UNITED STATES DISTRICT COURT
DISTRICT OF MASSACHUSETTS

ALNYLAM PHARMACEUTICALS, INC., a Delaware corporation, and ISIS PHARMACEUTICALS, INC., a Delaware corporation,	)	**C.A. NO.:**
Plaintiffs,	)	**COMPLAINT FOR PATENT INFRINGEMENT**
v.	)	
TEKMIRA PHARMACEUTICALS CORPORATION, a Canadian corporation,	)	**JURY TRIAL DEMANDED**
Defendant.	)	

THE PARTIES

1. Plaintiff Alnylam Pharmaceuticals, Inc. ("Alnylam") is a corporation existing under the laws of the State of Delaware with its principal place of business in Cambridge, Massachusetts.

2. Plaintiff Isis Pharmaceuticals, Inc. ("Isis") is a corporation existing under the laws of the State of Delaware with its principal place of business in Carlsbad, California.

3. On information and belief, defendant Tekmira Pharmaceuticals Corporation ("Tekmira") is a corporation existing under the laws of British Columbia, Canada, with its principal place of business in Burnaby, British Columbia.

JURISDICTION AND VENUE

4. This is an action for patent infringement arising under the patent laws of the United States (Title 35 of the United States Code) and arising from Tekmira's sale, offer to sell, use, or importation of the patented compositions and methods prior to the expiration of the patents-in-suit. The Court has subject matter jurisdiction over this action pursuant to 28 U.S.C. §§ 1331, 1338(a) and Section 2201.

5. This Court has personal jurisdiction over Tekmira by virtue of the fact that Tekmira conducts business in the State of Massachusetts, and has availed itself of the rights and benefits under Massachusetts law, including submitting to jurisdiction in the State of Massachusetts by filing a complaint in the Superior Court for the Commonwealth of Massachusetts at Suffolk, Civil Action No. 11-1010-BLS2, presently pending.

6. Venue is proper in this district pursuant to 28 U.S.C. §§ 1391(b) and 1400.

THE PATENTS-IN-SUIT

7. On April 13, 2010, United States Patent No. 7,695,902 (the "'902 Patent"), entitled "Oligoribonucleotides and Ribonucleases for Cleaving RNA," issued to Isis Pharmaceuticals, Inc., as assignee of the inventors. (A copy of the '902 Patent is attached as Exhibit 1.) Alnylam is the co-exclusive licensee of the '902 Patent by operation of an agreement with Isis, dated April 28, 2009.

8. On February 22, 2005, United States Patent No. 6,858,225 (the "'225 Patent"), entitled "Lipid-Encapsulated Polyanionic Nucleic Acid," issued to Inex Pharmaceuticals Corporation, as assignee of the inventors. (A copy of the '225 Patent is attached as Exhibit 2.) On information and belief, Tekmira is the successor-in-interest to Inex Pharmaceuticals Corporation's ownership rights in the '225 Patent.

9. On November 9, 2004, United States Patent No. 6,815,432 (the "'432 Patent"), entitled "Methods for Encapsulating Plasmids in Lipid Bilayers," issued to Inex Pharmaceuticals Corporation, as assignee of the inventors. (A copy of the '432 Patent is attached as Exhibit 3.) The Patent and Trademark Office records list the University of British Columbia and Tekmira as the recorded assignees of the '432 Patent.

10. On March 18, 2003, United State Patent No. 6,534,484 (the "'484 Patent"), entitled "Methods for Encapsulating Plasmids in Lipid Bilayers," issued to Inex Pharmaceuticals Corporation, as assignee of the inventors. (A copy of the '484 Patent is attached as Exhibit 4.) The Patent and Trademark Office records list the University of British Columbia and Tekmira as the recorded assignees of the '484 Patent.

11. On July 1, 2003, United States Patent No. 6,586,410 (the "'410 Patent"), entitled "Lipid-Nucleic Acid Particles Prepared Via Hydrophobic Lipid-Nucleic Acid Complex Intermediate and Use for Gene Transfer," issued to Inex Pharmaceuticals Corporation, as assignee of the inventors. (A copy of the '410 Patent is attached as Exhibit 5.) The Patent and Trademark Office records list the University of British Columbia and Tekmira as the recorded assignees of the '410 Patent.

