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212-218-2100

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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ALNYLAM PHARMACEUTICALS, INC.,  
Petitioner,

v.

SILENCE THERAPEUTICS GMBH,  
Patent Owner.

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Case No. Not Yet Assigned  
U.S. Patent No. 9,790,501

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**PETITION FOR POST GRANT REVIEW OF  
U.S. PATENT NO. 9,790,501**

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## **I. INTRODUCTION**

To date, Alnylam Pharmaceuticals, Inc. (“Petitioner”) has challenged the patentability of several patents assigned to Silence Therapeutics GmbH (“Patent Owner”). Each challenged patent purports to cover an enormous genus of structurally diverse small interfering RNA (“siRNA”) molecules that far exceeds any invention actually described in or enabled by the patent specification.

U.S. Patent No. 9,790,501 (“the ’501 patent”) is no exception. Its patent claims are so broad, in fact, that they cover modifications and genetic targets that have yet to be discovered. By claiming broadly yet again, 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, 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 Petitioner. 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 '501 patent claims are unpatentable under 35 U.S.C. §§ 112 and 102. While the patent claims encompass an enormous genus of chemically-modified siRNA molecules, including molecules with any type of chemical modification, diverse modification patterns, multiple end structures and varying double-stranded lengths, the patent and its underlying applications describe only a tiny fraction of structurally similar molecules within the claimed genus. 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 is directed against any nucleic acid target in the entire genome, Patent Owner has only shown that this narrow sliver of siRNA molecules has RNA interference activity ("RNAi") against up to three nucleic acids. Patent Owner also concedes that siRNA molecules encompassed by the 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, a person of ordinary skill in the art ("POSA") would understand that the inventors were not in

possession of the claimed genus of modified siRNA molecules and would be unable to make and use the full scope of the claims without undue experimentation.

Because the '501 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 '501 patent claims, thereby anticipating the genus.

For the foregoing reasons, and as explained in detail below, Petitioner requests post grant review ("PGR") and cancellation of claims 1-30 of the '501 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”). On June 11, 2018 Petitioner filed PGR2018-00067 seeking review of related U.S. Patent No. 9,758,784 (“’784 patent”). On July 9, 2018, Petitioner filed PGR2018-00075 seeking review of related U.S. Patent No. 9,783,802 (“’802 patent”). Concurrently with this Petition, Petitioner is filing a petition for PGR of related U.S. Patent No. 9,790,505 (“’505 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 or No. 06-1205.

**F. Time for Filing Petition**

The '501 patent issued on October 17, 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 '501 patent is available for PGR, and that Petitioner is not barred or estopped from requesting PGR of the '501 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 '501 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 1-30 of the '501 patent and cancellation of claims 1-30 as unpatentable under 35 U.S.C. §§ 102 and/or 112. It is more likely than not that claims 1-30 are unpatentable in view of the following unpatentability grounds and prior art references:

Ground	Claims	Statutory Basis	Prior Art References
1	1-30	35 U.S.C. § 112(a) Lack of Written Description	
2	1-30	35 U.S.C. § 112(a) Lack of Enablement	
3	1, 2, 9, 10, 12, 13, 16-20, 22, 24, 25	35 U.S.C. § 102	Allerson
4	1, 3-5, 7, 9-11, 14, 15, 20, 21, 23	35 U.S.C. § 102	Choung
5	1, 16, 19, 26, 27, 29	35 U.S.C. § 102	Podbevsek

### **III. THE '501 PATENT**

The '501 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<sup>1</sup> at ¶¶57-58.) The '501 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 '501 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 '501 patent also asserts that “[a]ll of the ribonucleic acids of the present invention are suitable to

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<sup>1</sup> Exh. 1002 is the expert declaration of Dr. Jonathan K. Watts of the RNA Therapeutics Institute at the University of Massachusetts Medical School.

cause or be[] involved in methods of RNA mediated interference.” (Exh. 1001 at 12:41-45, Exh. 1002 at ¶62.)

The ’501 patent claims recite an extremely broad genus of chemically-modified siRNA molecules. (Exh. 1001 at Claims 1-30.) 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 the same  
length as the first stretch and is complementary to the first stretch,  
wherein the first strand and the second strand form a double-stranded  
structure comprising the first stretch and the second stretch,  
wherein the first stretch and the second stretch each comprises  
contiguous alternating 2’-O-alkyl ribonucleotides,  
wherein the 2’-O-alkyl ribonucleotides alternate with unmodified or  
differently modified ribonucleotides,

wherein the 2'-O-alkyl ribonucleotides of the first strand are shifted by one ribonucleotide relative to the 2'-O-alkyl ribonucleotides of the second strand, and

wherein each of the first stretch and the second stretch consists of at least 17 and fewer than 30 ribonucleotides.

(*Id.* at Claim 1.)

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

<b>Modification Patterns Encompassed by '501 Patent Claim 1</b>		
... (M <sub>m</sub> ) (U) (M <sub>m</sub> ) (U) . . .	... (M <sub>m</sub> ) (D <sub>n</sub> ) (M <sub>m</sub> ) (D <sub>n</sub> ) . . .	.. (M <sub>m</sub> ) (U/D <sub>n</sub> ) (M <sub>m</sub> ) (U/D <sub>n</sub> ) ..

(M<sub>m</sub>) – 2'-O-alkyl modified where m is any 2'-O-alkyl modification; (U) – unmodified; (D<sub>n</sub>) – differently modified where n is any type of modification which can be the same or different for each differently modified ribonucleotides (Exh. 1002 at ¶¶178-80.)

Within these recited modification patterns, claim 1 encompasses an enormous number of siRNA molecules that may vary with respect to the particular



alkyl group of the 2'-O-alkyl ribonucleotides and include any additional modifications to the:

- ribonucleotide sugar;
- ribonucleotide base;
- backbone; and
- ends of the molecules.

(*Id.* at ¶¶178-99.)

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 the 2'-O-alkyl, unmodified and/or differently modified ribonucleotides;
- ribonucleotide position within the stretch, strand, or molecule that contains a base modification;
- ribonucleotide position within the stretch, strand, or molecule that contains a backbone modification;
- location and composition of any end modification;
- number of 2'-O-alkyl, unmodified and/or differently 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 17-30 ribonucleotides; and
- length of the strands.

(*Id.*)

Additionally, the claimed siRNA molecules are not limited to targeting a particular gene or gene sequence. The '501 patent claims thereby encompass siRNA molecules that target every nucleic acid in the entire genome – an enormous number of possibilities. (*Id.* at ¶¶174-77.) For example, as of 2003, approximately 17,700 human genes had been identified resulting in almost 47.5 million siRNA sequence options. (*Id.* at ¶177.) 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.* at ¶177.)

The dependent claims recite additional limitations related to end structures (Exh. 1001 at Claims 2-8, 25-30); strand length (*id.* at Claim 9); the particular alkyl group of the 2'-O-alkyl ribonucleotides (*id.* at Claims 10, 11, 13, 15, 17, 19, 21, 22, 25-30); whether the 2'-O-alkyl ribonucleotides alternate with either unmodified

(*id.* at Claims 11, 14, 15, 21, 23) or differently modified ribonucleotides (*id.* at Claims 13, 16-19, 22, 24, 25-30); the particular modification to the differently modified ribonucleotides (*id.* at Claims 12, 13, 18, 19, 22, 25-30); the number of 2'-O-alkyl ribonucleotides that alternate unmodified or differently modified ribonucleotides (*id.* at Claims 14-19, 23-30); and the modification of the 5' ribonucleotide of the first stretch (*id.* at Claims 20-24). Despite these limitations, the dependent claims still encompass an extremely broad genus of diverse siRNA molecules. (Exh. 1002 at ¶¶84-118, 173-204.)

As discussed throughout this Petition, the '501 patent (including its original claims) and its underlying applications fail to describe or enable the full scope of the genus of siRNA molecules claimed. (*Id.* at ¶¶128-273.) For example, while at least claims 1-10, 12-13, 16-20, 22, and 24-30 encompass, or require, siRNA molecules that contain modified ribonucleotides that alternate with *differently modified ribonucleotides* and 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 ¶¶130-71, 191-93, 205-14.) Further, while at least claims 1-9, 12, 14, 16, 18, 20, 23, and 24 do not limit the type of 2'-O-alkyl modifications, neither the patent nor its underlying applications disclose even a single siRNA molecule comprising any 2'-O-alkyl

modification *other than a 2'-O-methyl modification*. (*Id.* at ¶¶130-71, 190, 205-14.) Additionally, while claims 1 and 3-30 encompass, or require, overhangs, the '501 patent and its underlying applications do not disclose even a single siRNA molecule that *meets the other structural requirements of the claims and has an overhang*. (*Id.* at ¶¶130-71, 194, 200, 221-27.) The patent and its underlying applications also fail to provide any siRNA molecules with a double-stranded length *greater than 21 ribonucleotides*, despite such molecules being encompassed, or required, by claims 1-30. (*See, e.g.*, Exh. 1001 at Examples; Exh. 1002 at ¶¶130-71, 200, 220, 249-50.) And, nothing in the '501 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. (Exh. 1002 at ¶¶130-71, 206-08, 236-37.) Indeed, while claims 1-30 encompass siRNA molecules wherein the double-stranded region comprises as few as 17 ribonucleotides, the '501 patent and its underlying applications concede that such

molecules are not functional.<sup>2</sup> (*See, e.g.*, Exh. 1001 at 12:22-26, 24:49-54, 25:44-48; Exh. 1002 at ¶¶68, 74-75, 215-20, 247.)

#### **IV. THE PRIORITY APPLICATIONS**

The '501 patent issued on October 17, 2017 from U.S. Application No. 15/589,968 (“’968 application,” Exh. 1004 at 43-121), which was filed on May 8, 2017. (Exh. 1001 at Cover.) The ’968 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:

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<sup>2</sup> The claim term “at least 17 and fewer than 30 ribonucleotides” does not require construction and would include siRNA molecules having a double-stranded length of 17 nucleotides. (Exh. 1002 at ¶215.)

<b>Application</b>	<b>Filing Date</b>	<b>Exhibit</b>
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 ¶¶128-71.)

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 ¶¶132-33.)

