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January 18, 2017

The Honorable Daniel R. Levinson  
U.S. Department of Health & Human Services  
Office of Inspector General  
330 Independence Avenue, SW  
Washington, DC 20201  
via email: Dan.Levinson@oig.hhs.gov

Dear Inspector General Levinson:

**RE: Allegation of Isis Pharmaceuticals Failure to Satisfy Disclosure Requirements for a Subject Invention Under the Bayh-Dole Act, 35 U.S.C. §§ 200 et seq.**

This letter requests that you investigate substantial evidence that Isis Pharmaceuticals (now known as Ionis Pharmaceuticals) and Cold Spring Harbor Laboratory failed to satisfy disclosure requirements under the Bayh-Dole Act, 35 U.S.C. §§ 200 et seq., and Federal regulations, 37 C.F.R. §§ 401.3(a) & 401.14, with regard to federally-funded subject inventions related to the composition and methods of use of nusinersen, an antisense oligonucleotide (ASO), for the treatment of spinal muscular atrophy (SMA), embodied in U.S. Patent Nos. 8,361,977 (hereinafter the "977 patent") and 8,980,853 (hereinafter the "853 patent").

We have a high degree of confidence that both the '977 patent and the '853 patent are subject inventions under the Bayh-Dole Act, in that they were "conceived or first actually reduced to practice in the performance of work under a funding agreement." 35 U.S.C. § 201(e).

Specifically, we present evidence that both inventions benefitted from the grant of funds from the National Institutes of Health (NIH) to support the research of Dr. Adrian R. Krainer at Cold Spring Harbor Laboratory, which was then used to file patents that have been assigned to Isis.

In addition, the National Institutes of Health (NIH) gave several grants to Isis, and those grants appear to have directly contributed to the reduction to practice of the patented inventions assigned to Isis.

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## I. About Us

Knowledge Ecology International (KEI) is a 501(c)(3) non-profit non-governmental organization based in Washington, D.C., that advocates for access to affordable medicines, with a focus on human rights and social justice.

KEI has conducted oversight of federal intellectual property policy as it relates to federally-funded inventions. Over the years, we have filed petitions and comments with various federal agencies, including the National Institutes of Health, in regards to the grant of intellectual property licenses and the use of federal authorities to end monopolies under the

Bayh-Dole Act. See, for example, our recent work on the exclusive licensing of federally owned inventions by the National Institutes of Health, <http://keionline.org/nih-licenses>. See also our petition to the National Institutes of Health and the U.S. Army to use march-in rights (35 U.S.C. § 203) or the government's royalty-free license in the patents (35 U.S.C. § 202(c)(4)) on the prostate cancer drug Xtandi as a mechanism to lower the excessive price of the drug in the United States, <http://keionline.org/xtandi>.

## **II. Spinal Muscular Atrophy (SMA) and Nusinersen (Spinraza)**

### *II.A. Spinal Muscular Atrophy Incidence, Presentation, and Genetics*

Spinal Muscular Atrophy (SMA) is a genetic neuromuscular disease that affects the nervous system, in particular control of muscle movement.<sup>1</sup> The disease results in muscle weakness and wasting, difficulty breathing, and paralysis.

SMA is the primary genetic cause of infant death.<sup>2</sup>

Current estimates for incidence range from 1 in 6,000 to 1 in 10,000 live births. Approximately 1 in 40 to 1 in 60 people carry the gene that contributes to the disorder. Because SMA is recessive, both parents must carry the gene in order for the disease to present.

Clinicians classify SMA “into four phenotypes on the basis of age of onset and motor function achieved.”<sup>3</sup>

The following table from D’Amico et al. shows the classifications:

**Table II.1: Classifications of Spinal Muscular Atrophy (SMA)**

	<b>Age of Onset</b>	<b>Highest function achieved</b>
Type I (Werdnig-Hoffmann disease)	0-6 months	Never sit
Type II (intermediate)	7-18 months	Sit never stand
Type III (mild, Kugelberg-Welander disease) in adulthood	> 18 months	Stand and Walk during adulthood
Type IV (adult)	2°-3° decade	Walk unaided

<sup>1</sup> This section draws upon Adele D’AMico et al., *Spinal Muscular Atrophy*, 6 Orphanet J. Rare Diseases 71 (2011), unless otherwise stated.

<sup>2</sup> Cure SMA, About SMA, <http://www.curesma.org/sma/about-sma/>.

<sup>3</sup> D’Amico, *Spinal Muscular Atrophy*.

The most common form of SMA is Type I, causing severe symptoms and death, as D'Amico *et al.* write:

SMA type 1 (Werdnig-Hoffmann disease) is the most severe and common type, which accounts for about 50% of patients diagnosed with SMA. Classically infants with SMA type I have onset of clinical signs before 6 months of age, never acquire the ability to sit unsupported and, if no intervention is provided, generally do not survive beyond the first 2 years. These patients have profound hypotonia, symmetrical flaccid paralysis, and often no head control. Spontaneous motility is generally poor and antigravity movements of limbs are not typically observed. In the most severe forms decreased intrauterine movements suggest prenatal onset of the disease and present with severe weakness and joint contractures at birth and has been labeled SMN 0. Some of these children may show also congenital bone fractures and extremely thin ribs. (Citations excluded.)

Everyone has two SMN genes, SMN1 and SMN2, to produce the SMN protein. In individuals with SMA, the SMN1 gene is defective and cannot be used to produce SMN protein. They must therefore rely solely on SMN2 gene to make the SMN protein. However, the SMN2 gene is not as efficient at making full length SMN protein and does not produce enough of the functional protein to make up for the loss of SMN1. This affects several cellular processes in motor neurons resulting in their degeneration, causing the muscles under their control begin to atrophy.<sup>4</sup>

### *II.B. Nusinersen (Spinraza) Mechanism of Action and Efficacy*

Nusinersen, marketed by Biogen under license from Ionis Pharmaceuticals as Spinraza, is the first treatment for pediatric and adult SMA approved for sale in the United States by the Food and Drug Administration.<sup>5</sup>

The FDA approved nusinersen as a New Drug Application under Priority Review. In addition, the FDA granted nusinersen Orphan Designation, which enabled Biogen to claim the 50-percent orphan drug tax credit on qualifying clinical trials, and affords Biogen seven years of marketing exclusivity from the date of approval of the NDA.<sup>6</sup>

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<sup>4</sup> Saif Ahmad et al., *Molecular Mechanisms of Neurodegeneration in Spinal Muscular Atrophy*, 10 J. Experimental Neurosci. 39 (2016).