12. On February 22, 2005, United States Patent No. 6,858,224 (the "'224 Patent"), entitled "Method of Preventing Aggregation of a Lipid: Nucleic Acid Complex," issued to Inex Pharmaceuticals Corporation, as assignee of the inventors. (A copy of the '224 Patent is attached as Exhibit 6.) The Patent and Trademark Office records list the University of British Columbia and Tekmira as the recorded assignees of the '224 Patent.

THE DRUG DISCOVERY AND DEVELOPMENT PROCESS

13. In the fields of medicine and biotechnology, drug discovery is the process by which drugs are designed and/or identified. The process of drug discovery involves target validation and drug candidate identification. During the target validation phase, pharmaceutical researchers test a hypothesis that, for example, the reduction of a given protein target will yield a biochemical change potentially relevant to the treatment of the disease. Candidate identification commences after a target has been validated in relevant disease models and often involves screening numbers of compounds for their biological activity. Once a compound has been identified through the foregoing process and shown to have the desired specific activity, it will enter the process of drug development.

14. Drug development refers to activities undertaken after a compound has been identified as a potential drug that seeks to establish its suitability as a medication. This process determines appropriate formulation and dosing, as well as establishes safety. Research in these areas generally includes a number of required *in vivo* studies and clinical trials in healthy volunteers to assess safety, and ultimately in patients to assess therapeutic value as a medication. Certain pre-clinical and clinical data generated during the drug discovery phase may ultimately

form the basis for a filing with the Food and Drug Administration (FDA) as part of the process of seeking regulatory approval to market the drug in the United States.

BACKGROUND ON siRNA TECHNOLOGY

15. Proteins are fundamental components of all living cells, and include many types of molecules necessary for carrying out cellular functions. The overproduction or abnormal production of proteins is implicated or associated with many diseases. Genes are DNA chemical entities within the nuclei of cells that hold the information necessary to make proteins. This information is converted into proteins in two steps called transcription and translation. At the transcription step, the genetic information for a given protein is copied to a molecule called messenger ribonucleic acid (mRNA). During translation, cellular machinery converts the information embodied in the mRNA into proteins.

16. Small interfering RNA (siRNA; also called short interfering RNA) is a class of short, double-stranded ribonucleic acid molecules (dsRNA) that can play a variety of roles in a cell. Most notably, siRNA interferes with the production (*i.e.*, expression) of a particular protein through what is known as the RNA interference (RNAi) pathway. This pathway causes a given mRNA to degrade, thereby inhibiting the cell's production of that particular protein. The effect of dsRNA on gene expression makes it a valuable research tool because synthetic dsRNA introduced into cells can be used to identify, and induce suppression of, specific genes of interest. Exploiting the RNAi pathway further promises the potential development of pharmaceutical products that comprise dsRNA compounds.

BACKGROUND ON ALNYLAM AND ISIS

17. Alnylam, based in Cambridge, Massachusetts, was founded in 2002 by leading medical researchers who made a breakthrough discovery in biology known as RNA interference, or RNAi. With RNAi technology, disease may be treated in a fundamentally new way by silencing disease-causing genes upstream of today's medicines. Since its founding, Alnylam has been a leader in the discovery and development of siRNA that can be used to "silence" disease-causing genes. Alnylam's focus is bringing RNAi technology to the clinic and to patients. In

furtherance of that goal, the company has established and enjoys many collaborations with other leaders in the field, including leading universities and major pharmaceutical companies.

18. Alnylam has made very significant strides in the development and advancement of RNAi therapeutics. Recent months represent a remarkable period of clinical accomplishments for Alnylam's pipeline efforts. During this period Alnylam has demonstrated RNAi proof of mechanism in biopsy samples from their liver cancer program, showed clear human proof of concept in patients with robust silencing of a disease gene in their transthyretin amyloidosis program, and documented first-ever clinical efficacy for RNAi therapeutics in their hypercholesterolemia program. Transthyretin amyloidosis is a condition characterized by the abnormal buildup of protein deposits in the body's organs and tissues, and most commonly affects the heart and nervous system. Hypercholesterolemia involves very high levels of cholesterol in the blood and raises a person's risk of developing heart disease. The progression of both conditions might be moderated or even reversed through the therapeutic use of Alnylam RNAi.