EP1 and the ’541 provisional include generic language and claims describing the structural characteristics encompassed, or required, by the broadly claimed genus. (*See, e.g.*, Exhs. 1006-1007 at 4-7; *see also* Exh. 1002 at ¶¶134-37.) For instance, EP1 and the ’541 provisional provide a generic embodiment which may encompass siRNA molecules with contiguous alternating 2’-O-alkyl modified ribonucleotides and differently modified ribonucleotides and siRNA molecules with contiguous alternating 2’-O-alkyl modified ribonucleotides and a mixed motif of unmodified and differently modified ribonucleotides. (Exhs. 1006-1007 at 4-5.) But, there is no description of *any* of these molecules in the figures or examples.

(Exh. 1002 at ¶¶134-43.) As discussed throughout this petition, the mere fact that the words appear is not enough to support the full scope of the genus claimed. *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.***”) (emphasis added). Instead, “[o]ne needs to show that one has truly invented the genus, *i.e.*, that one has conceived and described sufficient representative species encompassing the breadth of the genus.” *Abbvie Deutschland GmbH & Co. v. Janssen Biotech, Inc.*, 759 F.3d 1285, 1300 (Fed. Cir. 2014); *see also Ariad Pharm.*, 598 F.3d at 1349-50.

In contrast to Patent Owner’s legal burden, EP1 and ’541 provisional fail to describe molecules representative of the full scope of the claimed genus. Instead, they disclose only structurally similar molecules having a modification pattern where ***modified nucleotides with the same modification (i.e., 2’-O-methyl only) alternate only with unmodified nucleotides*** across the full strand. (Exhs. 1006-1007; Exh. 1002 at ¶138.) Furthermore, EP1 and the ’541 provisional fail to disclose any siRNA molecule comprising any 2’-O-alkyl modification ***other than 2’-O-methyl.*** (Exh. 1002 at ¶138.) And EP1 and the ’541 provisional fail to disclose any siRNA molecule having a recited pattern of modification that also has

an *overhang* or has a double-stranded length *other than 21 ribonucleotides*. (Exh. 1002 at ¶¶139-40.)

Further, EP1 and the '541 provisional discourage the use of certain claimed characteristics. For instance, while claims 1-30 encompass molecules with a stretch length of 17 ribonucleotides, EP1 and the '541 provisional teach such molecules “are not functional in mediating RNAi.” (Exhs. 1006-1007 at 10, 31, 32; Exh. 1002 at ¶¶130, 215-20.) Similarly, while claims 1 and 3-30 encompass or require molecules with an overhang, EP1 and the '541 provisional teach “a blunt duplex is more stable than the duplex molecule with overhangs.” (Exhs. 1006-1007 at 33; Exh. 1002 at ¶¶221-27.)

And, 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 12:41-45; *see also* Exhs. 1006-1007; Exh. 1002 at ¶142.) 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.*, Exhs. 1006-1007 at Claims 48, 55), such claims do not establish that siRNA molecules meeting the structural requirements of the '501 patent claims would have the recited utility. And, as noted above, EP1 and the '541



provisional also concede that siRNA molecules with a double-stranded region of 17 ribonucleotides are ***not functional***. (Exhs. 1006-1007 at 10, 31, 32.)

Thus, EP1 and the '541 provisional fail to adequately support the full scope of the genus of siRNA molecules encompassed by the '501 patent claims. (Exh. 1002 at ¶¶130-43.)

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 ¶¶144-45.) 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 ¶¶145, 153.) One such new disclosure in EP2 describes 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 ¶148.)

Similar to EP1 and the '541 provisional, EP2 includes generic embodiments or claims describing the structural characteristics encompassed or required by the broadly claimed genus. (*See, e.g.*, Exhs. 1006-1007 at 4-7; *see also* Exh. 1002 at ¶¶146-47.) As discussed throughout this petition, such disclosures alone are not enough to adequately describe or enable the full scope of the claimed genus.

Indeed, just like in EP1 and the '541 provisional, the disclosures in EP2 are directed to a sliver of structurally similar siRNA molecules having a modification pattern of *alternating 2'-O-methyl and unmodified ribonucleotides*. (Exh. 1008; Exh. 1002 at ¶148.) EP2 also fails to disclose a single siRNA molecule comprising a 2'-O-alkyl modification *other than 2'-O-methyl*. (Exh. 1002 at ¶148.)

Additionally, EP2 fails to disclose a single siRNA molecule having a recited pattern of modification with an *overhang* or having a double-stranded length of *less than 19 or greater than 21 ribonucleotides*. (*Id.* at ¶149.) And like EP1 and the '541 provisional, EP2 teaches that molecules with stretch lengths of 17 ribonucleotides are “not functional in mediating RNAi” (Exh. 1008 at 11, 35, 36; Exh. 1002 at ¶218) and “a blunt duplex is more stable than the duplex molecule with overhangs” (Exh. 1008 at 37; Exh. 1002 at ¶¶150, 221-27).

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 having the claimed structural elements and across the full scope of the genus claimed would have the recited utility. (*See, e.g.*, Exh. 1008 at Claims 52, 59; Exh. 1002 at ¶151.) Furthermore, as noted above, EP2, like EP1 and the '541 provisional, concedes that siRNA molecules with a double-stranded region of 17

ribonucleotides are *not functional*. (Exh. 1008 at 11, 35, 36; Exh. 1002 at ¶¶215-27.)

Thus, EP2 also fails to adequately support the full scope of the genus of molecules encompassed by the '501 patent claims.

The continuation applications are substantially similar to EP2, and share a common specification with the '501 patent. (Exhs. 1005, 1008-1013; Exh. 1001; Exh. 1002 at ¶¶153-54.) The continuation applications add limited new disclosures, but none of the new disclosures relate to siRNA molecules comprising alternating 2'-O-alkyl modified ribonucleotides and *differently modified ribonucleotides*, or siRNA molecules comprising alternating 2'-O-alkyl modified nucleotides and a *mixed motif* of differently modified and unmodified ribonucleotides. (Exh. 1002 at ¶153.) Nor do any of the new disclosures relate to siRNA molecules comprising a 2'-O-alkyl modification *other than 2'-O-methyl*, a double-stranded length *greater than 21 ribonucleotides* or a recited pattern of modification and an *overhang*. (*Id.* at ¶153.) The continuation applications also teach “a blunt duplex is more stable than the duplex molecule with overhangs” (*see, e.g.*, Exh. 1009 at 37:33-34) and concede that siRNA molecules with a double-stranded region of 17 ribonucleotides or fewer are *not functional* (*see, e.g.*, Exh. 1009 at 16:25-28, 10:26-27; Exh. 1002 at ¶¶153-71, 215-20).

Certain original claims of the continuation applications include generic language that may encompass siRNA molecules that fall within the scope of the '501 patent claims. (*See, e.g.*, Exh. 1012 at Claim 16; Exh. 1002 at ¶¶153-71.) Further, the original claims of the '968 application, directly underlying the '501 patent, are identical to the issued claims. (Exh. 1004 at 88-91; Exh. 1002 at ¶¶272-73.) As discussed throughout the petition, the mere fact that words appear alone does not demonstrate that the inventors possessed or enabled those siRNA molecules.

Thus, the continuation applications also fail to adequately support the full scope of the genus of molecules encompassed by the '501 patent claims. (Exh. 1002 at ¶¶153-71, 272-73.)

## **V. THE PROSECUTION HISTORY**

The '968 application was examined under pre-AIA first to invent provisions. (*See, e.g.*, Exh. 1004 at 375.) However, the legitimacy of the Applicant's priority claims was never evaluated during prosecution and, as discussed in Section VIII, none of the '501 patent claims is entitled to an effective filing date earlier than May 8, 2017 – the actual filing date of the '968 application.

The '968 application contained 30 claims, including one independent claim and 29 dependent claims. The original claims are identical to the issued claims. According to the Examiner, the claims of the '968 application were “drawn to a

*nucleic acid molecule* comprising a first and second strand comprising a first and second stretch wherein the first and second strand form a double-stranded structure comprising a first stretch and a second stretch, wherein said nucleic acid is ***blunt ended on a least one end or both ends.***” (*Id.* at 376 (emphasis added).) Only claims 2 and 19 recite limitations related to blunt-ends, suggesting the Examiner may not have carefully evaluated the claims during prosecution. (Exh. 1001 at Claims 2, 19.)

The Examiner issued a single non-final rejection finding claims 1-11, 14, 15 and 20-23 anticipated under 35 U.S.C. § 102(e) by U.S. Patent Pub. No. 2003/0190635 (“McSwiggen,” Exh. 1014), claims 1-30 obvious under 35 U.S.C. § 103 over McSwiggen in combination with other prior art, and claims 1-30 unpatentable on the ground of nonstatutory obviousness-type double patenting (“OTDP”) as being unpatentable over seven issued patents or pending applications in the patent family. (Exh. 1004 at 373-86.) 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 376.) The Examiner also found that McSwiggen taught the pattern of modification of the first strand is shifted by one nucleotide relative to the pattern of modification on the second strand. (*Id.* at 376-77.)

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 403; *see also id.* at 409-16.) 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 403.) The 131 Declaration similarly emphasized the exemplary siRNA molecule's ability to "inhibit expression of PTEN," and its effectiveness "at reducing PTEN mRNA expression in cells." (*Id.* at 410 (¶8).) The Applicant also filed terminal disclaimers in response to the OTDP rejections. (*Id.* at 417-18, 447.)

The Examiner found the 131 Declaration "sufficient to overcome" McSwiggen and allowed the claims. (*Id.* at 433.)

## **VI. A PERSON OF ORDINARY SKILL IN THE ART**

The '501 patent is directed at small interfering RNA molecules which inhibit the expression of a target gene. (*See, e.g.*, Exh. 1001 at 1:40-49.) 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 '501 patent claims expressly or via dependency. (Exh. 1001 at Claims 1-30.) 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 of the claims.”). 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. (Exh. 1002 at ¶¶122-27.) Petitioner’s construction is supported by the claim language, the patent specification, and the prosecution history of the ’501 patent and related patents, and is consistent with the meaning of the term “siRNA” as it is used in the field of RNAi.<sup>3</sup> (*Id.*)

First, the claim language emphasizes that the claimed molecules must be “siRNA molecule[s] ***against a target nucleic acid.***” The specification relates target nucleic acids to the “mode of action of interfering ribonucleic acids” (Exh. 1001 at 12:5-8) and indicates that interfering ribonucleic acids act, for instance, by “inhibiting expression of a target gene” (*id.* at 1:46-49), 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 and thus

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<sup>3</sup> Petitioner’s proposed construction would be same even if based only on the ’501 patent claims and specification.



would be expected of the “siRNA molecule[s] against a target nucleic acid” claimed in the ’501 patent. (Exh. 1002 at ¶¶124-25.)