<sup>5</sup> Biogen, *U.S. FDA Approves Biogen's SPINRAZA™ (nusinersen), The First Treatment for Spinal Muscular Atrophy*, Dec. 23, 2016, <http://media.biogen.com/press-release/neurodegenerative-diseases/us-fda-approves-biogens-spinraza-nusinersen-first-treatment>

<sup>6</sup> Nusinersen received orphan designation on April 18, 2011. See the FDA database of Orphan Drug Designations and Approvals, at <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=33671>. Both of the

The high price of nusinersen — \$750,000 for the first year of treatment and \$375,000 for every year thereafter — generated significant controversy, as reported in *FiercePharma*: “Regardless of how fair or reasonable Spinraza’s sticker might be in the ultra-orphan context, however, the outsize price tag was guaranteed to raise eyebrows, given the close scrutiny drug prices currently face.”<sup>7</sup>

As mentioned in the previous section, patients with SMA have a defective SMN1 gene, which leaves their body with an insufficient amount of the SMN protein and causes the death of motor neurons and muscular degeneration. Nusinersen acts on SMN2 unspliced mRNA transcripts and helps it make full length functional SMN protein, thus compensating for the malfunctioning SMN1 gene.

FDA approval of nusinersen was based on the interim results of a phase 3 double blind randomized clinical trial, ENDEAR (NCT02865109), and phase 3 open-label clinical trial, SHINE (NCT02594124).

ENDEAR enrolled 121 infants less than 7 months of age, and 82 were eligible for analysis at the time. According to the FDA label, the primary endpoint measured was “improvement in motor milestones according to Section 2 of the Hammersmith Infant Neurologic Exam (HINE).” The analysis demonstrated “statistically significant improvements in motor milestones, and the drug was generally well-tolerated, with a favorable safety profile and no significant adverse events.”<sup>8</sup>

The SHINE study, conducted in patients 30 days to 15 years, supported the ENDEAR results, such that, according to the FDA label, “some patients achieved milestones such as ability to sit unassisted, stand, or walk when they would otherwise be unexpected to do so, maintained milestones at ages when they would be expected to be lost, and survived to ages unexpected considering the number of SMN2 gene copies of patients enrolled in the studies.”

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phase III studies cited in the FDA label for nusinersen were conducted after the FDA granted orphan designation, making them eligible for the orphan drug tax credit.

<sup>7</sup> Tracy Staton, *Biogen's \$375K Spinraza Price Puts a Sovaldi-Style Spotlight on Rare Disease Meds*, FiercePharma, Jan. 3, 2017,

<http://www.fiercepharma.com/pharma/biogens-375k-spinraza-price-puts-a-sovaldi-style-spotlight-rare-disease-meds>.

<sup>8</sup> Carolina Henriques, *Regulatory Applications for SMA Therapy Nusinersen Accepted in US and EU*, SMA News Today, Nov. 1, 2016,

<https://smanewstoday.com/2016/11/01/regulatory-applications-sma-therapy-nusinersen-accepted-us-fda-eu-ema>.

### **III. The Bayh-Dole Act and Disclosure of Subject Inventions**

The Bayh-Dole Act and Federal regulations and guidelines make clear several obligations for contractors in the disclosure of government rights in subject inventions, including: (1) a requirement to disclose that federal funding contributed to an invention; (2) NIH contractual requirements for disclosure; and (3) required language to be inserted in patent applications and the patents, stating the role of federal funding and the government's rights.

First, contractors are required to disclose subject inventions discovered with federal funding in a timely manner and with sufficient detail to describe the invention.

Under 35 U.S.C. § 202(c)(1), any contractor that receives funding from the federal government is required to “disclose each subject invention to the Federal agency within a reasonable time after it becomes known to contractor personnel responsible for the administration of patent matters.”<sup>9</sup>

Under 37 C.F.R. § 401.3(a), each federal funding agreement shall contain the “standard patent rights clause” found at 37 C.F.R. § 401.14(a), barring specific circumstances and exceptions.<sup>10</sup> Subsection (c)(1) of the patent rights clause outlines the disclosure requirements, including a two month time limit on the disclosure of patents and a requirement that the disclosure have sufficient detail:<sup>11</sup>

#### **37 C.F.R. § 401.14(a)(c)(1)**

(c) Invention Disclosure, Election of Title and Filing of Patent Application by *Contractor*

(1) The *contractor* will disclose each subject invention to the *Federal Agency* within two months after the inventor discloses it in writing to *contractor* personnel responsible for patent matters. The disclosure to the *agency* shall be in the form of a written report and shall identify the contract under which the invention was made and the inventor(s). It shall be sufficiently complete in technical detail to convey a clear understanding to the extent known at the time of the disclosure, of the nature, purpose, operation, and the physical, chemical, biological or electrical characteristics of the invention. The disclosure shall also identify any publication, on sale or public use of the invention and whether a manuscript describing the invention has been submitted for publication and, if so, whether it has been accepted for publication at the time of disclosure. In addition, after disclosure to the *agency*,

<sup>9</sup> The statute defines a “subject invention” at 35 U.S.C. § 201(e) as “any invention of the contractor conceived or first actually reduced to practice in the performance of work under a funding agreement,” and defines a contractor at 35 U.S.C. § 201(c) as “any person, small business firm, or nonprofit organization that is party to a funding agreement.”

<sup>10</sup> The exceptions do not contain reference to the disclosure requirements.

<sup>11</sup> Italics in original.

the Contractor will promptly notify the agency of the acceptance of any manuscript describing the invention for publication or of any on sale or public use planned by the contractor.

...

(4) Requests for extension of the time for disclosure, election, and filing under subparagraphs (1), (2), and (3) may, at the discretion of the agency, be granted.

