

ALNYLAM PHARMACEUTICALS, INC.

Form 10-K

February 26, 2010

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**UNITED STATES SECURITIES AND EXCHANGE COMMISSION  
Washington, D.C. 20549**

**Form 10-K**

- ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES  
EXCHANGE ACT OF 1934**  
**For the fiscal year ended December 31, 2009**
- OR**
- TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES  
EXCHANGE ACT OF 1934**  
**For the transition period from        to**

**Commission File Number 000-50743**

**ALNYLAM PHARMACEUTICALS, INC.**  
*(Exact Name of Registrant as Specified in Its Charter)*

**Delaware**  
*(State or Other Jurisdiction of  
Incorporation or Organization)*

**77-0602661**  
*(I.R.S. Employer  
Identification No.)*

**300 Third Street, Cambridge, MA 02142**  
*(Address of Principal Executive Offices) (Zip Code)*  
**Registrant's telephone number, including area code: (617) 551-8200**  
**Securities registered pursuant to Section 12(b) of the Act:**

<b>Title of Each Class</b>	<b>Name of Each Exchange on Which Registered</b>
<b>Common Stock, \$0.01 par value per share</b>	<b>The Nasdaq Global Market</b>

**Securities registered pursuant to Section 12(g) of the Act: None**

Indicate by check mark if the registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes  No

Indicate by check mark if the registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes  No

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was

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required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes  No

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T (§ 232.405 of this chapter) during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). Yes  No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer  Accelerated filer  Non-accelerated filer  Smaller reporting company   
(Do not check if a smaller reporting company)

Indicate by check mark whether the registrant is a shell company (as defined in Rule 12b-2 of the Act). Yes  No

The aggregate market value of the voting Common Stock held by non-affiliates of the registrant, based on the last sale price of the registrant's Common Stock at the close of business on June 30, 2009, was \$916,012,936.

As of January 31, 2010, the registrant had 41,837,475 shares of Common Stock, \$0.01 par value per share, outstanding.

#### **DOCUMENTS INCORPORATED BY REFERENCE**

Portions of the registrant's definitive proxy statement for its 2010 annual meeting of stockholders, to be filed pursuant to Regulation 14A with the Securities and Exchange Commission not later than 120 days after the registrant's fiscal year end of December 31, 2009, are incorporated by reference into Part II, Item 5 and Part III of this Form 10-K.

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**ALNYLAM PHARMACEUTICALS, INC.  
ANNUAL REPORT ON FORM 10-K  
For the Year Ended December 31, 2009**

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*This annual report on Form 10-K contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended, and Section 21E of the Securities Exchange Act of 1934, as amended, that involve risks and uncertainties. All statements other than statements relating to historical matters should be considered forward-looking statements. When used in this report, the words believe, expect, anticipate, will, plan, target, and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these words. Our actual results could differ materially from those discussed in the forward-looking statements as a result of a number of important factors, including the factors discussed in this annual report on Form 10-K, including those discussed in Item 1A of this report under the heading Risk Factors, and the risks discussed in our other filings with the Securities and Exchange Commission. Readers are cautioned not to place undue reliance on these forward-looking statements, which reflect management's analysis, judgment, belief or expectation only as of the date hereof. We explicitly disclaim any obligation to update these forward-looking statements to reflect events or circumstances that arise after the date hereof.*

**PART I**

**ITEM 1. BUSINESS**

**Overview**

We are a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. RNAi is a naturally occurring biological pathway within cells for selectively silencing and regulating the expression of specific genes. Since many diseases are caused by the inappropriate activity of specific genes, the ability to silence genes selectively through RNAi could provide a new way to treat a wide range of human diseases. We believe that drugs that work through RNAi have the potential to become a broad new class of drugs, like small molecule, protein and antibody drugs. Using our intellectual property and the expertise we have built in RNAi, we are developing a set of biological and chemical methods and know-how that we apply in a systematic way to develop RNAi therapeutics for a variety of diseases.

We are applying our technological expertise to build a pipeline of RNAi therapeutics to address significant medical needs, many of which cannot effectively be addressed with small molecules or antibodies, the current major classes of drugs. We are working to develop RNAi therapeutics that are delivered directly to specific sites of disease, as well as RNAi therapeutics that are administered systemically through the bloodstream by intravenous, subcutaneous or intramuscular approaches. Our lead RNAi therapeutic program, ALN-RSV01, is in Phase II clinical trials for the treatment of human respiratory syncytial virus, or RSV, infection, which is reported to be the leading cause of hospitalization in infants in the United States and also occurs in the elderly and in immune compromised adults. In February 2008, we reported positive results from our Phase II experimental RSV infection clinical trial, referred to as the GEMINI study. In July 2009, we and Cubist Pharmaceuticals, Inc., or Cubist, reported results from a Phase IIa clinical trial assessing the safety and tolerability of aerosolized ALN-RSV01 versus placebo in adult lung transplant patients naturally infected with RSV. This study achieved its primary objective of demonstrating the safety and tolerability of ALN-RSV01. In February 2010, we initiated a multi-center, global, randomized, double-blind, placebo-controlled Phase IIb clinical trial to evaluate the clinical efficacy endpoints, as well as safety, of aerosolized ALN-RSV01 in adult lung transplant patients naturally infected with RSV. The objective of this Phase IIb study is to repeat and extend the clinical results observed in the Phase IIa study.

We have formed collaborations with Cubist and Kyowa Hakko Kirin Co., Ltd., or Kyowa Hakko Kirin, for the development and commercialization of RNAi products for RSV. We have an agreement to jointly develop and commercialize certain RNAi products for RSV with Cubist in North America. Cubist has responsibility for developing and commercializing any such products in the rest of the world outside of Asia, and Kyowa Hakko Kirin has the responsibility for developing and commercializing any RNAi products for RSV in Asia. In November 2009, we and

Cubist agreed that Alnylam would move forward with the development of ALN-RSV01, and together we would focus our collaboration and joint development efforts on ALN-RSV02, a second-generation compound, intended for use in pediatric patients. We and Cubist each bears one-half of the related development costs for ALN-RSV02. We are also continuing to develop ALN-RSV01 for adult transplant patients at our sole discretion and expense. Cubist has the right to resume the collaboration on ALN-RSV01 in the future, which right may be exercised for a specified period of time following the completion of our Phase IIb study, subject to the payment by

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Cubist of an opt-in fee representing reimbursement of an agreed upon percentage of certain of our development expenses for ALN-RSV01.