19. Isis is a Carlsbad, California-based company that employs nearly 350 people and Isis is the global leader in antisense drug discovery and development. Isis has expanded the reach of antisense drugs by addressing a wide range of diseases such as cancer, diabetes, cardiovascular disease, neurodegenerative disease and other diseases of genetic origin. Isis was founded in 1989 by antisense pioneer Stanley Crooke, M.D., Ph.D., and his colleagues. Since Isis' inception, the company has focused on studying how antisense mechanisms, including RNAi, work with the goal of translating this new knowledge into optimized antisense drug designs and methods of drug discovery. To this day, Dr. Crooke serves as Isis' Chief Executive Officer and actively leads a group of researchers looking to understand more fundamentally how antisense drugs work and how to further optimize them.

TEKMIRA AND ITS EXCLUSIVE LICENSES TO ALNYLAM

20. On information and belief, Tekmira is a biopharmaceutical company focused on RNAi therapeutics and lipid nanoparticle technology for nucleic acid delivery. On information

and belief, on or about July 1, 1998, the University of British Columbia (UBC) exclusively licensed to Tekmira's predecessor corporation, Inex Pharmaceuticals Corporation ("Inex"), certain patents and pending patent applications. By way of the original agreement and amendment thereto, Inex obtained an exclusive worldwide right to use and sublicense the licensed patents, patent applications, and the technology, and to manufacture, have made, distribute, import, use and sell products under said patents and patent applications. Inex further had the right to enforce the exclusively licensed patents and patent applications. Under the foregoing agreement and amendment thereto (and thus Tekmira as Inex's successor-in-interest thereto), UBC granted Inex all substantial rights in the foregoing '225, '432, '484, '410, and '224 Patents.

21. By way of a sublicense dated January 8, 2007 ("Sublicense Agreement"), Inex licensed to Alnylam the '225, '432, '484, '410, and '224 Patents to exclusively use, even as to Inex, and to sublicense such patents and technology, and to research, develop, manufacture, have made, distribute, import, use, sell and have sold products in the Alnylam Field. The Alnylam Field means the use of any product containing or comprising or based on small interfering RNAs or small interfering RNA derivatives, as defined in such Sublicense Agreement.

22. By way of a May 30, 2008, Amended and Restated License and Collaboration Agreement between Alnylam and Tekmira, Alnylam granted to Tekmira a narrow nonexclusive license under its exclusive sublicense from Tekmira for Tekmira to research, develop, manufacture and commercialize an RNAi containing or comprising product for up to three gene targets only. Tekmira has no licensed rights to use, sell, offer for sale, make or have made, or import any product under the foregoing patents exclusively licensed to Alnylam other than for use with identifying, developing and commercializing RNAi products to the three targets.

TEKMIRA'S ACTS OF INFRINGEMENT

23. On or about May 10, 2010, Tekmira issued a press release announcing that it had entered into a multi-year agreement with Bristol-Meyers Squibb (BMS) to provide BMS with siRNA molecules "formulated by Tekmira in stable nucleic acid-lipid particles (SNALP) to

silence gene targets of interest." (A true copy of the May 10, 2010, Press Release is attached hereto and incorporated herein as Exhibit 7.) The press release further described that the BMS Agreement provides BMS "with the opportunity to validate the function of certain cellular targets by using SNALP formulations supplied by Tekmira." As described in the Press Release, BMS paid an upfront fee of $3 million plus additional consideration. On or about May 17, 2011, in a press release, Tekmira announced an expansion of the BMS Agreement that included "additional cellular targets that were beyond the scope of the original agreement." (A true copy of the May 17, 2011, Press Release is attached hereto and incorporated herein as Exhibit 8.)

24. On information and belief, and confirming that a sale has occurred, Tekmira has recognized as revenue payments from BMS and used such revenue for Tekmira's commercial purposes.

25. On information and belief, BMS is a United States based company, incorporated under the laws of Delaware, and Tekmira's offer for sale and sale to BMS occurred in the United States. On information and belief, Tekmira infringed directly and indirectly the asserted patents by, *inter alia*, offering for sale and selling in the United States, and importing into the United States, dsRNA formulations comprising SNALP and methods for using such composition for BMS' use for target validation purposes. On information and belief, BMS has used such compositions and methods claimed in the asserted patents as a research tool for, *inter alia,* target validation purposes.