Second, in implementing this regulation, the National Institutes of Health requires contractors to disclose subject inventions via iEdison, an online electronic system for reporting inventions and patents discovered under federal grants, and via HHS Form 568, entitled, "Final Invention Statement and Certification (For Grant or Award)," available at:

<https://grants.nih.gov/grants/hhs568.pdf>.

The NIH specifies the required information on an FAQ related to the use of iEdison, and also notes that contractors should disclose the subject invention even if they have, in the past, failed to report the invention within the two month period:<sup>12</sup>

## **5. What information is required to report a subject invention?**

The invention disclosure must include the following information:

- Either the EIR Number, Invention Docket Number, or both.
- Invention Title
- Names of all of the inventors and the institutions with which they are associated
- Invention Report Date
- Description of the Invention that must meet the standards set forth per 37 CFR Sec. 401.14 (a)(c)(1):

**"... be sufficiently complete in technical detail to convey a clear understanding to the extent known at the time of the disclosure, of the nature, purpose, operation, and the physical, chemical, biological or electrical characteristics of the invention." 37 C.F.R. 401.14(a)(c)(1)"**
- Primary Funding Agency
- All funding agreement numbers and names of the funding agencies

<sup>12</sup> Available at: [https://era.nih.gov/iedison/iedison\\_faqs.cfm#VIII5](https://era.nih.gov/iedison/iedison_faqs.cfm#VIII5) (accessed Jan. 6, 2017).

- Any publication, on sale or public use of the invention and whether a manuscript describing the invention has been submitted for publication and, if so, whether it has been accepted for publication at the time of disclosure

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**9. If I upload a patent application, can that patent application satisfy the Invention Disclosure Report requirement?**

Yes, so long as the EIR Number or Invention Docket Number is included on the submission, the patent record containing the patent/patent application number has been reported in iEdison, and you upload proof that the patent application was filed with the USPTO, e.g., a USPTO submission receipt.

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**10. What should a grantee/contractor do if a subject invention hasn't been reported to the awarding agency within the required 2 month period?**

Always report the invention, even if it is late. The invention report date should be the date the inventor notified the awardee institution of the subject invention. Provide an explanation in the "Explanatory Notes" section of the invention record.

On February 17, 2016, NIH issued a notice entitled "Reminder: All Subject Inventions Must Be Reported on the HHS 568 - Final Invention Statement and Certification (For Grant or Award) and in iEdison." The notice explained that failure to disclose the subject invention via both iEdison and Form 568 could result in the loss of rights in the invention.<sup>13</sup> As explained below in section V on remedies, this notice is consistent with precedent related to failure to disclose.

Finally, under 35 U.S.C. § 202(c)(6) and 37 C.F.R. § 1.77(b)(3), contractors are required to state within the patent application that the federal government contributed funding to support the discovery of the invention and that the government retains certain rights:

**35 U.S.C. § 202(c)(6)**

(c) Each funding agreement with a small business firm or nonprofit organization shall contain appropriate provisions to effectuate the following:

...

(6) An obligation on the part of the contractor, in the event a United States patent application is filed by or on its behalf or by any assignee of the contractor, to include within the specification of such application and any patent issuing thereon, a statement specifying that the invention was made with Government support and that the Government has certain rights in the invention.

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<sup>13</sup> National Institutes of Health, Reminder: All Subject Inventions Must Be Reported on the HHS 568 - Final Invention Statement and Certification (For Grant or Award) and in iEdison, NOT-OD-16-066 (Feb. 17, 2016), NIH Guide Notice, <https://grants.nih.gov/grants/guide/notice-files/NOT-OD-16-066.html>

**35 C.F.R. § 1.77(b)(3)**

(b) The specification should include the following sections in order:

...

(3) Statement regarding federally sponsored research or development.

The Manual of Patent Examining Procedure contains the following recommended language:

“This invention was made with government support under (identify the contract) awarded by (identify the Federal agency). The government has certain rights in the invention.”<sup>14</sup>

#### **IV. The Nusinersen Patent Landscape and Failure to Disclose Government Rights in a Subject Invention**

This section will outline the patent landscape for nusinersen and explain the failure of Isis Pharmaceuticals to disclose federal funding in the work that contributed to the '977 and '853 patents, in violation of 35 U.S.C. § 202(c)(1).

Ionis claimed five United States patents as the “key … patents protecting nusinersen” in its 2015 Securities and Exchange Commission 10-K filing.<sup>15</sup>

**Table IV.1: Key United States Patents in Nusinersen**

Patent No.	Title	Priority Date	Filing Date	Expiration Date	Original Assignee
6,210,892	ALTERATION OF CELLULAR BEHAVIOR BY MODULATION OF mRNA PROCESSING	Oct. 7, 1998	Mar. 26, 1999	2018	Isis Pharmaceuticals, Inc.

<sup>14</sup> MPEP (9th ed. Rev. 07.2015, Nov. 2015), § 310.

<sup>15</sup> Ionis Pharm., Inc., Annual Report (Form 10-K), (Feb. 25, 2016). The Food and Drug Administration (FDA) approved nusinersen for the treatment of spinal muscular atrophy based upon New Drug Application No. 209531 on December 23, 2016. Drugs@FDA Database. Due to the recent approval date, the patents for nusinersen are not yet listed in the FDA *Approved Drug Products with Therapeutic Equivalence Evaluations*, known as the Orange Book.

7,838,657	SPINAL MUSCULAR ATROPHY (SMA) TREATMENT VIA TARGETING OF SMN2 SPLICE SITE INHIBITORY SEQUENCES	Dec. 3, 2004	Dec. 5, 2005	2027	University of Massachusetts
8,110,560	SPINAL MUSCULAR ATROPHY (SMA) TREATMENT VIA TARGETING OF SMN2 SPLICE SITE INHIBITORY SEQUENCES	Dec. 3, 2004	Aug. 21, 2009	2025	University of Massachusetts
8,361,977	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING	June 23, 2005	June 23, 2006	2030	Isis Pharmaceuticals, Inc.
8,980,853	COMPOSITIONS AND METHODS FOR MODULATION OF SMN2 SPLICING IN A SUBJECT	June 17, 2009	June 17, 2010	2030	Isis Pharmaceuticals, Inc.; Cold Spring Harbor Laboratory

We will not address the '892 patent, which is set to expire next year, nor will we address a European patent that is identical to the '977 patent (European Patent No. 1910395).

