded siRNA molecule comprises a first strand and a second strand." (Exh. 1001 at Claim 1.) As shown in reproduced Figure 2A, duplex 8 is double-stranded and, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶293.)

c. <u>"wherein the first strand comprises a first stretch that is complementary to the target nucleic acid"</u>

Claim 1 of the '784 patent also recites "the first strand comprises a first stretch that is complementary to the target nucleic acid." (Exh. 1001 at Claim 1.)

Duplex 8 was "designed to target one of two sites within the coding region of the human PTEN mRNA, both previously reported as valid target sites for siRNA." (Exh. 1016 at 901; Exh. 1002 at ¶¶277, 294.) Allerson also indicates that the "bottom strand [*i.e.*, the first strand] of each duplex [*e.g.*, duplex 8] is complementary to the target mRNA." (Exh. 1016 at 902; Exh. 1002 at ¶¶284, 294.) Duplex 8, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶294.)

d. <u>"wherein the second strand comprises a second stretch that is complementary to the first stretch"</u>

Claim 1 of the '784 patent also recites "the second strand comprises a second stretch that is complementary to the first stretch." (Exh. 1001 at Claim 1.) As shown in reproduced Figure 2A, the first and second strands of duplex 8 are complementary to each other with each cytosine corresponding to guanine and each uracil corresponding to adenine. (Exh. 1002 at ¶295.) Because the strands of duplex 8 are complementary, so are the stretches in each strand. Duplex 8, therefore, satisfies this limitation of claim 1. (*Id*.)

e. <u>"wherein the first strand and the second strand form a double-stranded structure comprising the first stretch and the second stretch"</u>

Claim 1 of the '784 patent also recites "the first strand and the second strand form a double-stranded structure comprising the first and the second stretch." (Exh. 1001 at Claim 1.) As shown in reproduced Figure 2A, duplex 8 comprises two

stretches that form the double-stranded structure. (Exh. 1002 at ¶296.) Duplex 8, therefore, satisfies this limitation of claim 1. (*Id*.)

f. <u>"wherein the double-stranded siRNA molecule is blunt ended on at least one end, and"</u>

Claim 1 of the '784 patent also recites "the double-stranded siRNA molecule is blunt ended on at least one end." (Exh. 1001 at Claim 1.) As shown in reproduced Figure 2A, duplex 8 is blunt ended on each end. (Exh. 1002 at ¶297.) Duplex 8, therefore, satisfies this limitation of claim 1. (*Id*.)

g. <u>"wherein each stretch consists of at least 15 and fewer than 30 ribonucleotides and"</u>

Claim 1 of the '784 patent also recites "each stretch consists of at least 15 and fewer than 30 ribonucleotides." (Exh. 1001 at Claim 1.) As shown in reproduced Figure 2A, duplex 8 has a double-stranded region of 19 ribonucleotides. (Exh. 1002 at ¶298.) Because duplex 8 is blunt ended on both ends, its stretches are also each 19 ribonucleotides long, which falls within the claimed range. (*Id*. at ¶¶284, 298.) Duplex 8, therefore, satisfies this limitation of claim 1. (*Id*. at ¶298.)

h. <u>"wherein the first stretch and the second stretch each comprises contiguous alternating modified ribonucleotides"</u>

Claim 1 of the ’784 patent also recites “the first and the second stretch each comprise contiguous alternating modified ribonucleotides.” (Exh. 1001 at Claim 1.) As shown in reproduced Figure 2A, both strands, and, therefore, also both stretches, of duplex 8 comprise contiguous alternating 2’-O-methyl and 2’-fluoro ribonucleotides. (Exh. 1002 at ¶299.) Duplex 8, therefore, satisfies this limitation of claim 1. (*Id*.)

i. <u>“wherein the alternating modified ribonucleotides alternate with unmodified or differently modified ribonucleotides.”</u>

Claim 1 of the ’784 patent also recites “the alternating modified ribonucleotides alternate with unmodified or differently modified ribonucleotides.” (Exh. 1001 at Claim 1.) As shown in reproduced Figure 2A, both strands, and, therefore, also both stretches, of duplex 8 comprise contiguous alternating 2’-O-methyl ribonucleotides and 2’-fluoro ribonucleotides. (Exh. 1002 at ¶300.) Duplex 18, therefore, satisfies this limitation of claim 1. (*Id*.)