Furthermore, the ’501 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 12:41-45; *see also id.* at 2:29-31, 11:19-23 (emphasizing activity as an advantage of the siRNA molecules of the invention); 1:46-50, 1:53-56, 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, 19:67-20:8 (identifying “target validation” as one of the uses for the siRNA molecules of the invention); 6:31-42 (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 ¶¶59-64, 125.)

Likewise, all but one of the patent examples relate to the impact of various siRNA modifications on RNAi. (Exh. 1001 at Example 1 (investigating the impact of NH<sub>2</sub> 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 NH<sub>2</sub> 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 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), Examples 12 and 13 (investigating the impact of loop structures on activity); Exh. 1002 at ¶¶71-81, 126.)

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 403.) 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 29-38, 41-42.) In fact, in that

prosecution, Patent Owner submitted an expert declaration, which described the claimed “nucleic acid molecule” 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 a minimum, RNAi, 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 part of the claim.”).

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 ¶127.)

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 '501 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.*, 598 F.3d at 1351 (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. “Evidence showing that a claimed genus does not disclose a representative number of species may include evidence of species that fall within the claimed genus but are not disclosed by the patent, and evidence of such species is likely to postdate the priority date.” *Amgen Inc. v. Sanofi, Aventis LLC*, 872 F.3d 1367, 1374 (Fed. Cir. 2017).<sup>4</sup>

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<sup>4</sup> Any argument that post-priority date evidence is irrelevant to demonstrating a lack of possession of the claimed genus should be dismissed. Petitioner is using such evidence to show Patent Owner’s failure to disclose representative species. Moreover, Petitioner is challenging Patent Owner’s priority claims to multiple underlying applications dating from 2002 to 2015 and the lack of support in the patent specification itself as filed in 2017.

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 ’501 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). Post-priority date evidence may be used to “demonstrate[] that those of ordinary skill in the art would find that a particular invention was not enabled years after the filing date.” MPEP § 2164.05(a); *see also Amgen Inc.* 872 F.3d at 1375.<sup>5</sup>

Here, the ’968 application underlying the ’501 patent was filed on May 8, 2017, but, as detailed in Section IV, claims priority to a series of applications dating back to August 5, 2002. (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 nearly the entire family comprises continuation applications. Seven of the nine priority applications leading to the ’501 patent were filed before March 16, 2013. However, as discussed in detail below, the claims of the ’501 patent are not described or enabled by any of the priority applications (or even the ’501 patent specification itself as discussed in Sections IX.A and IX.B).

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<sup>5</sup> Again, any argument that post-priority date evidence is irrelevant to show a lack of enablement should be dismissed. Such evidence is relevant at least to showing the amount of experimentation required to practice the claimed invention, and to challenging Patent Owner’s priority claims and the enablement support in the patent specification itself.

Accordingly, the '501 patent is eligible for PGR and none of the challenged claims is entitled to an effective filing date earlier than May 8, 2017 – the actual filing date of the '501 patent.

**A. The Applications Fail to Describe Representative siRNA Molecules Across the Full Scope of the Vast Genus Encompassed by Claims 1-30**

As discussed in Section III, the '501 patent claims recite an enormous genus of diverse chemically-modified siRNA molecules, which may vary chemically, structurally and/or with respect to the particular gene or gene sequence being targeted. (Exh. 1002 at ¶¶117-18, 173-204.)

As detailed in Section III, the dependent claims introduce additional structural limitations that narrow the scope of the claimed genus. (Exh. 1001 at Claims 2-30; Exh. 1002 at ¶¶190-94.) Nevertheless, the dependent claims are still extremely broad. For example, claim 21, which specifies a genus of siRNA molecules that comprise contiguous alternating 2'-O-methyl modified ribonucleotides and unmodified ribonucleotides wherein the 5' ribonucleotide of the first stretch is a 2'-O-methyl modified ribonucleotide, encompasses molecules that may vary in terms of at least the:

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



- number of unmodified ribonucleotides in each stretch, strand, or molecule.

(Exh. 1002 at ¶¶178-79, 193.)

The full scope of the genus of siRNA molecules of claim 21 also includes siRNA molecules with:

- modifications to the ribonucleotide sugar of the 2'-O-methyl modified ribonucleotide in addition to 2'-O-methyl;
- modifications to the ribonucleotide base;
- modifications to the backbone;
- modifications to the ends; and
- stretch lengths between 17 and 30 ribonucleotides.

(*Id.* at ¶¶193, 195-202, 215.)

There is also no limit on the length of each strand or the siRNA target. (*Id.* at ¶¶174, 200.)

Patent Owner previously confirmed the enormous size of a similar genus of siRNA molecules to that of claim 21. During prosecution of the related '630 application (of which the '501 patent is a continuation), Patent Owner submitted a declaration by Dr. Jörg Kaufmann, an inventor on the '501 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 “ $7.0 \times 10^{13}$  [70 trillion] possible arrangements.” (Exh. 1018 at 130-31 (¶¶2-5); *id.* at 36.)

While Patent Owner may argue that the genus of the ’501 patent claims is somehow narrower than the genus assessed in the ’630 prosecution, Dr. Kaufmann’s assessment does not consider many of the variables contemplated by the ’501 patent claims. In fact, Patent Owner admitted that if other variables were included “the number of possible arrangements becomes *unimaginably high*.” (*Id.* at 36 (emphasis added); *see also* Exh. 1002 at ¶203.) Patent Owner was specifically talking about different 2’-modifications (such as, other alkyl groups) but the same is true if other variables, such as possible chemical modifications to ribonucleotide bases, strand lengths, stretch lengths, end modifications, backbone modifications, target genes, etc., are included. (Exh. 1002 at ¶203.)

In stark contrast to the broad genus of the ’501 patent claims, 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 ¶¶130-71, 205-27.)<sup>6</sup>

The examples fail to disclose any siRNA molecules that comprise 2'-O-alkyl modified ribonucleotides that alternate with *differently modified* ribonucleotides or 2'-O-alkyl modified ribonucleotides that alternate with a *mixed motif* of differently modified and unmodified ribonucleotides as encompassed or required by at least claims 1-10, 12-13, 16-20, 22, and 24-30. (Exhs. 1005-1013 at Examples; Exh. 1002 at ¶¶128-71, 205-14.) The examples also fail to disclose any siRNA molecules where the 2'-O-alkyl ribonucleotides have a 2'-O-alkyl modification *other than 2'-O-methyl* as encompassed by at least claims 1-9, 12, 14, 16, 18, 20, 23, and 24. (Exhs. 1005-1013 at Examples; Exh. 1002 at ¶¶128-71, 204, 206-08, 237.) Additionally, the examples fail to disclose any siRNA molecules comprising a recited pattern of modification with a double-stranded length *greater than 21 nucleotides* as encompassed or required by claims 1-30. (Exh. 1005-1013 at Examples; Exh. 1002 at ¶¶128-71, 200, 249-50.) And, the examples fail to disclose

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<sup>6</sup> Certain examples describe siRNA molecules with different features (e.g., different double-stranded lengths, overhang). However, such molecules are not encompassed by the '501 patent claims because they are either completely unmodified or fully modified. (See, e.g., Exh. 1001 at Examples 2-5; Exh. 1002 at ¶207, n.25.)

any siRNA molecules comprising a recited pattern of modification with an ***overhang*** as encompassed or required by claims 1 and 3-30. (Exh. 1005-1013 at Examples; Exh. 1002 at ¶¶128-71, 200, 204, 221-27.)

This disclosure of a sliver of structurally similar siRNA molecules is not representative of the full genus claimed and does not provide adequate written description. (Exh. 1002 at ¶¶128-71, 205-27.); *see, e.g., Abbvie*, 759 F.3d at 1300 (“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”); *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 “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, 1125-27 (Fed. Cir. 2008) (affirming summary judgment of invalidity where claims to broad genus were unsupported by disclosure of single species); *see also 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).

Furthermore, to the extent the Board finds that the claimed siRNA molecules require RNAi – consistent with the express disclosure of the '501 patent (*see* Section VII.A) – Patent Owner's failure to provide adequate written description of the full scope of the claimed genus of siRNA molecules is even more compelling. As the Board has recognized, where there is a functionally-defined genus, in order to satisfy the written description requirement, “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, 2016) (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*, 759 F.3d at 1301-02 (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 siRNA activity data in any of its applications – provide data only for a narrow sliver of siRNA molecules that fall within the claimed genus. These siRNA molecules are all structurally similar, having 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 ¶¶153-71, 205-27; see also *id.* at ¶¶234, 245.) The RNAi data provided for these molecules is, likewise, limited to only up to three target genes (i.e., PTEN, Akt and p110β). (See, e.g., Exh. 1009 at Examples; Exh. 1002 at ¶¶175, 206-07, 244.) Additionally, the '501 patent claims encompass siRNA molecules comprising a double-stranded region of 17 ribonucleotides or fewer, which the underlying applications (and the '501 patent itself) expressly teach “are not functional in mediating RNAi.” (Exhs. 1006-1007 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, 24:49-54, 25:44-48; Exh. 1002 at ¶¶215-18.)

As explained above, this narrow disclosure of structurally similar molecules is not representative of the full scope of the genus claimed. For instance, there is *no disclosure of any active siRNA molecules comprising:*

- a modification pattern of 2'-O-alkyl modified ribonucleotides alternating with *differently modified* ribonucleotides;
- a modification pattern of 2'-O-alkyl modified ribonucleotides alternating with a *mixed motif* of unmodified and differently modified ribonucleotides;
- any modification other than a *2'-O-methyl modification*;
- a recited pattern of modification and having an *overhang*; or
- a double-stranded length equal to *17 nucleotides or greater than 21 ribonucleotides*.

(See, e.g., Exhs. 1005-1013 at Examples; see also Exh. 1002 at ¶¶130, 138-39, 148-49, 153-54, 205-37.)