#### *IV.A. The University of Massachusetts Patents*

The patents owned by the University of Massachusetts describe the composition (U.S. Patent No. 7,838,657) and the method of use (8,110,560) of “oligonucleotide reagents (e.g., oligoribonucleotides) that effectively target the SMN2 ISS-N1 site in the SMN2 pre-mRNA, thereby modulating the splicing of SMN2 pre-mRNA to include exon 7 in the processed transcript.”

The laboratory of Dr. Ravindra N. Singh invented the '657 and '560 patents in the course of research on the “molecular basis of Spinal Muscular Atrophy.”<sup>16</sup>

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<sup>16</sup> Iowa State University, Ravindra N. Singh, Research Focus & Interests, <https://vetmed.iastate.edu/users/singhr>

The patents list Dr. Ravindra N. Singh, Dr. Natalia N. Singh, Dr. Nirmal K. Singh, and Dr. Elliot J. Androphy as inventors.

Both patents acknowledge federal funding from the National Institutes of Health in support of the work described in the patent, and also acknowledge the government's retained rights:

Funding for the work described herein was at least in part provided by the federal government (N.I.H. grant R01 NS40275). The government may, therefore, have certain rights in the invention.

The NIH awarded grant R01 NS40275 to Dr. Elliot J. Androphy, who at the time of the discovery of the invention directed the joint M.D./Ph.D. program at the University of Massachusetts Medical School.<sup>17</sup>

The University of Massachusetts licensed the patents to Isis Pharmaceuticals on January 14, 2010.<sup>18</sup>

KEI has requested additional information on the research and resulting intellectual property from the University of Massachusetts through a request under the Massachusetts Public Records Law, Mass. Gen. Laws ch. 66, §10 (2017).

#### *IV.B. The '977 and '853 Patents: Failure to Disclose Government Rights in the Patents*

The '977 and '853 Patents are, respectively, a compound patent and method of use patent for nusinersen as a treatment for SMA. We believe that Isis Pharmaceuticals and Cold Spring Harbor Laboratory failed to disclose that the inventions in the patents are subject inventions under the Bayh-Dole Act, as required by 35 U.S.C. § 202(c)(1).

The '977 patent is assigned to Isis Pharmaceuticals, and was invented by employees of Isis and Cold Spring Harbor Laboratory, a nonprofit research laboratory located on Long Island in New York. The inventor Brenda F. Baker was at the time of the patent application filing date employed by Isis, while Adrian R. Krainer was a Professor at Cold Spring Harbor Laboratory, and Yimin Hua was a Postdoctoral Fellow and later a Research Investigator at Cold Spring Harbor Laboratory. Before joining Cold Spring Harbor Laboratory in July 2004, Yimin Hua was a postdoctoral fellow at Tufts and the University of Massachusetts, studying SMA/SMN.<sup>19</sup>

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<sup>17</sup> See the NIH RePORTER database for additional information on the UMass grants:  
[https://projectreporternih.gov/Reporter\\_Vewsh.cfm?sl=12EBCD0F4888C4D37598B8961CAA4A01A2FFCEB861BF](https://projectreporternih.gov/Reporter_Vewsh.cfm?sl=12EBCD0F4888C4D37598B8961CAA4A01A2FFCEB861BF).

<sup>18</sup> UMass Agreement No: UMMS 05-19-03,  
[https://www.sec.gov/Archives/edgar/data/874015/000087401514000095/ex10\\_1.htm](https://www.sec.gov/Archives/edgar/data/874015/000087401514000095/ex10_1.htm)

<sup>19</sup> <https://www.linkedin.com/in/yimin-hua-6b583956>

The '853 patent is assigned to both Isis and Cold Spring, and lists amongst its inventors employees of Isis, Genzyme, and Cold Spring Harbor.<sup>20</sup>

- C. Frank Bennett — Isis Senior Vice President for Research
- Gene Hung — Isis
- Frank Rigo — Isis
- Adrian R. Krainer — Professor, Cold Spring Harbor Lab
- Yimin Hua — Postdoctoral Fellow and Research Investigator, Cold Spring Harbor Lab
- Marco A. Passini — Researcher, Genzyme
- Lamya Shihabuddin — Senior Director, Genzyme
- Seng H. Cheng — Group Vice President, Genetic Diseases Science, Genzyme
- Katherine W. Klinger — Senior Vice President, Genetics and Genomics, Genzyme

A news story published in October 2016 in *Nature Biotechnology* describes how the collaboration between Isis and Dr. Krainer of Cold Spring Harbor came about:

"The one-nucleotide change that causes SMN2 to skip an exon prevents a splicing activator from binding. Krainer began experimenting with a peptide designed to trigger the splicing of SMN2 exon 7 and its inclusion in the SMN2 pre-mRNA, thus creating a full-length, stable SMN2 protein. **He linked an antisense molecule to the peptide just to direct it to the correct region on SMN2, but to Krainer's surprise the antisense alone was able to correct the splicing defect, although not as potently.** "An important and lucky observation," says Krainer. "We didn't expect it, and we didn't initially understand it." Upon publication of the finding, Ionis contacted Krainer and began collaborating with him (*Nat. Struct. Biol.* 10, 120–125, 2003).

"Ionis brought its antisense technology to the table. The company's 2'-O-methoxyethyl (2'MOE) phosphorothioate chemistry, with sulfur substituting for one of the non-bridging oxygen atoms in the phosphate backbone, and chemical modification of the sugar at the 2' position, helps resist nuclease degradation and enhances cell penetration. It thus was an excellent *in vivo* splicing modifier. **Krainer and Isis screened over 500 different antisense molecules against various sites on SMN2 exon 7 and its adjacent introns. The best at splicing exon 7 into the SMN2 pre-mRNA was nusinersen, an 18-nucleotide antisense oligo that blocks the intronic binding site of a splicing repressor.** Because nusinersen binds a unique sequence, it shouldn't have off-target effects, says Krainer, and because the target is on an intron that's spliced out of the protein, the drug comes off and doesn't interfere with SMN2 translation. Blocking this single site is enough for the drug to achieve up to

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<sup>20</sup> All employments listed below indicate employment at the time that the patent application for the '853 patent was filed.