* * * * * * * * * * * *

As explained above, duplex 8 contains each limitation of claim 1 of the ’784 patent and is a species encompassed by that claim. Therefore, duplex 8 anticipates claim 1. (*Id*. at ¶301.)

2. Claims 2-4 and 6

Claims 2-4 and 6 depend from claim 1. Claim 2 additionally recites "the double-stranded siRNA molecule is blunt ended on the end defined by the 5' end of the first strand and the 3' end of the second strand." (Exh. 1001 at Claim 2; Exh. 1002 at ¶302.) Claim 3 additionally recites "the double-stranded siRNA molecule is blunt ended on the end defined by the 3' end of the first strand and the 5' end of the second strand." (Exh. 1001 at Claim 3; Exh. 1002 at ¶302.) Claim 4 additionally recites "the double-stranded siRNA molecule is blunt ended on both ends." (Exh. 1001 at Claim 4; Exh. 1002 at ¶302.) Claim 6 additionally recites "the first and second stretch are of the same length." (Exh. 1001 at Claim 6; Exh. 1002 at ¶302.)

As discussed in Section IX.D.1, duplex 8 contains all of the features of claim 1 and is blunt ended on both ends. (Exh. 1002 at ¶303.) As an siRNA molecule that is blunt ended on both ends, each stretch is the same length. (Exh. 1016 at Figure 2A; Exh. 1002 at ¶303.) Therefore, duplex 8 is a species encompassed by claims 2-4 and 6 and anticipates those claims. (Exh. 1002 at ¶303.)

3. Claims 5, 7 and 8

Claims 5, 7 and 8 depend from claim 1. Claim 5 additionally recites "the first and second strand consists of 17 to 30 ribonucleotides." (Exh. 1001 at Claim 5.) Claim 7 additionally recites "each of the first strand and the second strand is 17

to 23 nucleotides long." (*Id*. at Claim 7.) Claim 8 additionally recites "each of the first strand and the second strand is 19 nucleotides long." (*Id*. at Claim 8.) As discussed in Section IX.D.1, duplex 8 contains all of the features of claim 1 and each strand is 19 ribonucleotides in length. (Exh. 1002 at ¶¶304-305.) Therefore, duplex 8 is a species encompassed by claims 5, 7 and 8 and anticipates those claims. (*Id*.)

4. Claims 11 and 13

Claims 11 and 13 depend from claim 1. Claim 11 additionally recites "the modified ribonucleotides are selected from the group consisting of 2'-O-alkyl ribonucleotides, 2'-fluoro ribonucleotides and 2'-amino ribonucleotides." (Exh. 1001 at Claim 11.) Claim 13 additionally recites "the modified ribonucleotides are 2'-O-methyl ribonucleotides." (*Id*. at Claim 13.) As discussed in Section IX.D.1, duplex 8 contains all of the features of claim 1 and comprises contiguous alternating 2'-O-alkyl ribonucleotides, and specifically 2'-O-methyl ribonucleotides. (Exh. 1002 at ¶¶306-307.) Therefore, duplex 8 is a species encompassed by claims 11 and 13 and anticipates those claims. (*Id*.)

5. Claims 12 and 15

Claims 12 and 15 depend from claims 11 and 13, respectively. Claim 12 specifies "the 2'-O-alkyl ribonucleotides are selected from the group consisting of 2'-O-methyl ribonucleotides and 2'-O-ethyl ribonucleotides." (Exh. 1001 at Claim

12.) Claim 15 additionally recites: "the 2'-O-methyl ribonucleotides alternate with the differently modified ribonucleotides." (*Id*. at Claim 15.) As discussed above, duplex 8 contains all the features of claims 11 and 13. As shown in reproduced Figure 2A, duplex 8 comprises contiguous alternating 2'-O-alkyl (specifically, 2'-O-methyl) ribonucleotides and 2'-fluoro ribonucleotides. (Exh. 1002 at ¶¶308-309.) Therefore, duplex 8 is a species encompassed by claims 12 and 15 and anticipates those claims. (*Id*.)