In March 2009, we initiated a Phase I study for ALN-VSP, our second clinical program and our first systemically delivered RNAi therapeutic candidate. We are developing ALN-VSP for the treatment of liver cancers, including hepatocellular carcinoma, or HCC, and other solid tumors with liver involvement. This Phase I study is a multi-center, open label, dose escalation study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous ALN-VSP in up to approximately 55 patients with advanced solid tumors with liver involvement, including HCC.

In December 2009, we filed regulatory applications to initiate a clinical trial for ALN-TTR01, our second systemically delivered RNAi therapeutic candidate. We are developing ALN-TTR, which targets the transthyretin, or TTR, gene, for the treatment of TTR-mediated amyloidosis, or ATTR. We plan to initiate a Phase I trial of ALN-TTR01 in ATTR patients in the first half of 2010. ALN-TTR01 employs a first generation lipid nanoparticle, or LNP, formulation. In parallel, we are also advancing ALN-TTR02 utilizing second-generation LNPs.

In January 2010, we announced that we expect ALN-PCS, a systemically delivered RNAi therapeutic candidate for the treatment of hypercholesterolemia, to be our next clinical candidate. ALN-PCS targets a gene called proprotein convertase subtilisin/kexin type 9, or PCSK9.

We are also working on a number of programs in pre-clinical development, including ALN-HTT, an RNAi therapeutic candidate targeting the huntingtin gene, for the treatment of Huntington's disease, which we are developing in collaboration with Medtronic, Inc., or Medtronic. We have additional discovery programs for RNAi therapeutics for the treatment of a broad range of diseases.

In addition, we are working internally and with third-party collaborators to develop capabilities to deliver our RNAi therapeutics directly to specific sites of disease, such as the delivery of ALN-RSV to the lungs. We are also working to extend our capabilities to advance the development of RNAi therapeutics that are administered systemically by intravenous, subcutaneous or intramuscular approaches. Over the past 12 to 18 months, we have made several of what we believe to be major advances relating to the delivery of RNAi therapeutics, both internally and together with our collaborators. We have numerous RNAi therapeutic delivery collaborations and intend to continue to collaborate with government, academic and corporate third parties to evaluate different delivery options.

We rely on the strength of our intellectual property portfolio relating to the development and commercialization of small interfering RNAs, or siRNAs, as therapeutics. This includes ownership of, or exclusive rights to, issued patents and pending patent applications claiming fundamental features of siRNAs and RNAi therapeutics as well as those claiming crucial chemical modifications and promising delivery technologies. We believe that no other company possesses a portfolio of such broad and exclusive rights to the patents and patent applications required for the commercialization of RNAi therapeutics. Given the importance of our intellectual property portfolio to our business operations, we intend to vigorously enforce our rights and defend against challenges that have arisen or may arise in this area.

In addition, our expertise in RNAi therapeutics and broad intellectual property estate have allowed us to form alliances with leading companies, including Isis Pharmaceuticals, Inc., or Isis, Medtronic, Novartis Pharma AG, or Novartis, Biogen Idec Inc., or Biogen Idec, F. Hoffmann-La Roche Ltd, or Roche, Takeda Pharmaceutical Company Limited, or Takeda, Kyowa Hakko Kirin and Cubist. We have also entered into contracts with government agencies, including the National Institute of Allergy and Infectious Diseases, or NIAID, a component of the National Institutes of Health, or NIH. We have established collaborations with and, in some instances, received funding from major medical and disease associations. Finally, to further enable the field and monetize our intellectual property rights, we



also grant licenses to biotechnology companies for the development and commercialization of RNAi therapeutics for specified targets in which we have no direct strategic interest under our InterfeRx™ program, and to research companies that commercialize RNAi reagents or services under our research product licenses.

We also seek opportunities to form new ventures in areas outside our core strategic focus. For example, during 2009, we presented new data regarding the application of RNAi technology to improve the manufacturing processes for biologics, which is comprised of recombinant proteins, monoclonal antibodies and vaccines. This initiative,

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which we are advancing in an internal effort referred to as Alnylam Biotherapeutics, has the potential to create new business opportunities. Additionally, during 2007, we and Isis established Regulus Therapeutics Inc., formerly Regulus Therapeutics LLC, or Regulus, a company focused on the discovery, development and commercialization of microRNA-based therapeutics. Because microRNAs are believed to regulate whole networks of genes that can be involved in discrete disease processes, microRNA-based therapeutics represent a possible new approach to target the pathways of human disease. Given the broad applications for RNAi technology, we believe additional opportunities exist for new ventures.

Below is a list of some of our key developments in 2009 and early 2010.

### **2009 and Early 2010 Key Developments**

#### ***Product Pipeline and Scientific Developments***

We advanced development of our ALN-RSV program focused on the treatment of RSV infection. We and Cubist presented complete data from a Phase IIa randomized, double-blind study of inhaled ALN-RSV01 or placebo in RSV-infected adult lung transplant patients. This study achieved its primary objective of demonstrating safety and tolerability of ALN-RSV01. In order to repeat and extend the Phase IIa results, we recently initiated a multi-center, global, randomized, double-blind, placebo-controlled Phase IIb study of ALN-RSV01 in RSV-infected adult lung transplant patients.

We initiated a Phase I multi-center, open label, dose escalation trial to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous ALN-VSP in patients with advanced solid tumors with liver involvement, including HCC. ALN-VSP is our first systemic RNAi program and represents our first clinical program in oncology.