90% exon 7 inclusion in SMN2 transgenic mice (Am. J. Hum. Gen. 82, 834–848, 2008). Human trials began in 2011.”<sup>21</sup>

Dr. Krainer published his initial findings (the first finding described above in the Nature Biotechnology story, that we should target SMN2 to treat SMA) in 2003 in Nature Structural Biology with Dr. Luca Cartegni, then a Post-Doc at Cold Spring Harbor:

- Luca Cartegni and Adrian R. Krainer, *Correction of Disease-Associated Exon Skipping by Synthetic Exon-Specific Activators*, 10 Nature Structural Biology 120-125 (2003).

In the acknowledgements section, Dr. Cartegni and Dr. Krainer acknowledged support from the National Institutes of Health, without providing a particular grant number. Cartegni and Krainer, 125.

In 2008, Dr. Krainer and members of his lab co-authored a paper with C. Frank Bennett and Timothy A. Vickers of Isis Pharmaceuticals identifying the sequence for nusinersen:

- Yimin Hua, Timothy A. Vickers, Hazeem L. Okunola, C. Frank Bennett & Adrian R. Krainer, *Antisense Masking of an hnRNP A1/A2 Intronic Splicing Silence Corrects SMN2 Splicing in Transgenic Mice*, 82 Am. J. Human Genetics 834-848 (2008).

The acknowledgements in this paper also cited NIH funding, this time providing a particular grant number:

"We thank Chaolin Zhang for help with hnRNP A1 PWM analysis and Xavier Roca and Michelle Hastings for useful comments on the manuscript. We also thank A. Burghes for helpful discussions. Y.H. and A.R.K. gratefully acknowledge support for this work from the SMA Foundation, the Muscular Dystrophy Association, the Louis Morin Charitable Trust, and **National Institutes of Health grant GM42699**. T.A.V. and C.F.B. are employees of Isis Pharmaceutical, the owner of the antisense oligonucleotide chemistry used in this report, and materially benefit either directly or indirectly through stock options. Y.H. and A.R.K., along with their employer, Cold Spring Harbor Laboratory, could materially benefit if a therapeutic for SMA results from this work. A.R.K. serves on the scientific advisory board of two nonprofit SMA foundations.”<sup>22</sup>

The NIH RePORTER database shows that Dr. Krainer has received funding from the NIH under grant number GM42699 since at least 1993 (the earliest date in the database). Between 2006 and 2007 (the year in which the paper was submitted to the journal), Dr. Krainer received \$1,175,935 in funding under the grant. Over the course of the past 23 years,

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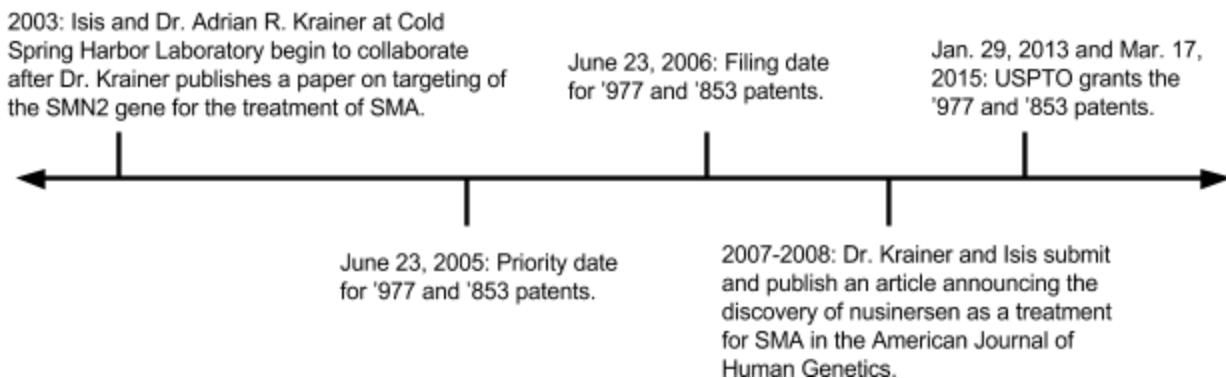
<sup>21</sup> Ken Garber, *Big Win Possible for Ionis/Biogen Antisense Drug in Muscular Atrophy*, 34 Nature Biotech. 1002, 100 (2016) (emphasis added).

<sup>22</sup> Hua et al., 846 (emphasis added).

Dr. Krainer has received \$11,701,483 in funding under this grant. See Appendix I for additional information on Dr. Krainer's grants.

We have a high degree of confidence that the Krainer grants contributed directly to the reduction of practice of nusinersen as a treatment for SMA because of the federal funding acknowledged in the paper and the overlap between the findings described in the paper and the patent.

#### Figure IV.1: Timeline of Publications , Collaborations, and Patent Filings/Grants



The above timeline of events shows that Isis and Dr. Krainer started their collaboration shortly after Dr. Krainer published his 2003 paper, which benefitted from public funding. The research that led to the discovery of nusinersen as a treatment for SMA, then, was conducted between 2003 and 2005 — the priority date listed on both the '977 and '853 patents. Shortly after the patent filing date of June 23, 2006, Isis and Dr. Krainer likely began work on drafting their paper, which was submitted in 2007 and accepted for publication in 2008. The paper, as stated previously, acknowledged that NIH funding contributed to the research to discover that nusinersen could be used as a treatment for SMA.

Dr. Krainer and colleagues identified the antisense oligonucleotide (ASO) that would best correct SMN2 splicing in their 2008 *American Journal of Human Genetics* publication:

"After elucidating the exact position and mechanism of the intron 7 ISS, we optimized the most potent ASOs that target this silencer and used them to try to rescue SMN2 splicing in mice harboring a human SMN2 transgene. First, we synthesized 38 ASOs of different lengths and examined their effects on splicing of transcripts of the endogenous SMN2 gene in HEK293 cells."<sup>23</sup>

<sup>23</sup> Yimin Hua, Timothy A. Vickers, Hazeem L. Okunola, C. Frank Bennett & Adrian R. Krainer, *Antisense Masking of an hnRNP A1/A2 Intronic Splicing Silencer Corrects SMN2 Splicing in Transgenic Mice*, 82 Am. J. Human Genetics 834, 842-3 (2008).