26. 35 U.S.C. § 271(e)(1) ("Section 271(e)(1)") defines a safe harbor against patent infringement:

> It shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention…solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products.

27. This provision entered title 35 in 1984 as part of the Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984) (the "1984 Act"). The House Committee that initiated this provision characterized its limits, noting that the "nature

of the interference with the rights of the patent holder" would not be substantial," but "*de minimus* [sic]." H.R. Rep. No. 857, reprinted in 1984 U.S.C.C.A.N. at 2692, 2714 (stating that "all that the generic can do is test the drug for purposes of submitting data to the FDA for approval. Thus, the nature of the interference is *de minimus* [sic].").

28. In 2005, the Supreme Court reaffirmed that not all drug discovery and research under the 1984 Act was subject to the Section 271(e)(1) clinical trial exemption, holding that the exemption may exist where "a drug-maker has a reasonable basis for believing that a patented compound may work, through a particular biological process, to produce a particular physiological effect, and uses the compound in research that, if successful, would be appropriate to include in a submission to the FDA, that use is 'reasonably-related' to the 'development and submission of information under . . . federal law.'" *Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 207 (2005) (quoting the text of Section 271(e)(1)). Moreover, the Federal Circuit has held that research tools used in drug discovery and development, and are not themselves the subject of regulatory approval, fall outside the protection of Section 271(e)(1). *Proveris Scientific Corp. v. Innovasystems, Inc.*, 536 F.3d 1256, 1265 (Fed. Cir. 2008).

29. On information and belief, Tekmira's activity as alleged in this Complaint is not exempt under Section 271(e)(1) because: (a) it constitutes an offer for sale, a sale, use and/or importation of a research tool or method of using a research tool that is not itself the subject of FDA approval; (b) it constitutes an offer for sale, a sale, use and/or importation of siRNA compositions and methods claimed in the asserted patents in discovery activity before the trained researcher formed a reasonable basis for believing that a specific compound may work through a particular biological process to produce the particular physiological effect of inhibiting the specified target; and/or (c) is a commercial offer for sale and/or sale that is not reasonably related to FDA approval, as further evidenced by Tekmira's recognition of revenue from BMS.

FIRST CAUSE OF ACTION
(By Isis and Alnylam)
(Infringement of the '902 Patent)

30. Plaintiffs reallege and incorporate by reference the allegations contained in paragraphs 1-29.

31. On information and belief, Tekmira has infringed the '902 Patent, pursuant to 35 U.S.C. § 271(a)-(c), by engaging in the commercial manufacture, use, offer to sell, sale, or importation of the patented methods prior to the expiration of the '902 Patent, or inducing or contributing to BMS' use of such methods.

32. Plaintiffs will be substantially and irreparably harmed if Tekmira is not enjoined from infringing the '902 Patent.

33. Tekmira's infringement is willful.

34. Plaintiffs have been injured by Tekmira's infringement.

35. This case is exceptional, and Plaintiffs are entitled to an award of attorneys' fees under 35 U.S.C. § 285

SECOND CAUSE OF ACTION
(By Alnylam)
(Infringement of the '225 Patent)

36. Alnylam realleges and incorporates by reference the allegations contained in paragraphs 1-29.

37. On information and belief, Tekmira has infringed the '225 Patent, pursuant to 35 U.S.C. § 271(a)-(c), by engaging in the commercial manufacture, use, offer to sell, sale, or importation of the '225 patented compositions prior to the expiration of the '225 Patent, or inducing or contributing to BMS' use of such compositions.

38. Alnylam will be substantially and irreparably harmed if Tekmira is not enjoined from infringing the '225 Patent.

39. Tekmira's infringement is willful.

40. Alnylam has been injured by Tekmira's infringement.

41. This case is exceptional, and Alnylam is entitled to an award of attorneys' fees under 35 U.S.C. § 285.

THIRD CAUSE OF ACTION
(By Alnylam)
(Infringement of the '432 Patent)

42. Alnylam realleges and incorporates by reference the allegations contained in paragraphs 1-29.

43. On information and belief, Tekmira has infringed the '432 Patent, pursuant to 35 U.S.C. § 271(a)-(c), by engaging in the commercial manufacture, use, offer to sell, sale, or importation of the '432 patented compositions prior to the expiration of the '432 Patent, or inducing or contributing to BMS' use of such compositions.