We filed regulatory applications to initiate a clinical trial for our ALN-TTR program for ATTR. We expect to initiate a Phase I trial of ALN-TTR01 in ATTR patients in the first half of 2010. ALN-TTR01 is a systemically delivered RNAi therapeutic that employs first generation LNPs. In parallel, we are also advancing ALN-TTR02 utilizing second generation LNPs.

We continued to advance additional development and pre-clinical programs including ALN-PCS, an RNAi therapeutic targeting PCSK9 for the treatment of hypercholesterolemia. We expect that ALN-PCS will be our next clinical candidate. In addition, in collaboration with Medtronic, we continued to advance ALN-HTT, an RNAi therapeutic targeting the huntingtin gene for Huntington's disease.

We have made what we believe to be several major advances relating to the delivery of RNAi therapeutics. In collaboration with scientists at the Massachusetts Institute of Technology, or MIT, and, separately, in collaboration with scientists at AICana Technologies, Inc., or AICana, Tekmira Pharmaceuticals Corporation, or Tekmira, and The University of British Columbia, or UBC, we published on the discovery of novel lipids that enable formulation of second generation LNPs with markedly enhanced gene silencing potency, with *in vivo* effects achieved at doses as low as 0.01 mg/kg in rodents and non-human primates.

We formed new collaborations focused on the delivery of RNAi therapeutics. We formed a new research collaboration with scientists at UBC and AICana, in addition to Tekmira, focused on the discovery of novel cationic lipids for use in LNPs for the systemic delivery of RNAi therapeutics. We also established a new collaboration with Isis focused on the development of single-stranded RNAi, or ssRNAi, technology.

We launched Alnylam Biotherapeutics, which is an internal effort regarding the application of RNAi technology to improve the manufacturing processes for biologics. In particular, Alnylam Biotherapeutics is advancing RNAi technologies to improve the quantity and quality of biologics manufacturing processes using mammalian cell culture, such as Chinese hamster ovary, or CHO, cells. This RNAi technology potentially could be applied to the improvement of manufacturing processes for existing marketed drugs, new drugs in development and for the emerging biosimilars market.

During 2009, our scientists and scientists from Regulus demonstrated continued scientific leadership with the publication of 24 peer-reviewed scientific papers in some of the world's top journals.

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### ***Business Execution***

We formed a strategic collaboration with Cubist for the development and commercialization of our ALN-RSV program. Our collaboration with Cubist is a 50-50 co-development and profit share arrangement in North America, and a milestone- and royalty-bearing license arrangement in the rest of the world outside of Asia, where we collaborate on the ALN-RSV program with Kyowa Hakko Kirin. In November 2009, we and Cubist agreed that Alnylam would move forward with the development of ALN-RSV01 in adult transplant patient populations, and together we would focus our collaboration and joint development efforts on ALN-RSV02 in pediatric patients.

Novartis elected to extend our RNAi therapeutics collaboration for a fifth and final planned year, through October 2010, resulting in continued research and development funding to us.

We and Roche initiated the drug discovery phase of our 2007 alliance. In addition, we received a milestone payment from Roche related to the initiation of pre-investigational new drug application, or IND, studies for an RNAi therapeutic product candidate.

We and Isis continued our investment in Regulus with a \$20.0 million Series A preferred equity financing.

Regulus, of which we own 49%, formed a new collaboration with GlaxoSmithKline, or GSK, to develop and commercialize microRNA-based therapeutics targeting miR-122 in all fields, with hepatitis C virus, or HCV, infection, as the lead indication. This new collaboration includes the potential for Regulus to earn more than \$150.0 million in upfront and milestone payments, in addition to royalties, on worldwide sales of products, if any, as Regulus and GSK advance microRNA-based therapeutics targeting miR-122.

### ***Intellectual Property***

We advanced our intellectual property estate, receiving over 40 new patents worldwide during 2009.

We joined GSK in donating intellectual property to a patent pool for neglected tropical diseases.

We joined the Max Planck Society in taking legal action toward the Whitehead Institute for Biomedical Research, or Whitehead. Also named in the suit are MIT and the Board of Trustees of the University of Massachusetts, or UMass. The complaint alleges that Whitehead has breached its contractual obligations to Max Planck and us in the manner in which it is prosecuting the so-called Tuschl I patent applications and in its fiduciary duty to all of the co-owners of the Tuschl I patent series.

### ***RNA Interference***

RNAi is a natural biological pathway that occurs within cells and can be harnessed to selectively silence the activity of specific genes. The discovery of RNAi first occurred in plants and worms in 1998, and two of the scientists who made this discovery, Dr. Andrew Fire and Dr. Craig Mello, received the 2006 Nobel Prize for Physiology or Medicine.

### ***Opportunity for Therapeutics Based on RNAi***

Beginning in 1999, our scientific founders described and provided evidence that the RNAi mechanism occurs in mammalian cells and that its immediate trigger is a type of molecule known as a small interfering RNA, or siRNA. They showed that laboratory-synthesized siRNAs could be introduced into the cell and suppress production of specific

target proteins by cleaving and degrading the messenger RNA, or mRNA, of the specific gene that encodes that specific protein. Because it is possible to design and synthesize siRNAs specific to any gene of interest, the entire human genome is accessible to RNAi, and we therefore believe that RNAi therapeutics have the potential to become a broad new class of drugs.

In May 2001, one of our scientific founders, Thomas Tuschl, Ph.D., published the first scientific paper demonstrating that siRNAs can be synthesized in the laboratory using chemical or biochemical methods and when introduced, or delivered, into mammalian cells can silence the activity of a specific gene. Since the Tuschl publication, the use of siRNAs has been broadly adopted by academic and industrial researchers for the

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fundamental study of the function of genes. This has resulted in a significant number of publications focused on the use of RNAi and has made the 2001 paper one of the most cited papers in basic biologic research. Reflecting this, siRNAs are a growing segment of the market for research reagents and related products and services.