They found that ASO 10-27 and 09-23 were the best candidates for further testing in transgenic mice. Ultimately, the ASO 10-27 sequence was chosen for nusinersen.

ASO 10-27 is the same as the gene sequence for nusinersen as listed in the '977 and '853 patents.

The '853 patent claims the following:

1. A method comprising administering by a bolus injection into the intrathecal space of a subject with infantile-onset type I spinal muscular atrophy (SMA) an antisense compound comprising an antisense oligonucleotide consisting of 18 linked nucleosides, wherein the oligonucleotide has a nucleobase sequence consisting of the nucleobase sequence SEQ ID NO: 1, wherein each internucleoside linkage of the oligonucleotide is a phosphorothioate linkage, wherein each nucleoside of the oligonucleotide is a 2'-MOE nucleoside, and wherein the administering of the antisense compound ameliorates at least one symptom of SMA in the subject.
2. The method of claim 1, wherein the antisense compound is administered at a dose from 0.5 to 10 milligrams of antisense compound per kilogram of body weight of the subject.
3. The method of claim 1, wherein inclusion of exon 7 of SMN2 mRNA in a motoneuron in the subject is increased.
4. The method of claim 1, wherein a 5 mg to 20 mg dose of antisense is administered.

SEQ ID NO: 1, as described in claim 1, is the following: TCACCTTCATAATGCTGG.

The 2008 collaborative paper published by Cold Spring Harbor and Isis, which benefitted from federal funding, also identifies sequence number 1 in Table 1, as ASO 10-27:

Microwalk in Intron 7\*

08-25	5'-ACTTTCATAATGCTGGCA-3'	8 to 25
09-26	5'-CACTTTCATAATGCTGGC-3'	9 to 26
10-27	5'-TCACTTTCATAATGCTGG-3'	10 to 27
11-28	5'-TTCACTTTCATAATGCTG-3'	11 to 28
15-29	5'-ATTCACTTTCATAAT-3'	15 to 29
14-28	5'-TTCACTTTCATAATG-3'	14 to 28
13-27	5'-TCACTTTCATAATGC-3'	13 to 27
12-26	5'-CACTTCATAATGCT-3'	12 to 26
10-24	5'-CTTTCATAATGCTGG-3'	10 to 24
09-23	5'-TTTCATAATGCTGGC-3'	9 to 23
08-22	5'-TTCATAATGCTGGCA-3'	8 to 22
07-21	5'-TCATAATGCTGGCAG-3'	7 to 21
18-29	5'-ATTCACTTTCAT-3'	18 to 29
17-28	5'-TTCACTTTCATA-3'	17 to 28
16-27	5'-TCACTTTCATAA-3'	16 to 27
15-26	5'-CACTTCATAAT-3'	15 to 26
14-25	5'-ACTTTCATAATG-3'	14 to 25
13-24	5'-CTTTCATAATGC-3'	13 to 24
12-23	5'-TTTCATAATGCT-3'	12 to 23

The '853 patent makes the link explicit by citing the 2008 paper.

The '977 patent also relied on the research from the Cold Spring Harbor/Isis collaboration, similarly identifying the sequence in the first claim of the '853 patent.

#### *IV.B.1 Federal grants to ISIS Pharmaceuticals*

Isis has also received federal funding for its work on antisense-based drugs, which may have contributed to the research on the development of nusinersen.<sup>24</sup> For example, project number 1R43GM058974-01 describes the development of antisense oligonucleotides, with the following proposed commercial applications:

"Therapeutic antisense oligonucleotides are potentially a multibillion-dollar industry. Commercialization of antisense oligonucleotides against viral, cellular and cancer targets is limited by the pharmacokinetic and pharmacodynamic properties of existing first generation 2'-deoxy phosphorothioate drugs. RNA modifications which enhance target affinity and biostability can lead to antisense drugs of (i) shorter length (which translates to improved absorption and lower production cost), and (ii) less frequent dosing, and (iii) higher target specificity, and hence less toxicity."<sup>25</sup>

Overall, the NIH has provided Isis with at least \$17,509,977 in total funding since 1993. Between 2003 and 2006, the period that nusinersen was in development, Isis received \$10,821,633 in grants from DHHS, not including grants received from the US Army and

<sup>24</sup> See Appendix I for additional information on the Isis grants.

<sup>25</sup>

[https://projectreporternih.gov/project\\_info\\_description.cfm?aid=2792656&icde=32525907&ddparam=&ddvalue=&ddsub=&cr=25&csb=default&cs=ASC&pball=](https://projectreporternih.gov/project_info_description.cfm?aid=2792656&icde=32525907&ddparam=&ddvalue=&ddsub=&cr=25&csb=default&cs=ASC&pball=)

DARPA. In general, however, the NIH funding to Cold Spring Harbor Laboratory is the most direct and compelling evidence regarding the federal funding of the inventions.

## **V. Remedies**

In addition to investigating the above evidence related to the possibility that Isis failed to disclose subject inventions, the Office of the Inspector General should explore relevant remedies to rectify the alleged failure to disclose the subject inventions in the '977 and '853 patents.

In particular, failure to disclose subject inventions pursuant to 35 U.S.C. § 202(c)(1) permits the Federal Government to "receive title to any subject invention not disclosed to it within such time" (emphasis added).

In the past, the Federal Government has utilized its authority to claim title in subject inventions that have not been properly disclosed, as in the case of *Campbell Plastics Engineering & Mfg., Inc. v. Brownlee*, 389 F.3d 1243 (Fed. Cir. 2004) (finding that federal government claim of title in invention was legitimate under federal acquisition regulations and supported by the Bayh Dole Act where disclosure submissions were "piecemeal" and violated the contractual agreement with the government); see also *Central Admixture Pharmacy Services, Inc. v. Advanced Cardiac Solutions, P.C.*, 482 F.3d 1347, 1352-53 (Fed. Cir. 2007) ("Critically, *Campbell Plastics* holds that a Bayh–Dole violation grants the government *discretionary* authority to take title. . . . When a violation occurs, the government can choose to take action; thus, title to the patent may be voidable.").