Patent Owner's failure to provide a representative number of species is compounded by the unpredictability of the effect of different modifications on RNAi. *US Endodontics, LLC*, Case PGR2015-00019, Paper 54 at 35; (Exh. 1002 at ¶¶228-35.) Indeed, the field of RNAi was in its infancy in August 2002 – the time period to which Patent Owner claims priority. (Exh. 1002 at ¶¶213, 228-35, 251-71.) 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 the various modifying groups differ in their chemical and



physical properties.” (Exh. 1018 at 59 (¶15) (emphasis added).) 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.” (Exh. 1018 at 55-56 (¶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).)

Although the underlying applications include generic embodiments or broad claims that arguably encompass siRNA molecules that fall within the claimed genus (as discussed in Section IV), the underlying applications, like the '501 patent itself, discourage the use of certain claimed limitations. For example, whereas the claimed genus and sub-genera of claims 1 and 3-30 encompass or require overhangs, the underlying applications (and the '501 patent itself) distinguish overhang-containing siRNA molecules from what the inventors understood to be their invention, blunt-ended siRNA molecules, by teaching “a blunt duplex is more

stable than the duplex molecule with overhangs.” (See, e.g., Exh. 1008 at 37; Exh. 1001 at 26:34-36; Exh. 1018 at 62 (¶25); Exh. 1002 at ¶¶221-27.) Similarly, whereas the claimed genus encompasses molecules comprising a double-stranded region with a length of 17 nucleotides, as noted above, the underlying applications teach such siRNA molecules “are not functional in mediating RNAi.” (Exhs. 1006-1007 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, 24:49-54, 25:44-48; Exh. 1002 at ¶¶215-17.) This further evidences the inventors’ lack of possession of molecules across the full scope of the claimed genus. *Tronzo v. Biomet, Inc.*, 156 F.3d 1154, 1158-59 (Fed. Cir. 1998) (finding lack of possession where patent specification “specifically distinguishes [a prior art embodiment] as inferior”); see also *Bamberg v. Dalvey*, 815 F.3d 793, 797-98 (Fed. Cir. 2016) (finding lack of possession where patent specification described a claimed embodiment as inferior); *In re Curtis*, 354 F.3d 1347, 1352-53 (Fed. Cir. 2004) (affirming lack of possession of later-claimed broader genus based on statements made in the specification and during prosecution of the parent application as to the unexpected properties of a particular species).

Moreover, 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 1350. Here, the generic disclosures in the underlying

applications are too broad to meaningfully define the scope of any alleged invention. And, they encompass molecules comprising structural elements (*e.g.*, overhangs, double-stranded length of 17 ribonucleotides) the use of which the patent discourages. (Exh. 1002 at ¶¶128-71; *see also id.* at ¶¶68-70, 74, 172-227, 236-37.) The generic disclosures of the underlying applications are all the more meaningless based on the unpredictability of the effect of different modifications on RNAi. (*Id.* at ¶¶228-36, 251-71.)

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For at least these reasons, none of the applications leading to the '501 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 '501 patent is PGR eligible.

**B. The Applications Fail to Enable siRNA Molecules Across the Full Scope of the Vast Genus Encompassed by Claims 1-30**

In addition to failing to provide adequate written description for claims 1-30, the priority applications fail to enable the full scope of the claims without undue experimentation. This is an additional and independent reason the '501 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 '501 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 '501 patent relate to chemically-modified siRNA molecules. (Exh. 1002 at ¶¶57-68.) As discussed in Section VII.A, the claim language, the patent specification and the prosecution history of the '501 patent and related patents establish that the utility of the claimed siRNA molecules is that they possess RNAi activity. (Exh. 1002 at ¶241.)

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 priority applications. (*Id.* at ¶¶228-35, 251-64.)

The underlying applications confirm the unpredictability of the field of RNAi. For instance, Examples 1 and 6 (which appear in all of the underlying applications and the '501 patent itself) show that inclusion or exclusion of 3'-amino end caps can drastically impact function. (*Id.* at ¶¶72, 78, 233, 256; *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 '501 patent itself) demonstrate that siRNA molecules with internal 2'-O-methyl modified and unmodified nucleotides 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 ¶¶79-83, 233, 244, 256; *see also* 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 ¶261.)

Even after the alleged priority date of the '501 patent, the inventors acknowledged a lack of understanding of the effect of chemical modifications:

It was *puzzling* that not all siRNA molecules with alternating 2'-O-methyl modifications on both strands were functional.

(Exh. 1028 at 2713 (emphasis added); *see also* Exh. 1002 at ¶254.)

Others also observed that while some 2'-O-methyl modified siRNA molecules retained activity, some did not. (Exh. 1072 at 921; *see also* Exh. 1002 at ¶¶229, 251-71.)

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 ¶¶228-35, 251-71); *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 ¶271; 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 ¶271, *see also id.* at 228-35, 251-70.) 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.* at ¶271.)

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).

Here, as discussed in Section VIII.A, the ’501 patent claims encompass an enormous genus of structurally diverse chemically-modified siRNA molecules directed to any genetic targets. (Exh. 1002 at ¶¶240-43.) The ’501 patent claims are broad enough to cover structural modifications and genetic targets that have yet to be discovered. (*Id.* at ¶242; *see also id.* at ¶¶174, 195.) Nevertheless, the underlying applications disclose only a sliver of structurally similar siRNA molecules encompassed by the claims have any utility whatsoever. In fact, of the approximately 120 siRNA molecules disclosed in the ’501 patent, less than about 50 have internal 2’-O-alkyl (specifically, 2’-O-methyl) modified ribonucleotides. (*Id.* at ¶¶207, 244-45.) And, of those 50, only 25 are non-duplicative and less than ten of those have been reported by Patent Owner as having RNAi. (*Id.* at ¶¶207,

244.) 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. (Exhs. 1006-1007 at 10, 31, 32; Exh. 1008 at 11, 12, 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, 24:49-54, 25:44-48; Exh. 1002 at ¶¶130-71, 215-20, 247.)

The broad scope of the claimed genus, and the failure to disclose any practical utility for the vast majority of the encompassed siRNA molecules, provides additional support for a finding of lack of enablement. (Exh. 1002 at ¶¶240-50.)

**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 at 496. 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) (citation omitted).



Here, as discussed in Section VIII.A, the applications underlying the '501 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 ¶¶236-37, 244-50.)

What is not disclosed, although claimed is:

- any siRNA molecule that comprises modified ribonucleotides that alternate with *differently modified ribonucleotides* or a *mixed motif* of differently modified and unmodified ribonucleotides as encompassed by at least claims 1-10, 12-13, 16-20, 22, 24-30;
- any siRNA molecule that comprises any 2'-O-alkyl modification to the 2'-O-alkyl ribonucleotides other than *2'-O-methyl* as encompassed by at least claims 1-9, 12, 14, 16, 18, 20, 23, and 24;
- any siRNA molecule with a double-stranded length *greater than 21 ribonucleotides* as encompassed by claims 1-30;
- any active siRNA molecule with a double-stranded length of *17 nucleotides* as encompassed by claims 1-30;
- any siRNA molecule with a required pattern of modification that also has an *overhang* as encompassed by claims 1, and 3-30;

(Exhs. 1005-1013 at Examples; Exh. 1002 at ¶¶238-50.)

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), a single end structure (*i.e.*, blunt-ended on both ends) and target only three genes (*i.e.*, Akt, PTEN, p110 $\beta$ ), would be expected to reasonably predict siRNA activity for molecules across the full scope of the genus. (Exh. 1002 at ¶¶238-64.)

Moreover, as explained in Section VIII.A, the underlying applications concede that siRNA molecules comprising a double-stranded region of 17 nucleotides in length, as encompassed by all of the claims of the '501 patent, are not functional. (Exhs. 1006-1007 at 10, 31, 32; Exh. 1008 at 11, 12, 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, 24:49-54, 25:44-48.) There is no information in the underlying applications as to how to use these non-functional siRNA molecules. (Exh. 1002 at ¶¶130-71, 215-20, 247.)

Further, there is no guidance in any of the underlying applications as to how to practice the claimed invention without undue experimentation. (*Id.* at ¶¶244-50.) The applications provide no guidance as to how to structurally modify the claimed siRNA molecules, let alone in ways that would preserve their utility—RNAi. And,

the applications provide no correlation between structure and function. (*Id.* at ¶¶246-50.)

While the applications leading to the '501 patent disclose some screening methods to measure RNAi (*see, e.g.*, Exhs. 1005-1013 at Examples; Exh. 1004 at 71-87; Exh. 1001 at Examples; Exh. 1002 at ¶246), the Board has previously found that such disclosure “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*, Case IPR2015-00291, Paper 75 at 14-15.

As a result of the lack of guidance in the applications, in order to practice the full scope of the claimed invention, significant work would be necessary to select, design, synthesize, and screen siRNA molecules encompassed by the vast claimed genus and determine which of those would have any utility. (Exh. 1002 at ¶¶82-83, 265-71.) At minimum, for each siRNA molecule of this enormous genus, a POSA would have to engage in a laborious iterative screening process involving at least: (1) selecting target nucleic acid or sequences, (2) selecting a duplex architecture for the siRNA molecules, (3) selecting a chemical modification strategy, (4) synthesizing the siRNA molecule, and (5) testing the siRNA molecule for activity. (*Id.* at ¶266.) This 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 ¶¶82-83, 267, 270.) Even the patent acknowledges that functionality is assay dependent. (Exh. 1001 at 8:46-49.) At best, the applications disclose a starting point for further iterative research in an unpredictable field. *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 Pharm., 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*, 413 F.3d at 1325 (“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.”).

This lack of guidance and extensive experimentation required to use claimed molecules across the full scope of the genus supports a finding of lack of enablement.

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For at least these reasons, claims 1-30 are not enabled by the applications leading to the '501 patent and none of the claims are entitled to an effective filing date earlier than May 8, 2017. Therefore, the '501 patent is PGR eligible.

## **IX. THE CHALLENGED CLAIMS ARE UNPATENTABLE**

As described below, the challenged claims are unpatentable.

### **A. Ground 1: Claims 1-30 Lack Written Description**

As discussed in Section VIII.A, none of the underlying applications provide adequate written description for the full scope of the '501 patent claims. As noted in Section IV, the '501 patent specification is identical or nearly identical to all the underlying applications and, therefore, also fails to provide adequate written description of the '501 patent claims. Specifically, the '501 patent specification, like the underlying applications, fails to demonstrate that the inventors were in possession of the full scope of the structurally diverse siRNA molecules, let alone molecules across the full scope of the claimed genus that have RNAi. (Exh. 1002 at ¶¶172-237.)