Beyond its use as a basic research tool, we believe that RNAi can form the basis of a completely new class of drugs for the treatment of disease. Drugs based on the RNAi mechanism could offer numerous opportunities and benefits, which may include:

**Ability to target proteins that cannot be targeted effectively by existing drug classes.** Over the last decade, the understanding of human disease has advanced enormously and many proteins have been identified that play fundamental roles in human disease. Paradoxically, greater than 80% of these key proteins cannot be targeted effectively with existing drug approaches like small molecules or proteins such as monoclonal antibodies. These so called undruggable targets are potentially accessible to siRNAs as they are made by mRNAs that can be targeted with RNAi.

**Ability to treat a broad range of diseases.** The ability to make siRNAs that target virtually any gene to suppress the production of virtually any protein whose presence or activity causes disease suggests a broad potential for application in a wide range of diseases.

**Inherently potent mechanism of action.** We expect the inherent catalytic nature of the RNAi mechanism to allow for a high degree of potency and durability of effect for RNAi-based therapeutics, which we believe distinguishes RNAi from other approaches.

**Simplified discovery of product candidates.** In contrast to the often arduous and slow drug discovery process for proteins and small molecules, the identification of siRNA product candidates has been, and we expect will continue to be, much simpler, quicker and less costly because it involves relatively standard processes that are directed by the known gene target sequences and can be applied in a similar fashion to many successive product candidates.

We have reported on our advances in developing siRNAs as potential drugs in a large number of peer-reviewed publications and meetings, including publications by Alnylam scientists in the journals *Nature*, *Cell*, *Nature Medicine*, *Nature Biotechnology* and *Proceedings of the National Academy of Sciences*, or *PNAS*.

## **Our Product Platform**

Our product platform provides a capability for a systematic approach to identifying RNAi therapeutic candidates through sequence selection, potency selection, stabilization by chemical modification, improvement of biodistribution and cellular uptake by various chemical conjugates and formulations. Key to the therapeutic application of siRNAs is the ability to successfully deliver siRNAs to target tissues and achieve cellular uptake of the siRNA into the inside of the cell where the RNAi machinery, called RNA-induced silencing complex, or RISC, is active. In some tissues, including the lung and central nervous system, the direct RNAi delivery approach, which employs the direct or local application of siRNAs, achieves cellular uptake and gene knockdown. For other tissues, such as the liver, systemic RNAi delivery has been employed, where tissue access comes via intravenous or subcutaneous injection of the siRNA into the bloodstream and where cellular uptake can be achieved by the conjugation of the siRNA with other molecules, such as small chemical groups, or by formulation with other biomaterials, such as LNPs. siRNA delivery is a key focus for our internal research team and is also the focus of numerous current government, academic and corporate collaborations. We have demonstrated RNAi therapeutic activity towards multiple genes, in multiple organs and in multiple species, including humans, as demonstrated by our results in the GEMINI trial for ALN-RSV01.

We believe that we have made considerable progress in developing our product platform, as documented in several recent publications. Over the past 12 to 18 months, we have made several of what we believe to be major advances relating to the delivery of RNAi therapeutics, both internally and together with our collaborators. The first relates to the discovery of new LNP compositions that provide dramatic improvements in the potency of gene silencing as compared to first generation LNPs. Additionally, we believe we have discovered an important *in vivo* mechanism for delivery relating to the role of endogenous apolipoprotein E, or ApoE, a plasma protein involved in lipoprotein metabolism, in the delivery of certain LNPs into the cytoplasm of certain cells. The latter discovery has

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allowed the specific targeting of LNPs and allows the possibility of delivery beyond the liver. We discuss these advances and our overall delivery efforts in more detail below in the section entitled Delivery Initiatives. With the progress we have made to date and expect to make in the future, we believe we will be well positioned to pursue multiple therapeutic opportunities.

Our progress has enabled us to advance a number of development programs for RNAi therapeutics that are administered directly to diseased tissues, including ALN-RSV01 and ALN-HTT. Our progress in achieving delivery of RNAi therapeutics through systemic RNAi was demonstrated by the advancement in early 2009 of our first systemically delivered RNAi therapeutic candidate ALN-VSP, for the treatment of liver cancers, to the clinic, and the filing of regulatory applications in December 2009 to initiate a clinical trial for ALN-TTR01, our second systemically delivered RNAi therapeutic candidate, for the treatment of ATTR. ALN-VSP and ALN-TTR01 both utilize a first generation LNP formulation known as stable nucleic acid-lipid particles, or SNALP, developed in collaboration with Tekmira. In parallel with ALN-TTR01, we are also advancing ALN-TTR02 utilizing the newer second-generation LNPs. In addition, we have published pre-clinical results from development programs for other systemically delivered RNAi therapeutic candidates, including ALN-PCS, for the treatment of hypercholesterolemia, which we recently identified as our next clinical candidate. ALN-PCS is being advanced using second-generation LNPs for systemic delivery. We recognize, however, that challenges remain with respect to the development of RNAi-based therapeutics, including achieving effective delivery of siRNAs to target cells and tissues, and we therefore regard further development of our product platform as an ongoing priority.

## **Our Product Pipeline**

The following is a summary of our development programs as of January 31, 2010:

Our most advanced program is focused on the treatment of RSV, a virus that infects the respiratory tract. In January 2008, we completed our GEMINI study, a Phase II clinical trial designed to evaluate the safety, tolerability and anti-viral activity of ALN-RSV01 in adult subjects experimentally infected with RSV. In July 2009, we and Cubist reported results from a Phase IIa clinical trial assessing the safety and tolerability of aerosolized ALN-RSV01 versus placebo in adult lung transplant patients naturally infected with RSV. This study achieved its primary objective of demonstrating the safety and tolerability of ALN-RSV01. In February 2010, we initiated a multi-center, global, randomized, double-blind, placebo-controlled Phase IIb clinical trial to evaluate the clinical efficacy endpoints as well as safety of aerosolized ALN-RSV01 in adult lung transplant patients naturally infected with RSV. The objective of this Phase IIb study is to repeat and extend the clinical results observed in the Phase IIa study.