6. Claim 16

Claim 16 depends from claim 15 and additionally recites "the differently modified ribonucleotides are 2'-fluoro ribonucleotides." (Exh. 1001 at Claim 16.) As discussed above, duplex 8 contains all the features of claim 15 and comprises contiguous alternating 2'-O-methyl ribonucleotides and 2'-fluoro ribonucleotides. (Exh. 1002 at ¶¶310-11.) Therefore, duplex 8 is a species encompassed by claim 16 and anticipates that claim. (*Id*.)

7. Claim 21

Claim 21 depends from claim 1 and additionally recites "the first stretch and the second stretch each comprises contiguous alternating single 2'-O-alkyl modified ribonucleotides, and wherein the single 2'-O-alkyl modified ribonucleotides alternate with the differently modified ribonucleotides." (Exh. 1001 at Claim 21.) As discussed in Section IX.D.1, duplex 8 contains all of the

features of claim 1. As shown in reproduced Figure 2A, both stretches of duplex 8 comprise contiguous alternating single 2'-O-methyl ribonucleotides and 2'-fluoro ribonucleotides. (Exh. 1002 at ¶¶312-13.) Therefore, duplex 8 is a species encompassed by claim 21 and anticipates that claim. (*Id*.)

8. Claim 22

Claim 22 depends from claim 21 and additionally recites "the single 2'-O-methyl modified ribonucleotides of the first strand are shifted by one ribonucleotide relative to the single 2'-O-alkyl modified ribonucleotides of the second strand." (Exh. 1001 at Claim 22.) As discussed above, duplex 8 contains all of the features of claim 21. As shown in reproduced Figure 2A, the single 2'-O-methyl modified ribonucleotides of the first strand of duplex 8 are shifted by one ribonucleotide relative to the single 2'-O-methyl ribonucleotides of the second strand. (Exh. 1002 at ¶¶314-15.) Therefore, duplex 8 is a species encompassed by claim 22 and anticipates that claim. (*Id*.)

9. Claim 23

Claim 23 also depends from claim 21 and additionally recites "the single 2'-O-alkyl modified ribonucleotides are 2'-O-methyl ribonucleotides." (Exh. 1001 at Claim 23.) As discussed above, duplex 8 contains all of the features of claim 21. As shown in reproduced Figure 2A, its strands comprise single 2'-O-methyl

modified ribonucleotides. (Exh. 1002 at ¶¶314-15.) Therefore, duplex 8 is a species encompassed by claim 23 and anticipates that claim. (*Id*.)

10. Claim 24

Claim 24 depends from claim 23 and additionally recites "the differently modified ribonucleotides are 2'-fluoro ribonucleotides." (Exh. 1001 at Claim 24.) As discussed above, duplex 8 contains all the limitations of claim 23. As shown in reproduced Figure 2A, both stretches of duplex 8 comprise contiguous alternating single 2'-O-methyl ribonucleotides and 2'-fluoro ribonucleotides. (Exh. 1002 at ¶¶316-17.) Therefore, duplex 8 is a species encompassed by claim 24 and anticipates that claim. (*Id*.)

E. Ground 5: Claims 1-7, 10-14 and 18-20 Are Anticipated by Feinstein

U.S. Patent Publication No. 2011/0112168, entitled "Novel siRNA Structures," ("Feinstein") was filed on September 4, 2008 and published on May 12, 2011. (Exh. 1017 at Cover; Exh. 1002 at ¶319.) Although these dates are both after the EPP for the '784 patent, as explained in Section VIII, none of the challenged claims are entitled to an effective filing date earlier than May 8, 2017 – the actual filing date of the '784 patent. Therefore, Feinstein is prior art to the '784 patent at least as of May 12, 2011 under 35 U.S.C. § 102(a)(1) and at least as of September 4, 2008 under 35 U.S.C. § 102(a)(2). (Exh. 1002 at ¶320.) As explained

below, Feinstein discloses a double-stranded siRNA molecule, duplex 2+19+2 of Figure 3 that anticipates claims 1-7, 10-14 and 18-20. (*Id.* at ¶¶321-54.)