As discussed in Sections III and VIII.A, the '501 patent claims encompass an enormous number of chemically and structurally diverse siRNA molecules. (*Id.* at ¶¶173-204.) In addition, the '501 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 ¶¶174-77.) 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. (*Id.* at ¶¶190-94.)

Nevertheless, the '501 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 '501 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 up to three genes* (*i.e.*, Akt1, PTEN, p110 $\beta$ ). (Exh. 1001 at Examples 7-11; Exh. 1002 at ¶¶205-27, 234, 245.) As discussed in Section VIII.A, this narrow disclosure is not representative of the full scope of the genus claimed. (Exh. 1002 at ¶¶205-09, 221-23.)

Moreover, like the underlying applications, the patent teaches that certain structural elements lead to siRNA molecules with inferior stability or result in molecules that are non-functional, further evidencing the inventors' lack of possession. (*See, e.g.*, Exh. 1001 at 12:22-26, 24:49-54, 25:44-48, 26:34-36; Exh. 1002 at ¶¶215-27, 247.); *see also Tronzo*, 156 F.3d at 1158-59; *Bamberg*, 815 F.3d at 797-98; *In re Curtis*, 354 F.3d at 1352-53.

Further, if the Board finds the '501 patent claims require the claimed siRNA molecules have RNAi – consistent with the express disclosure of the '501 patent (*see* Section VII.A) – Patent Owner's written description problems are exacerbated. The '501 patent specification discloses activity data for only a few 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 either PTEN, Akt1 or p110 $\beta$ . (*See, e.g.*, Exh. 1001 at Examples 9-11; Exh. 1002 at ¶¶236-37.) Furthermore, like the underlying applications, the '501 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 24:49-54, 25:44-48; Exh. 1002 at ¶¶68, 74, 215-20, 247.) Therefore, the inventors were not in possession of the claimed siRNA molecules having a double-stranded region of 17 ribonucleotides in length with RNAi as encompassed by all of the claims of the '501 patent. (Exh. 1002 at ¶¶215-20.)

While the patent, like the underlying applications include generic embodiments that arguably encompass siRNA molecules that fall within the claimed genus, such disclosures do not establish possession. As discussed in Section VIII.A, the generic disclosures are too broad to adequately show

possession of the vast genus of siRNA molecules claimed and do not overcome the unpredictable nature of the field of RNAi. (Exh. 1002 at ¶¶173-237.)

For the foregoing reasons, and those discussed in Section VIII.A, claims 1-30 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 1-30 Lack Enablement**

As discussed in Section VIII.B, none of the applications underlying the '501 patent enable the broad scope of the patent claims. As also discussed in Section IV, the '501 patent specification is identical or nearly identical to the underlying applications and, therefore, also fails to enable the full scope of the patent claims. (Exh. 1002 at ¶¶130, 153-54, 238-71.) Specifically, claims 1-30 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 ¶¶238-71.) Furthermore, the '501 patent claims are not enabled because they encompass siRNA molecules comprising a double-stranded region of 17 ribonucleotides in length, which the patent concedes are not functional. (*Id.* at ¶¶68, 74, 215-20, 247.)

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 1-30 are unpatentable for lack of enablement under 35 U.S.C. § 112(a). (Exh. 1002 at ¶¶238-71.)

**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 '501 patent relates to the field of RNAi technology and recites claims to chemically-modified siRNA molecules. (*Id.* at ¶¶57-68, 240-41.)

Unpredictability was, and remains, typical to the field of RNAi. (*Id.* at ¶¶228-35, 251-71.) 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 ¶¶228-35, 251-71) – making the showing required for enablement all the more demanding. *See, e.g., Genentech, Inc.*, 108 F.3d at 1367-68. Moreover, despite the nearly 15-year gap between the filing of the earliest priority application and the filing of the application directly underlying the '501 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 '501 patent specification. (Exh. 1002 at ¶¶228-35, 251-71.)

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

As discussed in Sections III and VIII, the '501 patent claims encompass an enormous genus of structurally diverse chemically-modified siRNA molecules directed to an unlimited genus of genetic targets. (Exh. 1002 at ¶¶240-43.) 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.A, the practical utility here is RNAi. (*Id.* at ¶241; *see also id.* at ¶¶57-63.)

Nevertheless, the '501 patent specification and its underlying applications disclose *fewer than ten structurally similar siRNA molecules* encompassed by the claims that have RNAi. (*Id.* at ¶¶207, 244-50.) This provides further support for a finding of lack of enablement.

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

As discussed in Section VIII.B.3, the applications leading to the '501 patent provide siRNA activity data for, only a small sliver of siRNA molecules that fall within the broadly claimed and structurally diverse genus. The same is true for the

'501 patent specification. (*Id.* at ¶¶205-27, 236-37, 244-50.) Further, as with the underlying applications, the '501 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 ¶¶244-50.) In fact, the patent specification, like the underlying applications, concedes that siRNA molecules encompassed by the genus, *i.e.*, those having a double-stranded length of 17 ribonucleotides or less, do not have utility. (*See, e.g.*, Exh. 1001 at 12:22-26, 24:49-54, 25:44-48.) There is no information in the patent specification or the underlying applications as to how to use such siRNA molecules. (Exh. 1002 at ¶¶130-71, 215-20, 247.)

Furthermore, the '501 patent specification, like the underlying applications, fails to provide any guidance on how to select siRNA molecules from the 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 ¶244.)

Therefore, 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 ¶¶265-71.) As noted above, there is little predictability between and among sequences, thereby necessitating a laborious and repetitive testing and screening

process. (*Id.* at ¶¶267, 270.) This is true between 2002 and 2017 despite advances in the field of RNAi. (*Id.* at ¶¶228-35, 251-71); *see also Wyeth*, 720 F.3d at 1386.

As discussed in Section VIII.B.3, the patent’s disclosure of screening methods such a disclosure is not sufficient to avoid undue experimentation. (*Id.* at ¶246); *see also Daiichi Sankyo*, Case IPR2015-00291, Paper 75 at 14-15.

For the foregoing reasons, and as discussed in Section VIII.B, claims 1-30 are unpatentable for lack of enablement under 35 U.S.C. § 112.

**C. Ground 3: Claims 1, 2, 9, 10, 12, 13, 16-20, 22, 24, and 25 Are Anticipated by Allerson**

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).

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 ¶275.) Although this date is after the earliest possible priority date (“EPP”) for the ’501 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 '501 patent. Therefore, Allerson is prior art to the '501 patent under 35 U.S.C. § 102(a)(1). (Exh. 1002 at ¶¶276.) As explained below, Allerson discloses a double-stranded siRNA molecule, duplex 8, which anticipates claims 1, 2, 9, 10, 12, 13, 16-20, 22, 24 and 25 regardless of whether the claims are construed to require RNAi because it satisfies the claimed structural limitations and exhibits RNAi. (*Id.* at ¶¶275-319.)

**1. Claim 1**

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

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 ¶¶277-82.)

Allerson discloses duplex 8 (reproduced and illustrated below), which has the following structure:



(Exh. 1016 at Figure 2A; Exh. 1002 at ¶¶283-86.)

### **Illustrated Duplex 8**

Sense Strand            5'    P-aaguaaggaccagagacaa            3'  
Antisense Strand 3'            uucauuccuggucucugu-P            5'

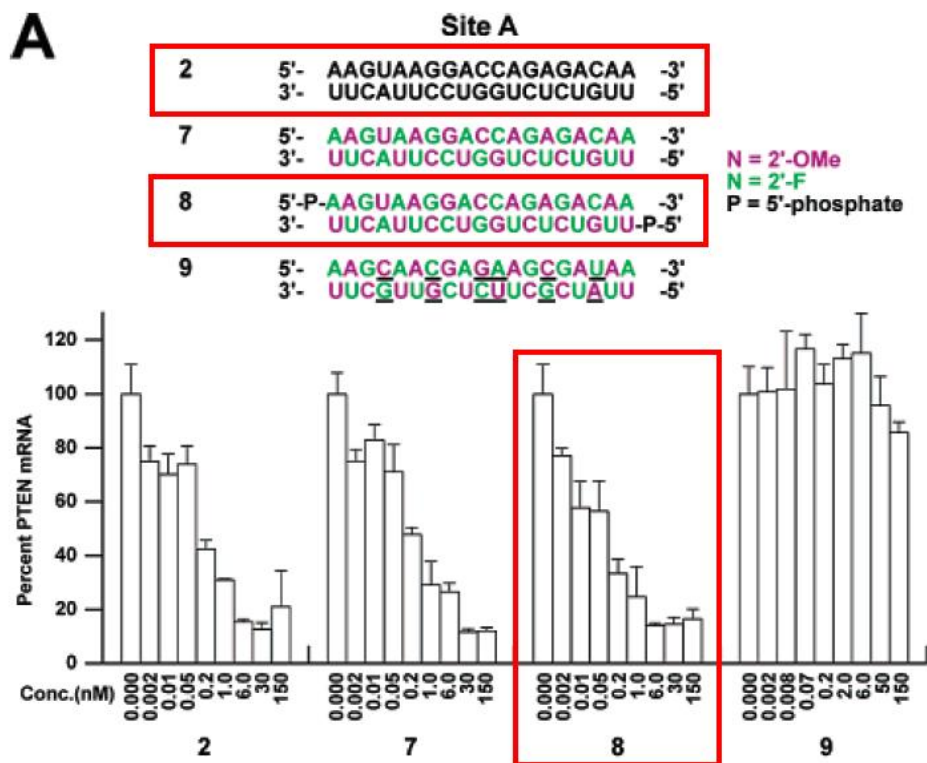
Lowercase = 2'-O-methyl ribonucleotide      P = 5'-phosphate

Lowercase = 2'-fluoro ribonucleotide

(Exh. 1016 at Figure 2A; Exh. 1002 at ¶284.)

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 ¶¶278, 288.)

Figure 2A of Allerson (reproduced and annotated below) provides RNAi data for duplex 8 demonstrating it has RNAi when compared to its unmodified analogue, duplex 2. (Exh. 1002 at ¶¶287-90.) Duplex 8, therefore, satisfies this limitation of claim 1. (*Id.* at ¶¶293, 319.)