We have formed collaborations with Cubist and Kyowa Hakko Kirin for the development and commercialization of RNAi products for RSV. We have an agreement to jointly develop and commercialize certain RNAi products for RSV with Cubist in North America. Cubist has responsibility for developing and



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commercializing any such products in the rest of the world outside of Asia, and Kyowa Hakko Kirin has the responsibility for developing and commercializing any RNAi products for RSV in Asia. In November 2009, we and Cubist agreed that Alnylam would move forward with the development of ALN-RSV01, and together we would focus our collaboration and joint development efforts on ALN-RSV02, a second-generation compound, intended for use in pediatric patients. We and Cubist each bears one-half of the related development costs for ALN-RSV02. We are also continuing to develop ALN-RSV01 for adult transplant patients at our sole discretion and expense. Cubist has the right to resume the collaboration on ALN-RSV01 in the future, which right may be exercised for a specified period of time following the completion of our Phase IIb trial, subject to the payment by Cubist of an opt-in fee representing reimbursement of an agreed upon percentage of certain of our development expenses for ALN-RSV01.

In March 2009, we initiated a Phase I study for ALN-VSP, our second clinical program and our first systemically delivered RNAi therapeutic candidate. We are developing ALN-VSP for the treatment of liver cancers, including HCC, and other solid tumors with liver involvement. This Phase I study is a multi-center, open label, dose escalation study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous ALN-VSP in up to approximately 55 patients with advanced solid tumors with liver involvement, including HCC.

In December 2009, we filed regulatory applications to initiate a clinical trial for ALN-TTR01, our second systemically delivered RNAi therapeutic candidate. We are developing ALN-TTR, which targets the TTR gene, for the treatment of ATTR. ALN-TTR targets wild-type and all mutant forms of TTR, and therefore is a potential therapeutic for the treatment of all forms of ATTR, including familial amyloidotic polyneuropathy, or FAP, and familial amyloidotic cardiomyopathy, or FAC. We plan to initiate a Phase I trial of ALN-TTR01 in ATTR patients in the first half of 2010. ALN-TTR01 employs a first generation LNP formulation. In parallel, we are also advancing ALN-TTR02 utilizing second-generation LNPs.

In January 2010, we announced that we expect ALN-PCS, a systemically delivered RNAi therapeutic candidate for the treatment of hypercholesterolemia, to be our next clinical candidate. ALN-PCS targets a gene called PCSK9. We are also working on a number of programs in pre-clinical development, including ALN-HTT, an RNAi therapeutic candidate for the treatment of Huntington's disease, which we are developing jointly with Medtronic. We have additional discovery programs for RNAi therapeutics for the treatment of a broad range of diseases.

We have spent substantial funds over the past three years to develop our product pipeline and expect to continue to do so in the future. We incurred research and development costs of \$108.7 million in 2009, \$96.9 million in 2008 and \$120.7 million in 2007. Research and development costs in 2007 included \$27.5 million in license fees paid to certain entities, primarily Isis, in connection with our alliance with Roche.

## **Development Programs**

### ***Respiratory Syncytial Virus (RSV) Infection***

**Market Opportunity.** RSV is a highly contagious virus that causes infections in both the upper and lower respiratory tract. RSV infects nearly every child by the age of two years and is responsible for a significant percentage of hospitalizations of infants, children with lung or congenital heart disease, the elderly and adults with immune-compromised systems, including lung transplant recipients. RSV infection typically results in cold-like symptoms, but can lead to more serious respiratory illnesses such as croup, pneumonia and bronchiolitis, and in extreme cases, severe illness and death. According to NIH, up to 125,000 children are hospitalized each year due to RSV infection. A study published in the *New England Journal of Medicine* estimates that over 170,000 elderly adults are hospitalized with RSV each year. In addition, experts estimate that the overall prevalence of lung transplants in the United States is between 8,000 to 10,000. The annual incidence of RSV infection in lung transplant patients can be up to ten percent.

**Current Treatments.** The only product currently approved for the treatment of RSV infection is Ribavirin, which is marketed as Virazole® by Valeant Pharmaceuticals International, or Valeant. However, this product is approved only for treatment of hospitalized infants and young children with severe lower respiratory tract infections

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due to RSV. Moreover, administration of the drug is complicated and requires elaborate environmental reclamation devices because of potential harmful effects on healthcare personnel exposed to the drug.

Two other products, a monoclonal antibody known as Synagis® and an immune globulin called RespiGam™, have been approved for the *prevention* of severe lower respiratory tract disease caused by RSV in infants at high risk of such disease. Neither of these products is approved for *treatment* of an existing RSV infection.

**Alnylam Program.** In June 2007, we initiated the GEMINI study, a double-blind, placebo-controlled, randomized Phase II trial designed to evaluate the safety, tolerability and anti-viral activity of ALN-RSV01 in adult subjects experimentally infected with RSV. In total, 88 subjects were randomized one-to-one to receive either ALN-RSV01 or placebo treatment prior to and after experimental infection with a wild-type clinical strain of RSV. In February 2008, we reported positive results from the GEMINI study. ALN-RSV01 was found to be safe and well tolerated and demonstrated statistically significant anti-viral activity, including an approximate 40% reduction in viral infection rate and a 95% increase in infection-free patients ( $p < 0.01$ ), as compared to placebo.