In *Campbell Plastics*, the court found that the contract was clear and unambiguous, but moreover the government's claim to title was "buttressed by the policy considerations behind the Bayh Dole Act." *Id.* at 1248. These include, specifically under 35 U.S.C. § 200, the need "to ensure that the Government obtains sufficient rights in federally supported inventions to meet the needs of the Government and protect the public against nonuse or unreasonable use of inventions."

## **VI. Concluding Comments**

On behalf of patients, taxpayers, employers and everyone who pays for health care, we ask your office to investigate whether Isis and/or Cold Spring Harbor failed to comply with the provisions of the Bayh-Dole Act requiring the disclosure of federal funding in patents related to nusinersen.

We also ask your office to investigate whether the National Institutes of Health failed to conduct proper oversight in administering its grants.

Finally, we ask you to recommend appropriate action to remedy the situation in line with the statute and prior decisions with regard to failure to disclose a subject invention.

The failure to disclose federal funding in nusinersen is significant because it affects the disposition of the federal government's rights to end the patent monopoly and authorize generic manufacture under the march-in provisions and government royalty-free right in the Bayh-Dole Act.

KEI and other public interest groups have asked the government to use those rights to lower the excessive price of pharmaceuticals in the past. (See <http://keionline.org/xtandi>). We intend to ask the NIH to initiate a march-in case for the federally-funded patents on nusinersen over the excessive price (\$750,000 in the first year and \$375,000 per year thereafter for maintenance doses), and also to ask Medicare or other federal agencies to use their royalty free rights in the drug to authorize the manufacture and sale of generic versions of the drug at reasonable prices. We believe the Trump administration will take a different view than the Obama Administration on the issue of charging excessive prices on federally funded medical inventions.

We recognize that nusinersen benefits from non-patent exclusivities, including Orphan Drug exclusivity and exclusive rights in test data. However, Congress is likely to consider exceptions to such exclusivity in the coming years, and in any event, the patent term exceeds any non-patent exclusivities. Resolving access to the federally-funded inventions via march-in or the royalty free right provides the federal government with much greater leverage to lower the price of this treatment for a very severe disease.

We would like to meet with you and your staff to discuss how we can assist you in moving forward with an investigation.

Sincerely Yours,

James Love, Director  
Knowledge Ecology International

Andrew Goldman, Legal Counsel  
Knowledge Ecology International

Zack Struver, Research Associate  
Knowledge Ecology International

Diane Singhroy, Scientific Advisor  
Knowledge Ecology International

CC: Gary Cantrell, Deputy Inspector General for Investigations, [Gary.Cantrell@oig.hhs.gov](mailto:Gary.Cantrell@oig.hhs.gov)

## **Appendix I: Information on Misc Grants**

### ***1. Adrian R. Krainer/Cold Spring Harbor Laboratory Grant No. GM42699***

For additional information, see the following query results from the NIH RePORTER database:  
[https://projectreporter.nih.gov/Reporter\\_Viewsh.cfm?sl=12EBCD034889C4DF\\_7598B8961CA\\_A4A01A2FFCEB861BF](https://projectreporter.nih.gov/Reporter_Viewsh.cfm?sl=12EBCD034889C4DF_7598B8961CA_A4A01A2FFCEB861BF)

Dr. Krainer's grants for the project entitled "Biochemistry of Pre-mRNA Splicing" are administered by the National Institute of General Medical Sciences (NIGMS).

<b>Fiscal Year (FY)</b>	<b>FY Total Cost</b>
2016	\$746,014
2015	\$746,014
2014	\$734,358
2013	\$708,654
2012	\$728,529
2010	\$656,937
2009	\$638,359
2008	\$643,281
2007	\$620,984
2006	\$554,951
2005	\$551,995
2004	\$535,378
2003	\$517,746
2001	\$451,541
2000	\$438,566
1999	\$425,968
1998	\$418,728
1997	\$349,086
1996	\$335,762
1995	\$323,426
1994	\$312,002
1993	\$263,204

## 2. Isis Pharmaceuticals' Grants from RePORTER query

For additional information, see the following query results from the NIH RePORTER database:  
[https://projectreporter.nih.gov/Reporter\\_Viewsh.cfm?sl=12EBCC094B84C6D0\\_7598B8961CA\\_A4A01A2FFCEB861BF](https://projectreporter.nih.gov/Reporter_Viewsh.cfm?sl=12EBCC094B84C6D0_7598B8961CA_A4A01A2FFCEB861BF)

Isis Pharmaceuticals' grants are administered by various components of the National Institutes of Health, or the CDC, under several different grant numbers.

Project Title	IC	Project Number	Contact PI / Project Leader	FY	FY Total Cost
ANTISENSE INHIBITORS OF HERPES SIMPLEX VIRUS REPLICATION	NIAID	2R44AI030331-02	ANDERSON, KEVIN P	1993	\$193,250
OLIGONUCLEOTIDES AS INHIBITORS OF PAPILLOMAVIRUSES	NCI	2R44CA052391-02	COWSERT, LEX	1993	\$118,544
ANTISENSE INHIBITORS OF HERPES SIMPLEX VIRUS REPLICATION	NIAID	5R44AI030331-03	ANDERSON, KEVIN P	1994	\$223,920
5' CAP--A NOVEL TARGET FOR ANTISENSE TECHNOLOGY	NIAID	2R44AI030333-02A1	BAKER, BRENDA F	1994	\$242,708
SEQUENCE SPECIFIC SYNTHETIC mRNA CLEAVING AGENTS	NIGMS	1R41GM051646-01	BAKER, BRENDA F	1994	\$100,000
OLIGONUCLEOTIDES AS INHIBITORS OF PAPILLOMAVIRUSES	NCI	5R44CA052391-03	COWSERT, LEX M	1994	\$246,302
5' CAP--A NOVEL TARGET FOR ANTISENSE TECHNOLOGY	NIAID	5R44AI030333-03	BAKER, BRENDA F	1995	\$253,349
OLIGONUCLEOTIDES AS INHIBITORS OF PAPILLOMAVIRUSES	NCI	5R44CA052391-04	COWSERT, LEX M	1995	\$127,758
ANTISENSE INHIBITION OF MULTIDRUG RESISTANCE IN CANCER	NCI	1R41CA068790-01	DEAN, NICHOLAS M	1995	\$99,865
SYNTHESIS AND SELECTION OF PLA2 INHIBITORS	NIAMS	1R43AR043034-01A1	WYATT, JACQUELINE R	1995	\$99,732
UTILITY OF CARBOCYCLIC NUCLEOSIDES FOR ANTISENSE THERAPY	NCI	1R43CA074636-01	GRIFFEY, RICHARD H	1997	\$100,000