(Exh. 1016 at Figure 2A.)

**b. “wherein the double-stranded siRNA molecule comprises a first strand and a second strand”**

Duplex 8 is double-stranded and, therefore, satisfies this limitation of claim

1. (Exh. 1016 at Figure 2A; Exh. 1002 at ¶294.)

**c. “wherein the first strand comprises a first stretch that is complementary to the target nucleic acid”**

Duplex 8 targets PTEN mRNA. (Exh. 1016 at 901; Exh. 1002 at ¶¶287-90.)

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 ¶285.) Duplex 8, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶295.)

d. **“wherein the second strand comprises a second stretch that is the same length as the first stretch and is complementary to the first stretch”**

Duplex 8 comprises two stretches that are each 19 ribonucleotides in length. (Exh. 1016 at Figure 2A; Exh. 1002 at ¶¶283-85, 296.) The stretches of duplex 8 comprise ribonucleotides that are complementary to each other. (Exh. 1016 at Figure 2A; Exh. 1002 at ¶296.) Duplex 8, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶296.)

e. **“wherein the first strand and the second strand form a double-stranded structure comprising the first stretch and the second stretch”**

Duplex 8 comprises a first strand and a second strand comprising a first and a second stretch that form the double-stranded structure. (Exh. 1016 at Figure 2A; Exh. 1002 at ¶297.) Duplex 8, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶297.)



- f. **“wherein the first stretch and the second stretch each comprises contiguous alternating 2’-O-alkyl ribonucleotides, wherein the the 2’-O-alkyl ribonucleotides alternate with unmodified or differently modified ribonucleotides”**

Both strands, and therefore, also both stretches, of duplex 8 comprise contiguous alternating 2’-O-alkyl (specifically, 2’-O-methyl) ribonucleotides that alternate with differently modified (specifically, 2’-fluoro) ribonucleotides. (Exh. 1016 at Figure 2A; Exh. 1002 at ¶¶298-99.) Duplex 8, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶¶298-99.)

- g. **“wherein the 2’-O-alkyl ribonucleotides of the first strand are shifted by one ribonucleotide relative to the 2’-O-alkyl ribonucleotides of the second strand”**

The 2’-O-alkyl (specifically, 2’-O-methyl) ribonucleotides of the first (bottom) strand of duplex 8 are shifted by one ribonucleotide relative to the 2’-O-alkyl (specifically, 2’-O-methyl) ribonucleotides of the second (top) strand. (Exh. 1016 at Figure 2A; Exh. 1002 at ¶300.) Duplex 8, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶300.)

- h. **“wherein each of the first stretch and the second stretch consists of at least 17 and fewer than 30 ribonucleotides”**

Both stretches of duplex 8 are 19 ribonucleotides long. (Exh. 1016 at Figure 2A; Exh. 1002 at ¶301.) Duplex 8, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶301.)

\*\*\*\*\*

As explained above, duplex 8 contains the structural limitations of claim 1 of the '501 patent and displays RNAi. Therefore, duplex 8 anticipates claim 1 regardless of whether it requires RNAi. (*Id.* at ¶¶292-302.)

**2. Claim 2**

Claim 2 depends from claim 1. Claim 2 additionally recites “the double-stranded siRNA molecule is blunt ended on both ends.” (Exh. 1001 at Claim 2) As discussed in Section IX.C.1, duplex 8 contains all of the features of claim 1. Duplex 8 is blunt-ended on both ends. (Exh. 1016 at Figure 2A; Exh. 1002 at ¶¶303-04.) Therefore, duplex 8 anticipates claim 2. (Exh. 1002 at ¶¶303-04.)

**3. Claim 9**

Claim 9 depends from claim 1. Claim 9 additionally recites “each of the first strand and the second strand consists of at least 18 nucleotides.” (Exh. 1001 at Claim 9.) As discussed in Section IX.C.1, duplex 8 contains all of the features of claim 1. Each strand of duplex 8 has 19 ribonucleotides. (Exh. 1016 at Figure 2A; Exh. 1002 at ¶¶305-06.) Therefore, duplex 8 anticipates claim 9. (Exh. 1002 at ¶¶305-06.)

**4. Claims 10, 12, 13, and 22**

Claims 10 and 12 depend from claim 1. Claim 10 additionally recites “the 2'-O-alkyl ribonucleotides are 2'-O-methyl ribonucleotides.” (Exh. 1001 at Claim 10.) Claim 12 additionally recites “the differently modified ribonucleotides have an

amino, fluoro, different alkoxy, or alkyl modification at the 2'-position.” (*Id.* at Claim 12.) As discussed in Section IX.C.1, duplex 8 contains all of the features of claim 1. Duplex 8 comprises 2'-O-methyl ribonucleotides and 2'-fluoro ribonucleotides. (Exh. 1016 at Figure 2A; Exh. 1002 at ¶¶307-08.) Therefore, duplex 8 anticipates claims 10 and 12. (Exh. 1002 at ¶¶307-08.)

Claim 13 depends from claim 10. Claim 13 additionally recites “the 2'-O-methyl ribonucleotides alternate with 2'-fluoro ribonucleotides.” (Exh. 1001 at Claim 13.) As discussed above, duplex 8 contains all of the features of claim 10 and comprises 2'-O-methyl ribonucleotides that alternate with 2'-fluoro ribonucleotides. (Exh. 1016 at Figure 2A; Exh. 1002 at ¶309.) Therefore, duplex 8 anticipates claim 13. (Exh. 1002 at ¶309.)

Claim 22 depends from claim 13. Claim 22 additionally recites “the 5' ribonucleotide of the first stretch is a 2'-O-methyl ribonucleotide.” (Exh. 1001 at Claim 22.) As discussed above, duplex 8 contains all the features of claim 13. The 5' ribonucleotide of the first (bottom) stretch of duplex 8 is a 2'-O-methyl ribonucleotide. (Exh. 1016 at Figure 2A; Exh. 1002 at ¶¶310-11.) Therefore, duplex 8 anticipates claim 22. (Exh. 1002 at ¶¶310-11.)

## **5. Claims 16-19**

Claim 16 depends from claim 1. Claim 16 additionally recites: “the first stretch and the second stretch each comprises contiguous alternating single 2'-O-

alkyl ribonucleotides, and wherein the single 2'-O-alkyl ribonucleotides alternate with the differently modified ribonucleotides.” (Exh. 1001 at Claim 16.) As discussed in Section IX.C.1, duplex 8 contains all of the features of claim 1. Both stretches of duplex 8 comprise single 2'-O-methyl ribonucleotides that alternate with 2'-fluoro ribonucleotides. (Exh. 1016 at Figure 2A; Exh. 1002 at ¶¶312-13.) Therefore, duplex 8 anticipates claim 16. (Exh. 1002 at ¶¶312-13.)

Claims 17-19 depend from claim 16. Claim 17 additionally recites “the single-2'-O-alkyl ribonucleotides are 2'-O-methyl ribonucleotides.” (Exh. 1001 at Claim 17.) Claim 18 additionally recites “the differently modified ribonucleotides have an amino, fluoro, different alkoxy, or alkyl modification at the 2'-position.” (*Id.* at Claim 18.) Claim 19 additionally recites “the single 2'-O-alkyl ribonucleotides are 2'-O-methyl ribonucleotides, and the differently modified ribonucleotides are 2'-fluoro ribonucleotides.” (*Id.* at Claim 19.) As discussed above, duplex 8 contains all the features of claim 16 and comprises single 2'-O-methyl ribonucleotides that alternate with 2'-fluoro ribonucleotides. (Exh. 1002 at ¶¶314-15.) Therefore, duplex 8 anticipates claims 17-19. (*Id.* at ¶¶314-15.)

## **6. Claims 20 and 24**

Claims 20 and 24 depend from claim 1 and claim 16, respectively. Claims 20 and 24 additionally recite “the 5' ribonucleotide of the first stretch is a 2'-O-alkyl modified ribonucleotide.” (Exh. 1001 at Claims 20, 24.) Claim 24 also

additionally requires the 2'-O-alkyl modified ribonucleotide alternates with a differently modified ribonucleotide. (*Id.* at Claim 24.) As discussed in Sections IX.C.1 and immediately above, duplex 8 contains all of the features of claims 1 and 16. The 5' ribonucleotide of the first stretch is a 2'-O-alkyl (specifically, 2'-O-methyl) ribonucleotide that alternates with a differently modified (specifically, 2'-fluoro) ribonucleotide. (Exh. 1016 at Figure 2A; Exh. 1002 at ¶¶310-11, 316.) Therefore, duplex 8 anticipates claims 20 and 24. (Exh. 1002 at ¶¶310-11, 316.)

## **7. Claim 25**

Claim 25 depends from claim 19 and additionally recites “the double-stranded siRNA molecule is blunt on at least one end.” (Exh. 1001 at Claim 25.) As discussed in Section IX.C.5, duplex 8 contains all of the features of claim 19. Duplex 8 is blunt-ended on both ends (and therefore, also, on at least one end). (Exh. 1016 at Figure 2A; Exh. 1002 at ¶¶317-18.) Therefore, duplex 8 anticipates claim 25. (Exh. 1002 at ¶¶317-18.)

## **D. Ground 4: Claims 1, 3-5, 7, 9-11, 14, 15, 20, 21, and 23 Are Anticipated by Choung**

Choung, et al., “Chemical modification of siRNAs to improve serum stability without loss of efficacy” (“Choung”) was published on February 20, 2006. (Exh. 1072 at 919; Exh. 1002 at ¶320.) Although this date is after the EPP for the '501 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

'501 patent. Therefore, Choung is prior art under 35 U.S.C. § 102(a)(1). (Exh. 1002 at ¶321.) As explained below, Choung discloses a double-stranded siRNA molecule, Sur10058-Me-AL3, which anticipates claims 1, 3-5, 7, 9-11, 14, 15, 20, 21 and 23 regardless of whether the claims are construed to require RNAi because it satisfies the claimed structural limitations and exhibits RNAi. (*Id.* at ¶¶320-58.)