In July 2009, we and Cubist reported results from a Phase IIa clinical trial assessing the safety and tolerability of aerosolized ALN-RSV01 versus placebo in adult lung transplant patients naturally infected with RSV. In total, 24 patients confirmed with RSV infection were randomized two-to-one to receive inhaled ALN-RSV01 or placebo once daily for three consecutive days. The study achieved its primary objective of demonstrating the safety and tolerability of ALN-RSV01. In particular, there were no drug-related serious adverse events or discontinuations, and there were no clinically significant differences in the overall adverse event profile between ALN-RSV01 and placebo. Importantly, there was no evidence of disease exacerbation related to ALN-RSV01 treatment. At the 90-day endpoint, all patients survived and the incidence of intubation, new respiratory infection, or acute rejection was comparable across ALN-RSV01 and placebo groups. In addition, 90-day clinical data were collected. The study was not powered to demonstrate clinical outcomes due to the small sample size and, accordingly, such data were therefore considered exploratory. Prospectively defined clinical secondary endpoints at 90 days included recovery of lung function (forced expiratory volume in the first second, or FEV<sub>1</sub>) as measured by spirometry and clinical determination of new or progressive bronchiolitis obliterans syndrome, or BOS. Based on the data from this small study, ALN-RSV01 treatment was associated with a statistically significant decrease in the total incidence of new or progressive BOS at 90 days compared to placebo ( $p = 0.02$ ) with 50% of placebo patients showing new or progressive BOS as compared with only 7.1% of ALN-RSV01-treated patients. Despite the small patient numbers, we believe that these data may be important since the incidence of BOS following RSV infection in lung transplant patients can be a predictor of graft failure and overall survival. The incidence of BOS in lung transplant patients infected with RSV results in approximately 50% mortality within three to five years of onset.

In February 2010, we initiated a multi-center, global, randomized, double-blind, placebo-controlled Phase IIb clinical trial to evaluate the clinical efficacy endpoints as well as safety of aerosolized ALN-RSV01 in adult lung transplant patients naturally infected with RSV. The objective of this Phase IIb study is to repeat and extend the clinical results observed in the Phase IIa study described above. This study is expected to enroll 76 adult lung transplant patients who will be randomized in a one-to-one drug to placebo ratio. The primary endpoint is reduction in the incidence of new or progressive BOS.

Prior to the GEMINI and Phase IIa studies, ALN-RSV01 was shown in pre-clinical testing to be effective in both preventing and treating RSV infection in mice when administered intranasally. ALN-RSV01 also showed no significant toxicities in animal toxicology studies performed to enable the filing of an IND. We submitted an IND for ALN-RSV01 to the United States Food and Drug Administration, or FDA, in November 2005, and have completed a number of Phase I clinical trials in both the United States and Europe. In these Phase I trials, ALN-RSV01 was found to be generally safe and well tolerated when administered by single or repeat administration at doses up to 150 milligrams intranasally or at doses up to 0.6 milligrams per kilogram by nebulizer. The results of our completed

ALN-RSV01 clinical trials have been presented at medical conferences. We also have an active program to identify second-generation RNAi-based RSV inhibitors, and have identified several candidates in pre-clinical studies. As discussed below, we and Cubist are focusing our collaboration and joint development efforts on ALN-RSV02, a second generation compound, intended for use in pediatric patients.

We have formed collaborations with Cubist and Kyowa Hakko Kirin for the development and commercialization of RNAi products for RSV. We have an agreement to jointly develop and commercialize

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certain RNAi products for RSV with Cubist in North America. Cubist has responsibility for developing and commercializing any such products in the rest of the world outside of Asia, and Kyowa Hakko Kirin has the responsibility for developing and commercializing any RNAi products for RSV in Asia. In November 2009, we and Cubist agreed that Alnylam would move forward with the development of ALN-RSV01, and together we would focus our collaboration and joint development efforts on ALN-RSV02, a second-generation compound, intended for use in pediatric patients. We and Cubist each bears one-half of the related development costs for ALN-RSV02. As described above, we are also continuing to develop ALN-RSV01 for adult transplant patients at our sole discretion and expense and have recently initiated a Phase IIB study. Cubist has the right to resume the collaboration on ALN-RSV01 in the future, which right may be exercised for a specified period of time following the completion of our Phase IIB trial, subject to the payment by Cubist of an opt-in fee representing reimbursement of an agreed upon percentage of certain of our development expenses for ALN-RSV01.

***Liver Cancer***

**Market Opportunity.** An estimated 700,000 patients worldwide are diagnosed with primary liver cancer each year. HCC is the most common form of liver cancer and is responsible for about 90% of primary malignant liver tumors in adults. HCC is the sixth most common cancer in the world and the third leading cause of cancer-related deaths globally. In addition to primary liver cancer patients, in whom the disease starts in the liver, another 500,000 patients are identified each year with secondary liver cancer, whereby the primary tumor of another tissue, such as colorectal, stomach, pancreatic, breast, lung or skin, has metastasized to the liver.

**Current Treatments.** The treatment options for liver cancer are dependent on the stage of disease, site of tumor and condition of the patient, but can include surgical resection, radiation, chemotherapy, chemoembolism, liver transplantation and various combinations of these approaches. In November 2007, the FDA approved Sorafenib, also called Nexavar<sup>®</sup>, for the treatment of un-resectable liver cancer. Even with relatively early diagnosis and resection, the prognosis remains very poor for liver cancer patients, who are often diagnosed late in their clinical course of disease. For primary liver cancer, with early diagnosis and a resectable tumor, the five-year disease free survival rate has been reported at approximately 20%. However, this applies only to about 15% of primary liver cancer patients. For most primary liver cancer patients, the disease is fatal within three to six months. The prognosis for secondary liver cancer is generally also very poor, due often to the late stage of the disease at the time of diagnosis and metastatic nature of the neoplasm. For example, in the absence of treatment, the prognosis for patients with hepatic colorectal metastases is extremely poor, with five-year survival rates of three percent or less. Among patients that can be treated with complete resection of hepatic colorectal metastases, only 30% to 40% will survive for five years following resection.

**Alnylam Program.** In December 2008, we submitted an IND to the FDA for ALN-VSP, our first systemically delivered RNAi therapeutic candidate for the treatment of liver cancers, including HCC, and other solid tumors with liver involvement. In March 2009, we initiated a Phase I, multi-center, open label, dose escalation study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of intravenous ALN-VSP in up to approximately 55 patients with advanced solid tumors with liver involvement, including HCC.