1. Claim 1

a. "A double-stranded siRNA molecule against a target nucleic acid"

Claim 1 of the '784 patent recites "a double-stranded siRNA molecule against a target nucleic acid." (Exh. 1001 at Claim 1.) As explained in Section VII, a POSA would have understood this term to require that the claimed "siRNA molecule" exhibits RNAi activity.

Feinstein "relates to siRNA compounds possessing novel sequences and structural motifs which down-regulate the expression of specific human genes." (Exh. 1017 at Abstract.) Further, Feinstein discloses double-stranded siRNA molecules with various 2'-O-methyl ribonucleotide modifications that alternate with unmodified ribonucleotides including duplex 2+19+2 (reproduced below, wherein the underlined comprise 2'-O-methyl modifications).

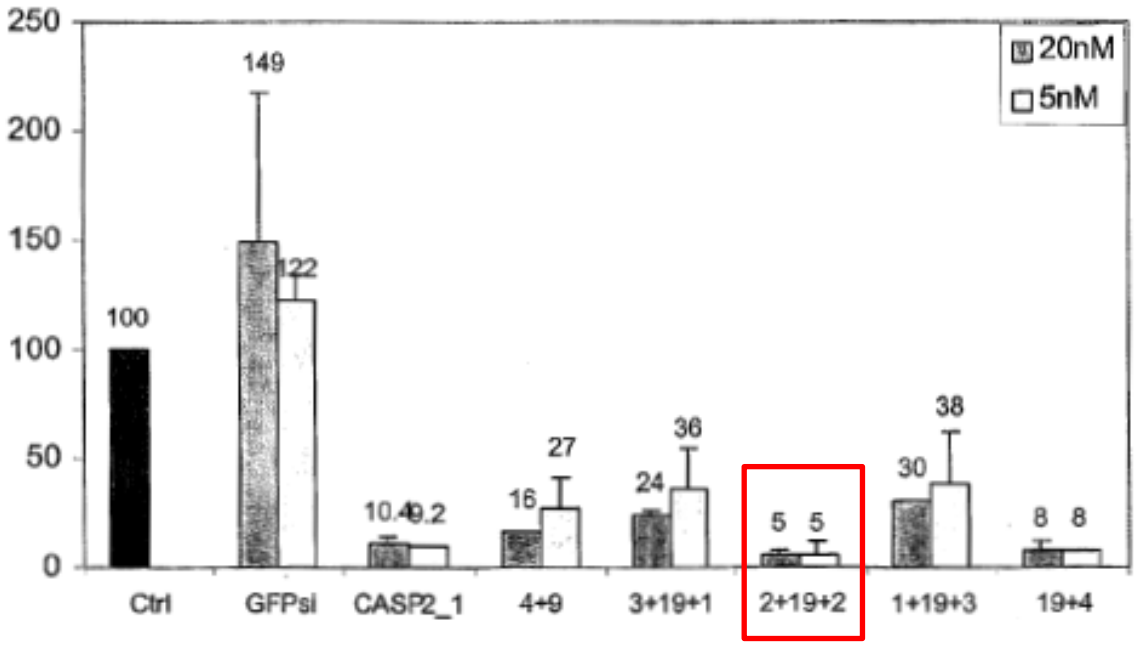
2+19+2	Sense	5'-UUGCACUCCUGAAUUUUAUCAAA-3'
	AS	5'-UUUGAUAAAAUUCAGGAGUGCAA-3'

(Exh. 1017 at Figure 3A; Exh. 1002 at ¶¶324-25.)