44. Alnylam will be substantially and irreparably harmed if Tekmira is not enjoined from infringing the '432 Patent.

45. Tekmira's infringement is willful.

46. Alnylam has been injured by Tekmira's infringement.

47. This case is exceptional, and Alnylam is entitled to an award of attorneys' fees under 35 U.S.C. § 285.

FOURTH CAUSE OF ACTION
(By Alnylam)
(Infringement of the '484 Patent)

48. Alnylam realleges and incorporates by reference the allegations contained in paragraphs 1-29.

49. On information and belief, Tekmira has infringed the '484 Patent, pursuant to 35 U.S.C. § 271(a)-(c), by engaging in the commercial manufacture, use, offer to sell, sale, or importation of the '484 patented compositions prior to the expiration of the '484 Patent, or inducing or contributing to BMS' use of such compositions.

50. Alnylam will be substantially and irreparably harmed if Tekmira is not enjoined from infringing the '484 Patent.

51. Tekmira's infringement is willful.

52. Alnylam has been injured by Tekmira's infringement.

53. This case is exceptional, and Alnylam is entitled to an award of attorneys' fees under 35 U.S.C. § 285.

FIFTH CAUSE OF ACTION
(By Alnylam)
(Infringement of the '410 Patent)

54. Alnylam realleges and incorporates by reference the allegations contained in paragraphs 1-29.

55. On information and belief, Tekmira has infringed the '410 Patent, pursuant to 35 U.S.C. § 271(a)-(c), by engaging in the commercial manufacture, use, offer to sell, sale, or importation of the '410 patented methods prior to the expiration of the '410 Patent, or inducing or contributing to BMS' use of such compositions.

56. Alnylam will be substantially and irreparably harmed if Tekmira is not enjoined from infringing the '410 Patent.

57. Tekmira's infringement is willful.

58. Alnylam has been injured by Tekmira's infringement.

59. This case is exceptional, and Alnylam is entitled to an award of attorneys' fees under 35 U.S.C. § 285.

SIXTH CAUSE OF ACTION
(By Alnylam)
(Infringement of the '224 Patent)

60. Alnylam realleges and incorporates by reference the allegations contained in paragraphs 1-29.

61. On information and belief, Tekmira has infringed the '224 Patent, pursuant to 35 U.S.C. § 271(a)-(c) & (g), by engaging in the commercial manufacture, use, offer to sell, sale, or importation of the '224 patented methods and products thereof prior to the expiration of the '224 Patent, or inducing or contributing to BMS' use of such methods and products.

62. Alnylam will be substantially and irreparably harmed if Tekmira is not enjoined from infringing the '224 Patent.

63. Tekmira's infringement is willful.

64. Alnylam has been injured by Tekmira's infringement.

65. This case is exceptional, and Alnylam is entitled to an award of attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for judgment against Defendant, Tekmira Pharmaceuticals Corporation, and respectfully request the following relief:

1. A judgment that the '225, '902, '432, '484, '410, and '224 Patents have been infringed by Tekmira;

2. A judgment for a permanent injunction enjoining Tekmira, its officers, agents, servants, employees, and those persons acting in active concert or participation with all or any of them from manufacturing, using, offering to sell, selling, or importing into the United States the patented products prior to the expiration of the '225, '902, '432 '484, '410, and '224 Patents, except as to such activities, if any, properly within the scope of 35 U.S.C. § 271(e)(1);

3. An award of damages together with interest, and a judgment that the damages so adjudged be trebled pursuant to 35 U.S.C. §§ 283 and 284;

4. A judgment that this is an exceptional case and that Plaintiffs be awarded their attorneys' fees incurred in this action pursuant to 35 U.S.C. § 285;

5. Costs and expenses in this action; and

6. Such other and further relief as the Court deems just and appropriate.

DEMAND FOR JURY TRIAL

In accordance with Rule 38 of the Federal Rules of Civil Procedure, Plaintiffs respectfully demand a jury trial of all issues triable to a jury in this action.

January 17, 2012

Respectfully submitted,

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AND ISIS PHARMACEUTICALS, INC.
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