ALN-VSP contains two siRNAs formulated using a first generation LNP formulation known as SNALP, developed in collaboration with Tekmira. ALN-VSP is designed to target two genes critical in the growth and development of cancer: kinesin spindle protein, or KSP, and vascular endothelial growth factor, or VEGF. KSP is a key component of the cellular machinery that mediates chromosome separation during cell division, which is critical for tumor proliferation. As such, it represents an important target for blocking tumor growth. VEGF is a potent angiogenic factor that drives the development of blood vessels that are critical to ensuring adequate blood supply to the growing tumor.

Pre-clinical data in mouse tumor model studies have demonstrated efficacy of ALN-VSP, including suppression of these targeted genes, demonstration of an RNAi mechanism of action, formation of monoesters, a characteristic

feature of KSP inhibition, anti-angiogenic effects resulting from VEGF inhibition, tumor reduction and extension of survival. Moreover, suppression of KSP has been shown in both hepatocellular and colorectal carcinoma models, and in liver tumors as well as metastases at other sites.

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We believe our strategy of using an RNAi therapeutic targeting two well-validated genes critical for tumor proliferation and survival has the potential of achieving meaningful clinical benefit for patients with liver cancer. In addition, we believe that this is the first dual targeting RNAi therapeutic program to advance to clinical development. This is an important milestone, as we view the ability to design and formulate multiple siRNAs against more than one target as a potentially attractive feature of our RNAi therapeutics platform, particularly in the setting of oncology drug development.

### ***TTR-Mediated Amyloidosis (ATTR)***

**Market Opportunity.** ATTR is a hereditary, systemic disease caused by a mutation in the TTR gene. The resulting abnormal protein is deposited as TTR-containing amyloid fibrils in extrahepatic tissues, including the peripheral nervous system and the heart, which leads to FAP and FAC, respectively. FAP is associated with severe pain and loss of autonomic nervous function, known as neuropathy, whereas FAC is associated with heart failure. Typical onset for ATTR is between the fourth and sixth decades of life and the disease is often fatal within five to 15 years of onset. In its severest form, ATTR represents a tremendous unmet medical need with significant morbidity and mortality. ATTR is an orphan, or rare, disease, affecting approximately 50,000 people worldwide.

**Current Treatments.** There are no existing disease-modifying treatments to address ATTR. Currently, liver transplantation is the only available treatment for FAP. However, only a subset of FAP patients qualify for this costly and invasive procedure and, even following liver transplantation, the disease continues to progress for many of these patients, presumably due to normal TTR being deposited into preexisting fibrils. Moreover, there is a shortage of donors to provide healthy livers for transplantation into eligible patients. There are currently no therapies available to treat FAC.

**Alnylam Program.** ALN-TTR is an RNAi therapeutic candidate targeting the TTR gene for the treatment of ATTR. TTR is a carrier for thyroid hormone and retinol binding protein and is produced almost exclusively in the liver. Thus, we believe TTR is a suitable target for an RNAi therapeutic formulated to maximize delivery to liver cells. ALN-TTR targets wild-type and all mutant forms of TTR, including the V30M mutation, and therefore is a potential therapeutic for the treatment of all forms of ATTR, including FAP and FAC.

In December 2009, we filed regulatory applications for ALN-TTR01 and plan to initiate a Phase I trial in ATTR patients in the first half of 2010. ALN-TTR01 is a systemically delivered RNAi therapeutic candidate that employs the first-generation LNP formulation known as SNALP, developed in collaboration with Tekmira. In parallel, we are also advancing ALN-TTR02 utilizing second-generation LNPs.

In pre-clinical studies with hTTR V30M transgenic mice, ALN-TTR treatment led to potent and robust reduction of mutant V30M TTR mRNA levels in the liver and mutant protein levels in the circulation. In non-human primates, administration of ALN-TTR resulted in potent reduction of wild-type TTR. Moreover, durability studies in transgenic mice and non-human primates demonstrated reduction of TTR serum protein and liver mRNA levels for at least three weeks post-administration of ALN-TTR. When administered to hTTR V30M transgenic mice, ALN-TTR blocked the deposition of mutant V30M TTR protein in a number of tissues known to be affected by the disease, including sciatic nerve, sensory ganglion, intestine, esophagus and stomach. These tissues are all sites of TTR deposition in FAP patients, and are locations of amyloid pathology associated with sensory and autonomic neuropathy and severe gastrointestinal dysfunction.

Our findings demonstrate the potential therapeutic benefit of an RNAi therapeutic targeting TTR for the treatment of ATTR. Moreover, siRNA treatment may be superior to liver transplantation based on the ability to simultaneously reduce the expression of mutant, as well as wild-type, TTR. ATTR is also one example of a number of orphan-like indications where there is a very high unmet need and the potential for early biomarker data in clinical studies,

enabling rapid proof-of-concept and a clear opportunity for a large therapeutic impact in patients.

***Hypercholesterolemia***

**Market Opportunity.** Coronary artery disease, or CAD, is the leading cause of mortality in the United States, responsible for 40% of all deaths annually. Hypercholesterolemia, defined as a high level of LDL cholesterol, or LDL-c, in the blood, is one of the major risk factors for CAD. Although current therapies are effective in many patients, studies have shown that as many as 45% of these patients do not achieve adequate control



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of their high cholesterol level with existing treatments, which include drugs known as statins. Currently in the United States, there are almost 500,000 patients with high cholesterol levels not controlled by the use of existing lipid lowering therapies. These patients are said to have refractory or poorly controlled hypercholesterolemia and constitute a potential target population for our product candidate.