TARGETING AN ESSENTIAL METHYLASE IN PATHOGENIC BACTERIA	NIAID	1R41AI041775-01A1	BLYN, LAWRENCE B	1998	\$99,939
TARGETING RHO--A TRANSCRIPTION TERMINATION FACTOR	NIAID	1R43AI043102-01	BLYN, LAWRENCE B	1998	\$100,000
UTILITY OF CARBOCYCLIC NUCLEOSIDES FOR ANTISENSE THERAPY	NCI	3R43CA074636-01S1	GRIFFEY, RICHARD H	1998	\$90,000
L11/23S RNA INTERACTION--ANTIMICROBIAL DRUG DEVELOPMENT	NIAID	1R43AI045210-01	BLYN, LAWRENCE B	1999	\$100,000
DISRUPTION OF EUBACTERIAL 4.5S RNA -P48 COMPLEX	NIAID	1R43AI044544-01A1	GRIFFEY, RICHARD H	1999	\$100,000
TARGETING 4.5S RNA ANTIMICROBIAL DRUG DISCOVERY	NIAID	1R41AI044515-01	JAMES, THOMAS L	1999	\$100,000
ANTISENSE THERAPY USING NOVEL RNA MIMETICS	NIGMS	1R43GM058974-01	MANOHARAN, MUTHIAH	1999	\$140,000
OLIGONUCLEOTIDES FOR DIRECTED GENE KNOCKOUT	NIGMS	1R43GM060087-01	MANOHARAN, MUTHIAH	1999	\$224,700
ORAL ANTISENSE THERAPY FOR CANCER	NCI	1R41CA083543-01	MANOHARAN, MUTHIAH	2000	\$123,990
A NOVEL ANTICANCER STRATEGY	NCI	1R43CA083601-01A1	SAMPATH, RANGARAJAN	2000	\$100,000
COMBINATORIAL CARBOHYDRATE LIBRARIES FOR DRUG DISCOVERY	NIAID	1R41AI050406-01	GRIFFEY, RICHARD H	2001	\$100,000
ANTIMICROBIAL AGENTS DIRECTED AGAINST L11/23S RRNA	NIAID	2R44AI045210-02A1	SWAYZE, ERIC E	2001	\$265,000
ANTIMICROBIAL AGENTS DIRECTED AGAINST L11/23S RRNA	NIAID	5R44AI045210-03	SWAYZE, ERIC E	2002	\$375,000
AUTOMATED SIMULTANEOUS DETECTION OF BIOTERRORISM AGENTS	CID	1R01CI000099-01	ECKER, DAVID J	2003	\$2,629,242
AUTOMATED SIMULTANEOUS DETECTION OF BIOTERRORISM AGENTS	CID	5R01CI000099-02	ECKER, DAVID J	2004	\$2,313,198
SINGLE WELL MPCR DONOR SCREEN TO ID BLOOD PATHOGENS	NHLBI	1R43HL076946-01	RANKEN, RAYMOND	2004	\$94,040

PATHOGEN DIAGNOSTIC PRODUCTS--BIODEFENSE DEVELOPMENTS	NIAID	1UC1AI067232-01	BLYN, LAWRENCE B	2005	\$4,649,863
AUTOMATED SIMULTANEOUS DETECTION OF BIOTERRORISM AGENTS	CID	5R01CI000099-03	ECKER, DAVID J	2005	\$1,036,103
CHEMICAL MODIFICATION TO IMPROVE SIRNA PHARMACOKINETICS IN ANIMALS	NIGMS	1R43GM076793-01	SWAYZE, ERIC E	2006	\$99,187
IDENTIFICATION OF AN INHIBITOR OF MICRORNA-122 IN LIVER	NIAID	1R43AI072802-01	FREIER, SUSAN M.	2007	\$299,390
CHEMICAL MODIFICATIONS TO IMPROVE RNAI DRUGS	NIGMS	2R44GM076793-02	SWAYZE, ERIC E	2007	\$482,643
IDENTIFICATION OF AN INHIBITOR OF MICRORNA-122 IN LIVER	NIAID	5R43AI072802-02	FREIER, SUSAN M.	2008	\$132,885
CHEMICAL MODIFICATIONS TO IMPROVE RNAI DRUGS	NIGMS	5R44GM076793-03	SWAYZE, ERIC E	2008	\$464,156
ASSESSING THE SAFETY OF CELL SUBSTRATES AND VACCINE COMPONENTS	NIAID	N01AI40100-5-0-1	SAMPATH, RANGARAJAN	2009	\$621,848
CHEMICAL MODIFICATIONS TO IMPROVE RNAI DRUGS	NIGMS	5R44GM076793-04	SWAYZE, ERIC E	2009	\$463,365
ASSESSING THE SAFETY OF CELL SUBSTRATES AND VACCINE COMPONENTS	NIAID	N01AI40100-6-0-1	SAMPATH, RANGARAJAN	2010	\$500,000

### 3. Selected DoD Army and DARPA SBIR and STTR grants

Grant title	Agency	Type	Year	Amount
TIGER Biosensor for Broad Viral Detection and Genetically Engineered Microbes	DoD, Army	SBIR	2005	\$119,663
TIGER Biosensor for Broad Viral Detection and Genetically Engineered Microbes	DoD, Army	SBIR	2007	\$728,422
Cells as Hierarchical Dynamic Systems	DoD, DARPA	STTR	1999	\$99,000