Figure 3B (reproduced and annotated below) demonstrates that duplex 2+19+2 inhibited CASP2 gene expression and thus exhibits RNAi activity. (Exh.

1017 at Figure 3B, [0459]-[0460]; Exh. 1002 at ¶¶328-29.) Duplex 2+19+2, therefore, satisfies this limitation of claim 1.[8] (Exh. 1002 at ¶332.)

Figure 3B



(Exh. 1017 at Figure 3B, [0459]-[0460]; Exh. 1002 at ¶328.)

b. <u>"wherein the double-stranded siRNA molecule comprises a first strand and a second strand"</u>

Claim 1 of the '784 patent also recites "the double-stranded siRNA molecule comprises a first strand and a second strand." (Exh. 1001 at Claim 1.) As shown

[8] Even if the patent claims are construed not to require RNAi activity, duplex 2+19+2 still anticipates claims 1-7, 10-14 and 18-20 because it meets all of the claims' structural requirements. (Exh. 1002 at ¶¶330-54.)

above, duplex 2+19+2 is double-stranded and, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶333.)

c. <u>"wherein the first strand comprises a first stretch that is complementary to the target nucleic acid"</u>

Claim 1 of the '784 patent also recites "the first strand comprises a first stretch that is complementary to the target nucleic acid." (Exh. 1001 at Claim 1.) Duplex 2+19+2 is "directed against CASP2." (Exh. 1017 at [0459]; Exh. 1002 at ¶334.) Duplex 2+19+2 is complementary to CASP2 mRNA. (Exh. 1002 at ¶334; Exh. 1067 at 7.) Duplex 2+19+2, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶334.)

d. <u>"wherein the second strand comprises a second stretch that is complementary to the first stretch"</u>

Claim 1 of the '784 patent also recites "the second strand comprises a second stretch that is complementary to the first stretch." (Exh. 1001 at Claim 1.) As shown in reproduced Figure 3A and illustrated below, the first and second strands of duplex 2+19+2 are complementary to each with each cytosine corresponding to guanine and each uracil corresponding to adenine:

2+19+2	Sense	5′-U**U**G**C**A**C**U**C**C**U**G**A**A**U**U**U**U**A**U**C**A**A**A-3′
	AS	3′-**A**A**C**G**U**G**A**G**G**A**C**U**U**A**A**A**A**U**A**G**U**U**U**-5′

(Exh. 1002 at ¶¶324-25, 335.) Because the strands of duplex 2+19+2 are complementary, so are the stretches. Duplex 2+19+2, therefore, satisfies this limitation of claim 1. (*Id*. at ¶335.)

e. <u>"wherein the first strand and the second strand form a double-stranded structure comprising the first stretch and the second stretch"</u>

Claim 1 of the '784 patent also recites "the first strand and the second strand form a double-stranded structure comprising the first and the second stretch." (Exh. 1001 at Claim 1.) As shown in reproduced Figure 3A, duplex 2+19+2 comprises two stretches that form the double-stranded structure. (Exh. 1002 at ¶336.) Duplex 2+19+2, therefore, satisfies this limitation of claim 1. (*Id*.)

f. <u>"wherein the double-stranded siRNA molecule is blunt ended on at least one end, and"</u>

Claim 1 of the '784 patent also recites "the double-stranded siRNA molecule is blunt ended on at least one end." (Exh. 1001 at Claim 1.) As shown in reproduced Figure 3A, duplex 2+19+2 is blunt ended on each (and therefore, also, at least one) end. (Exh. 1002 at ¶337.) Duplex 2+19+2, therefore, satisfies this limitation of claim 1. (*Id*.)

g. <u>"wherein each stretch consists of at least 15 and fewer than 30 ribonucleotides and"</u>

Claim 1 of the ’784 patent also recites “each stretch consists of at least 15 and fewer than 30 ribonucleotides.” (Exh. 1001 at Claim 1.) As shown in reproduced Figure 3A, duplex 2+19+2 has a double-stranded region of 23 ribonucleotides. (Exh. 1002 at ¶338.) Because duplex 2+19+2 is blunt ended on both ends, its stretches are also each 23 ribonucleotides long, which falls within the claimed range. (*Id*.) Duplex 2+19+2, therefore, satisfies this limitation of claim 1. (*Id*.)