**1. Claim 1**

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

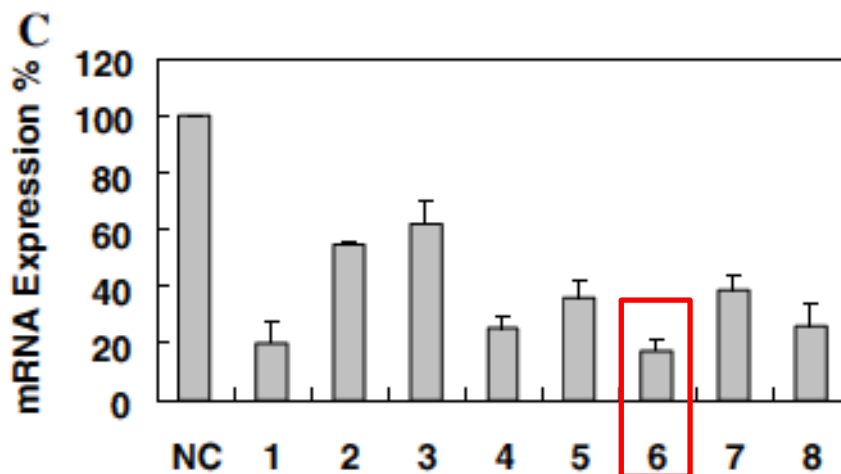
Choung studied the introduction of “various combination of chemical modifications into Sur10058 in order to identify the modified structures which can greatly enhance its serum stability without reducing its knockdown efficiency.” (Exh. 1072 at 920; Exh. 1002 at ¶322.) In particular, Choung discloses Sur10058-Me-AL3 (reproduced below), which has the following structure, wherein the lowercase letters are unmodified ribonucleotides and the underlined bold letters are 2'-O-methyl modified ribonucleotides on the antisense (bottom) and sense (top) strands:

**6) Sur10058-Me-AL3**

5'            **aagggaucaacauuuca** dTdT 3'  
 3' dTdT **uccucuaguguaaagu** 5'

(Exh. 1072 at Figure 3A; Exh. 1002 at ¶¶326-29.)

Figure 3C of Choung (reproduced and annotated below) provides RNAi data for Sur10058-Me-3 demonstrating it has RNAi. (Exh. 1072 at Figure 3C; Exh. 1002 at ¶¶330-31.) Sur10058-Me-3, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶334.)



(Exh. 1072 at Figure 3C.)

**b. “wherein the double-stranded siRNA molecule comprises a first strand and a second strand”**

Sur10058-Me-AL3 is double-stranded and, therefore, satisfies this limitation of claim 1. (Exh. 1072 at Figure 3A; Exh. 1002 at ¶335.)

**c. “wherein the first strand comprises a first stretch that is complementary to the target nucleic acid”**

Sur10058-Me-AL3 “specifically target[s] survivin” mRNA. (Exh. 1072 at 919; Exh. 1002 at ¶323.) Choung also indicates that the “antisense strand was composed of nucleotides that are complementary to the target sequence” in

survivin. (Exh. 1072 at 920; Exh. 1002 at ¶¶323, 326, 336.) Sur10058-Me-AL3, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶336.)

**d. “wherein the second strand comprises a second stretch that is the same length as the first stretch and is complementary to the first stretch”**

Sur10058-Me-AL3 comprises two stretches that are each 19 ribonucleotides in length. (Exh. 1072 at Figure 3A; Exh. 1002 at ¶337.) The stretches of Sur10058-Me-AL3 comprise ribonucleotides that are complementary to each. (Exh. 1072 at Figure 3A; Exh. 1002 at ¶337.) Sur10058-Me-AL3, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶337.)

**e. “wherein the first strand and the second strand form a double-stranded structure comprising the first stretch and the second stretch”**

Sur10058-Me-AL3 comprises a first and a second stretch that form the double-stranded structure. (Exh. 1072 at Figure 3A; Exh. 1002 at ¶338.) Sur10058-Me-AL3, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶338.)

**f. “wherein the first stretch and the second stretch each comprises contiguous alternating 2'-O-alkyl ribonucleotides, wherein the the 2'-O-alkyl ribonucleotides alternate with unmodified or differently modified ribonucleotides”**

Both stretches of both strands of Sur10058-Me-AL3 comprise contiguous alternating 2'-O-alkyl (specifically, 2'-O-methyl) and unmodified ribonucleotides.



(Exh. 1072 at Figure 3A; Exh. 1002 at ¶¶339-40.) Sur10058-Me-AL3, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶¶339-40.)

**g.     “wherein the 2’-O-alkyl ribonucleotides of the first strand are shifted by one ribonucleotide relative to the 2’-O-alkyl ribonucleotides of the second strand”**

The 2’-O-alkyl (specifically, 2’-O-methyl) ribonucleotides of Sur10058-Me-AL3’s first (bottom) strand are shifted by one ribonucleotide relative to the 2’-O-alkyl (specifically, 2’-O-methyl) ribonucleotides of its second (top) strand. (Exh. 1072 at Figure 3A; Exh. 1002 at ¶341.) Sur10058-Me-AL3, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶341.)

**h.     “wherein each of the first stretch and the second stretch consists of at least 17 and fewer than 30 ribonucleotides”**

Both stretches of Sur10058-Me-AL3 are 19 ribonucleotides long. (Exh. 1072 at Figure 3A; Exh. 1002 at ¶342.) Sur10058-Me-AL3, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶342.)

\* \* \* \* \*

As explained above, Sur10058-Me-AL3 contains the structural limitations of claim 1 of the ’501 patent and displays RNAi. Therefore, Sur10058-Me-AL3 anticipates claim 1 regardless of whether it is construed to require RNAi. (*Id.* at ¶¶333-43.)

## **2. Claims 3-5, and 7**

Claim 3 depends from claim 1. Claim 3 additionally recites “at least one end of the double-stranded siRNA molecule has an overhang.” (Exh. 1001 at Claim 3.) As discussed in Section IX.D.1, Sur10058-Me-AL3 contains all of the limitations of claim 1. Sur10058-Me-AL3 has a two-nucleotide overhang on the 3’ end of each of its strands. (Exh. 1072 at Figure 3A; Exh. 1002 at ¶¶344-45.) Therefore, Sur10058-Me-AL3 anticipates claim 3. (Exh. 1002 at ¶¶344-45.)

Claims 4, 5 and 7 each depend from claim 3. Claim 4 additionally recites “the overhang has one to eight nucleotides.” (Exh. 1001 at Claim 4.) Claim 5 additionally recites “the 3’ end of the first strand has an overhang.” (*Id.* at Claim 5.) Claim 7 additionally recites “the 3’ end of the second strand has an overhang.” (*Id.* at Claim 7.) As discussed above, Sur10058-Me-AL3 contains all the limitations of claim 3 and has a two-nucleotide overhang on the 3’ end of each of its strands. Therefore, Sur10058-Me-AL3 anticipates claims 4, 5, and 7. (Exh. 1002 at ¶¶346-47.)

## **3. Claim 9**

Claim 9 depends from claim 1. Claim 9 additionally recites “each of the first strand and the second strand consists of at least 18 nucleotides.” (Exh. 1001 at Claim 9.) As discussed in Section IX.D.1, Sur10058-Me-AL3 contains all of the features of claim 1. Each strand of 10058-Me-AL3 has 21 ribonucleotides. (Exh.

1072 at Figure 3A; Exh. 1002 at ¶¶348-49.) Therefore, Sur10058-Me-AL3 anticipates claim 9. (Exh. 1002 at ¶¶348-49.)

#### **4. Claims 10, 11, and 21**

Claim 10 depends from claim 1. Claim 10 additionally recites “the 2’-O-alkyl ribonucleotides are 2’-O-methyl ribonucleotides.” (Exh. 1001 at Claim 11.) As discussed in Section IX.D.1, Sur10058-Me-AL3 contains all the features of claim 1. Sur10058-Me-AL3 comprises 2’-O-methyl and unmodified ribonucleotides. (Exh. 1072 at Figure 3A; Exh. 1002 at ¶350.) Therefore, Sur10058-Me-AL3 anticipates claim 10. (Exh. 1002 at ¶350.)

Claim 11 depends from claim 10 and additionally recites “the 2’-O-methyl ribonucleotides alternate with the unmodified ribonucleotides.” (Exh. 1001 at Claim 11.) As discussed above, Sur10058-Me-AL3 contains all the features of claim 10 and comprises 2’-O-methyl ribonucleotides that alternate with unmodified ribonucleotides. (Exh. 1002 at ¶351.) Therefore, Sur10058-Me-AL3 anticipates claims 11. (*Id.*)

Claim 21 depends from claim 11 and additionally recites “the 5’ ribonucleotide of the first stretch is a 2’-O-methyl ribonucleotide.” (Exh. 1001 at Claim 21.) As discussed above, Sur10058-Me-AL3 contains all the features of claim 11. The 5’ ribonucleotide of the first (bottom) stretch of Sur10058-Me-AL3

is a 2'-O-methyl ribonucleotide. (Exh. 1072 at Figure 3A; Exh. 1002 at ¶353.)

Therefore, Sur10058-Me-AL3 anticipates claim 21. (Exh. 1002 at ¶353.)

## **5. Claims 14, 15, and 23**

Claim 14 depends from claim 1 and additionally recites “the first stretch and the second stretch each comprises contiguous alternating single 2'-O-alkyl ribonucleotides, and wherein the single 2'-O-alkyl ribonucleotides alternate with the unmodified ribonucleotides.” (Exh. 1001 at Claim 14.) As discussed in Section IX.D.1, Sur10058-Me-AL3 contains all the features of claim 1. Each stretch of Sur10058-Me-AL3 comprises single 2'-O-alkyl (specifically, 2'-O-methyl) ribonucleotides that alternate with unmodified ribonucleotides. (Exh. 1072 at Figure 3A; Exh. 1002 at ¶¶354-55.) Therefore, Sur10058-Me-AL3 anticipates claim 14. (Exh. 1002 at ¶¶354-55.)

Claims 15 and 23 depend from claim 14. Claim 15 additionally recites “the single 2'-O-alkyl ribonucleotides are 2'-O-methyl ribonucleotides.” (Exh. 1001 at Claim 15.) Claim 23 additionally recites “the 5' ribonucleotide of the first stretch is a 2'-O-alkyl modified ribonucleotide that alternates with an unmodified ribonucleotide.” (*Id.* at Claim 23.) As discussed above, Sur10058-Me-AL3 contains all the features of claim 14 and comprises 2'-O-methyl ribonucleotides. The 5' ribonucleotide of the first stretch of Sur10058-Me-AL3 is a 2'-O-alkyl (specifically, a 2'-O-methyl) ribonucleotide that alternates with an unmodified

ribonucleotide. (Exh. 1072 at Figure 3A; Exh. 1002 at ¶¶356-57.) Therefore, Sur10058-Me-AL3 anticipates claims 15 and 23. (Exh. 1002 at ¶¶356-57.)