h. <u>“wherein the first stretch and the second stretch each comprises contiguous alternating modified ribonucleotides”</u>

Claim 1 of the ’784 patent also recites “the first and the second stretch each comprise contiguous alternating modified ribonucleotides.” (Exh. 1001 at Claim 1.) As shown in reproduced Figure 3A, both strands (therefore, also both stretches) of duplex 2+19+2 comprise contiguous alternating 2’-O-methyl ribonucleotides and unmodified ribonucleotides. (Exh. 1002 at ¶339.) Duplex 2+19+2, therefore, satisfies this limitation of claim 1. (*Id*.)

i. <u>“wherein the alternating modified ribonucleotides alternate with unmodified or differently modified ribonucleotides.”</u>

Claim 1 of the ’784 patent also recites “the alternating modified ribonucleotides alternate with unmodified or differently modified ribonucleotides.” (Exh. 1001 at Claim 1.) As shown in reproduced Figure 3A, both strands

(therefore, also both stretches) of duplex 2+19+2 comprise contiguous alternating 2'-O-methyl ribonucleotides and single unmodified ribonucleotides. (Exh. 1002 at ¶340.) Duplex 2+19+2, therefore, satisfies this limitation of claim 1 as well. (*Id*.)

* * * * * * * * * * * *

As explained above, duplex 2+19+2 contains each limitation of claim 1 of the '784 patent and is a species encompassed by that claim. Therefore, duplex 2+19+2 anticipates claim 1. (*Id*. at ¶341.)

2. Claims 2-4 and 6

Claims 2-4 and 6 depend from claim 1. Claim 2 additionally recites "the double-stranded siRNA molecule is blunt ended on the end defined by the 5' end of the first strand and the 3' end of the second strand." (Exh. 1001 at Claim 2.) Claim 3 additionally recites "the double-stranded siRNA molecule is blunt ended on the end defined by the 3' end of the first strand and the 5' end of the second strand." (*Id*. at Claim 3.) Claim 4 additionally recites "the double-stranded siRNA molecule is blunt ended on both ends." (*Id*. at Claim 4.) Claim 6 additionally recites "the first and second stretch are of the same length." (*Id*. at Claim 6.)

As discussed in Section IX.E.1, duplex 2+19+2 contains all of the features of claim 1 and is blunt ended on both ends. (Exh. 1002 at ¶¶342-43.) As an siRNA molecule that is blunt ended on both ends, each stretch is the same length. (*Id*.)

Therefore, duplex 2+19+2 is a species encompassed by claims 2-4 and 6 and anticipates those claims. (*Id*.)

3. Claims 5, 7 and 10

Claims 5, 7 and 10 depend from claim 1. Claim 5 additionally recites "the first and second strand consists of 17 to 30 ribonucleotides." (Exh. 1001 at Claim 5.) Claim 7 additionally recites "each of the first strand and the second strand is 17 to 23 nucleotides long." (*Id*. at Claim 7.) Claim 10 additionally recites "each of the first strand and the second strand is 23 nucleotides long." (*Id*. at Claim 10.) As discussed in Section IX.E.1, duplex 2+19+2 contains all of the features of claim 1 and each strand of duplex 2+19+2 is 23 ribonucleotides in length. (Exh. 1002 at ¶¶344-45.) Therefore, duplex 2+19+2 is a species encompassed by claims 5, 7 and 10 and anticipates those claims. (*Id*.)

4. Claims 11 and 13

Claims 11 and 13 depend from claim 1. Claim 11 additionally recites "the modified ribonucleotides are selected from the group consisting of 2'-O-alkyl ribonucleotides, 2'-fluoro ribonucleotides and 2'-amino ribonucleotides." (Exh. 1001 at Claim 11.) Claim 13 additionally recites "the modified ribonucleotides are 2'-O-methyl ribonucleotides." (*Id*. at Claim 13.) As discussed in Section IX.E.1, duplex 2+19+2 contains all of the features of claim 1 and comprises 2'-O-alkyl, specifically 2'-O-methyl, ribonucleotides. (Exh. 1002 at ¶¶346-47.) Therefore,

duplex 2+19+2 is a species encompassed by claims 11 and 13 and anticipates those claims. (*Id*.)