## **6. Claim 20**

Claim 20 depends from claim 1. Claim 20 additionally recites “the 5’ ribonucleotide of the first stretch is a 2’-O-alkyl modified ribonucleotide.” (Exh. 1001 at Claim 20.) As discussed in Section IX.D.1, Sur10058-Me-AL3 contains all of the features of claim 1. The 5’ ribonucleotide of the first (bottom) stretch of Sur10058-Me-AL3 is a 2’-O-alkyl (specifically, 2’-O-methyl) ribonucleotide. (Exh. 1072 at Figure 3A; Exh. 1002 at ¶352.) Therefore, Sur10058-Me-AL3 anticipates claim 20. (Exh. 1002 at ¶352.)

## **E. Ground 5: Claims 1, 16, 19, 26, 27, and 29 Are Anticipated by Podbevsek**

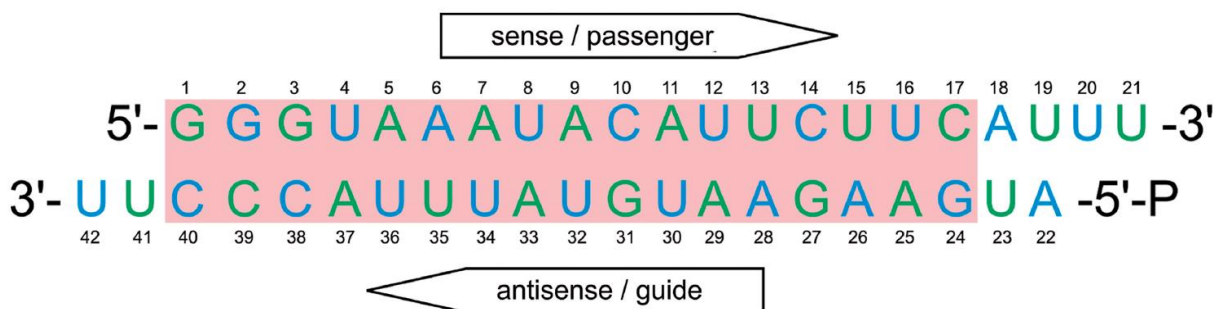
Podbevsek, et al., “Solution-state structure of a fully alternately 2’-F/2’-OMe modified 42-nt dimeric siRNA construct” (“Podbevsek”) was published on July 12, 2010. (Exh. 1082 at 7298; Exh. 1002 at ¶359.) Although this date is after the EPP for the ’501 patent, as explained in Section VIII, none of the challenged claims are entitled to an effective filing date earlier than May 8, 2017 – the actual filing date of the ’501 patent. Therefore, Podbevsek is prior art to the ’501 patent under 35 U.S.C. § 102(a)(1). (Exh. 1002 at ¶360.) As explained below, Podbevsek discloses a double-stranded siRNA molecule which anticipates claims 1, 16, 19,

26, 27, and 29 if the claims are not construed to require RNAi because each construct satisfies the claimed structural limitations. (*Id.* at ¶¶359-91.)

**1. Claim 1**

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

As reproduced and illustrated below, Podbevsek discloses a double-stranded siRNA molecule that is “fully 2’-F/2’-OMe modified,” wherein the 2’-fluoro modified nucleotides are depicted in green and the 2’-O-methyl modified nucleotides are depicted in blue. (Exh. 1082 at 7299; Exh. 1002 at ¶¶361-70.)



(Exh. 1082 at Figure 2; Exh. 1002 at ¶366.)

**Illustrated Podbevsek Molecule**

Sense Strand            5'     ggguaaauacauucuucauu            3'

Antisense Strand    3'    uucccauuuauguaagaagua-P            5'

Lowercase = 2’-O-methyl ribonucleotide

P = 5’-phosphate

Lowercase = 2’-fluoro ribonucleotide

(Exh. 1082 at Figure 2; Exh. 1002 at ¶367.)

The Podbevsek molecule targets PTEN mRNA. (Exh. 1002 at ¶368.)

Therefore, assuming the term is not construed to require RNAi, the Podbevsek molecule satisfies this limitation of claim 1. (Exh. 1002 at ¶¶373.)

**b. “wherein the double-stranded siRNA molecule comprises a first strand and a second strand”**

The Podbevsek molecule is double-stranded (with 2-nucleotide overhang on the 3’ end of each strand) and, therefore, satisfies this limitation of claim 1. (Exh. 1082 at Figure 2; Exh. 1002 at ¶374.)

**c. “wherein the first strand comprises a first stretch that is complementary to the target nucleic acid”**

The Podbevsek molecule targets PTEN mRNA and its first strand is complementary to the target mRNA. (Exh. 1082 at 7304-05; Exh. 1002 at ¶375.) The Podbevsek molecule, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶375.)

**d. “wherein the second strand comprises a second stretch that is the same length as the first stretch and is complementary to the first stretch”**

The Podbevsek molecule comprises two stretches that are each 19 ribonucleotides in length and comprise ribonucleotides that are complementary to each other. (Exh. 1082 at Figure 2; Exh. 1002 at ¶¶366-68.) The Podbevsek molecule, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶376.)

- e. **“wherein the first strand and the second strand form a double-stranded structure comprising the first stretch and the second stretch”**

The Podbevsek molecule comprises a first and a second stretch that form the double-stranded structure. (Exh. 1082 at Figure 2; Exh. 1002 at ¶377.) The Podbevsek molecule, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶377.)

- f. **“wherein the first stretch and the second stretch each comprises contiguous alternating 2’-O-alkyl ribonucleotides, wherein the the 2’-O-alkyl ribonucleotides alternate with unmodified or differently modified ribonucleotides”**

Both stretches of both strands of the Podbevsek molecule comprise contiguous alternating 2’-O-alkyl (specifically, 2’-O-methyl) that alternate with differently modified (specifically, 2’-fluoro) ribonucleotides. (Exh. 1082 at Figure 2; Exh. 1002 at ¶¶378-79.) The Podbevsek molecule, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶¶378-79.)

- g. **“wherein the 2’-O-alkyl ribonucleotides of the first strand are shifted by one ribonucleotide relative to the 2’-O-alkyl ribonucleotides of the second strand”**

The 2’-O-alkyl (specifically, 2’-O-methyl) ribonucleotides of the Podbevsek molecule’s first (bottom) strand are shifted by one ribonucleotide relative to the 2’-O-alkyl (specifically, 2’-O-methyl) ribonucleotides of its second (top) strand. (Exh.



1082 at Figure 2; Exh. 1002 at ¶380.) The Podbevsek molecule, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶380.)

**h. “wherein each of the first stretch and the second stretch consists of at least 17 and fewer than 30 ribonucleotides”**

Both stretches of the Podbevsek molecule are 19 ribonucleotides long. (Exh. 1082 at Figure 2; Exh. 1002 at ¶381.) The Podbevsek molecule, therefore, satisfies this limitation of claim 1. (Exh. 1002 at ¶381.)

\* \* \* \* \*

As discussed above, the Podbevsek molecule contains each of the structural limitations of claim 1 of the '501 patent. Therefore, if the claims are construed not to require RNAi, the Podbevsek molecule anticipates claim 1. (*Id.* at ¶¶372-82.)

**2. Claims 16 and 19**

Claim 16 depends from claim 1. Claim 16 additionally recites: “the first stretch and the second stretch each comprises contiguous alternating single 2'-O-alkyl ribonucleotides, and wherein the single 2'-O-alkyl ribonucleotides alternate with the differently modified ribonucleotides.” (Exh. 1001 at Claim 16.) As discussed in Section IX.E.1, the Podbevsek molecule contains all the structural features of claim 1. Both stretches of the Podbevsek molecule comprise single 2'-O-methyl ribonucleotides that alternate with 2'-fluoro ribonucleotides. (Exh. 1082

at Figure 2; Exh. 1002 at ¶¶383-84.) Therefore, the Podbevsek molecule anticipates claim 16. (Exh. 1002 at ¶¶383-84.)

Claim 19 depends from claim 16 and additionally recites “the single 2’-O-alkyl ribonucleotides are 2’-O-methyl ribonucleotides, and the differently modified ribonucleotides are 2’-fluoro ribonucleotides.” (Exh. 1001 at Claim 19.) As discussed above, the Podbevsek molecule contains all the features of claim 16 and comprises 2’-O-methyl and 2’-fluoro ribonucleotides. (Exh. 1002 at ¶¶385-86.) Therefore, the Podbevsek molecule anticipates claim 19. (*Id.* at ¶¶385-86.)

### **3. Claims 26, 27, and 29**

Claim 26 depends from claim 19 and additionally recites “at least one end of the double-stranded siRNA molecule has an overhang of one to eight nucleotides.” (Exh. 1001 at Claim 26.) As discussed above, the Podbevsek molecule contains all the features of claim 19. The Podbevsek molecule has an overhang of two nucleotides on the 3’ end of both (and, therefore, on at least one end) strands. (Exh. 1082 at Figure 2; Exh. 1002 at ¶¶387-88.) Therefore, the Podbevsek molecule anticipates claim 26. (Exh. 1002 at ¶¶387-88.)

Claims 27 and 29 depend from claim 26. Claim 27 additionally recites “the 3’ end of the first strand has an overhang.” (Exh. 1001 at Claim 27.) Claim 29 additionally recites “the 3’ end of the second strand has an overhang.” (*Id.* at Claim 29.) As discussed above, the Podbevsek molecule contains all the features of claim

26 and has an overhang on the 3' end of both strands. (Exh. 1002 at ¶¶389-90.)

Therefore, the Podbevsek molecule anticipates claims 27 and 29. (Exh. 1002 at ¶¶389-90.)

**X. CONCLUSION**

Petitioner requests that PGR be instituted for claims 1-30 of the '501 patent and that those claims be cancelled as unpatentable.

Dated: July 17, 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 16,576. 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: July 17, 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. 9,790,501 and  
EXHIBITS 1001-1090 were served on July 17, 2018 as follows:

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