5. Claims 12 and 14

Claims 12 and 14 depend from claims 11 and 13, respectively. Claim 12 specifies "the 2'-O-alkyl ribonucleotides are selected from the group consisting of 2'-O-methyl ribonucleotides and 2'-O-ethyl ribonucleotides." (Exh. 1001 at Claim 12.) Claim 14 recites "the 2'-O-methyl ribonucleotides alternate with the unmodified ribonucleotides." (*Id*. at Claim 14.) As discussed above, duplex 2+19+2 contains all the features of claims 11 and 13. As shown in reproduced Figure 3A, duplex 2+19+2 comprises 2'-O-methyl ribonucleotides that alternate with unmodified ribonucleotides. (Exh. 1002 at ¶¶348-49.) Therefore, duplex 2+19+2 is a species encompassed by claims 12 and 14 and anticipates those claims. (*Id*.)

6. Claim 18

Claim 18 depends from claim 1 and additionally recites "the first and the second stretch each comprises contiguous alternating single 2'-O-alkyl modified ribonucleotides, and wherein the single 2'-O-alkyl modified ribonucleotides alternate with the unmodified ribonucleotides." (Exh. 1001 at Claim 18.) As discussed in Section IX.E.1, duplex 2+19+2 contains all of the features of claim 1. As shown in reproduced Figure 3A, both strands (and, therefore, also both

stretches) of duplex 2+19+2 comprise contiguous alternating single 2'-O-alkyl ribonucleotides, and specifically, 2'-O-methyl) ribonucleotides, that alternate with unmodified ribonucleotides. (Exh. 1002 at ¶¶350-51.) Therefore, duplex 2+19+2 is a species encompassed by claim 18 and anticipates that claim. (*Id*.)

7. Claims 19-20

Claims 19 and 20 depend from claim 18. Claim 19 additionally recites "the single 2'-O-alkyl modified ribonucleotides of the first strand are shifted by one ribonucleotide relative to the single 2'-O-alkyl modified ribonucleotides of the second strand." (Exh. 1001 at Claim 19.) Claim 20 additionally recites "the single 2'-O-alkyl modified ribonucleotides are 2'-O-methyl ribonucleotides." (*Id*. at Claim 20.) As discussed above, duplex 2+19+2 contains all the features of claim 18. As shown in reproduced Figure 3A, the single 2'-O-alkyl (specifically, 2'-O-methyl) modified ribonucleotides of the first strand of duplex 2+19+2 are shifted by one ribonucleotide relative to the single 2'-O-alkyl (specifically, 2'-O-methyl) modified ribonucleotides of the second strand. (Exh. 1002 at ¶¶352-53.) Therefore, duplex 2+19+2 is a species encompassed by claims 19 and 20 and anticipates those claims. (*Id*.)

X. CONCLUSION

Petitioner requests that PGR be instituted for claims 1-24 of the '784 patent and that those claims be cancelled as unpatentable.

Dated: June 11, 2018

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION OF 37 C.F.R. § 42.24

Pursuant to Rule 37 C.F.R. § 42.24(d), the undersigned certifies that, based on the word count of the word-processing system used to prepare this paper, the number of words in this Petition is 17,769. This word count does not include the items that may be excluded from the count under 37 C.F.R. § 42.24(a), including the table of contents, table of authorities, mandatory notices, list of exhibits, certificate of service and certificate of word count.

Dated: June 11, 2018

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e)(4), I certify that a copy of the foregoing PETITION FOR POST GRANT REVIEW OF U.S. PATENT NO. 9,758,784 and EXHIBITS 1001-1068 were served on June 11, 2018 as follows:

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