**Current Treatments.** The current standard of care for patients with hypercholesterolemia includes the use of several agents. The first treatment often prescribed is a drug from the statin family. Commonly prescribed statins include Lipitor<sup>®</sup> (atorvastatin), Zocor<sup>®</sup> (simvastatin), Crestor<sup>®</sup> (rosuvastatin) and Pravachol<sup>®</sup> (pravastatin). A different type of drug, such as Zetia<sup>®</sup> (ezetimibe) and Vytorin<sup>®</sup> (ezetimibe/simvastatin), which reduces dietary cholesterol uptake from the gut, may also be used either on its own or in combination with a statin. Despite these therapies, there are many patients who have refractory or poorly controlled hypercholesterolemia and require more intensive treatment. In addition, some patients do not tolerate current treatments and at least five percent of those treated with a statin have to stop because of side-effects. In patients with very high uncontrolled cholesterol levels, a procedure called lipid apheresis is used, which effectively removes cholesterol from the blood using a machine specifically designed for this process. However, this procedure is inconvenient and uncomfortable, requiring regular weekly visits to a doctor's office.

**Alnylam Program.** In January 2010, we announced that we expect ALN-PCS, a systemically delivered RNAi therapeutic candidate targeting PCSK9 for the treatment of hypercholesterolemia, to be our next clinical candidate. ALN-PCS is being advanced using second-generation LNPs for systemic delivery.

PCSK9 is a widely acknowledged target for the treatment of hypercholesterolemia by lowering of LDL-c levels. PCSK9 is a protein that is produced by the liver but circulates in the bloodstream. The liver determines cholesterol levels, in part by taking up or absorbing LDL-c from the bloodstream. PCSK9 reduces the liver's capacity to absorb LDL-c. Recent evidence indicates that, if PCSK9 activity could be reduced, the liver should increase its uptake of LDL-c and blood cholesterol levels should decrease. In fact, some individuals have been shown to have a genetic mutation in PCSK9 that lowers its activity and results in increased liver LDL-c uptake and lowered blood cholesterol levels. In turn, these individuals have been shown to have a dramatically reduced risk of CAD, including myocardial infarction or heart attack. In addition, studies have shown that PCSK9 levels are increased by statin therapy while LDL-c levels are decreased, suggesting that the introduction of a PCSK9 inhibitor to statin therapy may result in even further reductions in LDL-c levels.

We began our ALN-PCS program in collaboration with The University of Texas Southwestern Medical Center, or UTSW. As part of the UTSW collaboration, we and UTSW are testing RNAi therapeutic candidates targeting PCSK9 in certain UTSW animal models. Non-human primate data for our ALN-PCS program has demonstrated efficient silencing of PCSK9 and rapid and durable reductions in LDL blood cholesterol levels by greater than 50%.

### ***Huntington's Disease (HD)***

**Market Opportunity.** Huntington's disease, or HD, is a fatal, inherited and progressive brain disease that results in uncontrolled movements, loss of intellectual faculties, emotional disturbance and premature death. HD patients typically first start to develop the disease in their third or fourth decade of life and have an average survival of only 10 to 20 years after initial diagnosis. The disease is associated with the production of an altered form of a protein known as huntingtin, the presence of which is believed to trigger the death of important cells in the brain. This autosomal dominant, neurodegenerative disease afflicts approximately 30,000 patients in the United States. An estimated 150,000 additional people in the United States carry the mutant huntingtin gene and, therefore, have an approximate 50% risk of developing the disease in their lifetimes.

**Current Treatments.** The current treatment of this severe disease is supportive care and symptomatic therapy, with no drugs or therapies available that have been shown to slow the underlying disease progression and the inexorable erosion of the patient's nerve cell functionality.

**Alnylam Program.** In collaboration with Medtronic, we are seeking to develop a novel drug-device product incorporating an RNAi therapeutic candidate targeting the huntingtin gene, delivered using an implantable infusion device, that will protect these cells by suppressing huntingtin mRNA and the disease causing protein. Alnylam scientists and collaborators have published and presented the data from our ALN-HTT program comprised of

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*in vitro*, rodent and non-human primate data demonstrating that the administration of ALN-HTT results in robust silencing of the huntingtin gene and reduced expression of the huntingtin protein, achieves broad distribution following continuous direct central nervous system administration, and is safe and well tolerated in rats and non-human primates at clinically relevant doses.

The ALN-HTT program is part of a 50-50 co-development/profit share relationship with Medtronic for the United States market. Outside the United States, Medtronic will be solely responsible for the development and commercialization of the drug-device.

## **Discovery Programs**

In addition to our development efforts on RSV, liver cancers, ATTR, hypercholesterolemia and HD, we are conducting research activities to discover RNAi therapeutics to treat various diseases. The diseases for which we have discovery programs include: viral hemorrhagic fever, including the Ebola virus, which can cause severe, often fatal infection and poses a potential biological safety risk and bioterrorism threat; Parkinson's disease, a progressive brain disease, which is characterized by uncontrollable tremor, and, in some cases, may result in dementia; and progressive multifocal leukoencephalopathy, or PML, which is a disease of the central nervous system caused by viral infection in immune compromised patients. We are also pursuing other undisclosed internal pre-clinical programs.

In addition to these programs, as part of our collaborations with Novartis, Roche and Takeda, we have research activities to discover RNAi therapeutics directed to a number of undisclosed targets.

## **Our Collaboration and Licensing Strategy**

Our business strategy is to develop and commercialize a pipeline of RNAi therapeutic products. As part of this strategy, we have entered into, and expect to enter into additional, collaboration and licensing agreements as a means of obtaining resources, capabilities and funding to advance our RNAi therapeutic programs.

Our collaboration strategy is to form (1) non-exclusive platform alliances where our collaborators obtain access to our capabilities and intellectual property to develop their own RNAi therapeutic products; and (2) 50-50 co-development and/or ex-U.S. market geographic partnerships on specific RNAi therapeutic programs. We have entered into broad, non-exclusive platform license agreements with Roche and Takeda, under which we are also collaborating with each of Roche and Takeda on RNAi drug discovery for one or more disease targets. We are pursuing 50-50 co-development programs with Cubist and Medtronic for the development and commercialization of ALN-RSV02 and ALN-HTT, respectively. In addition, we have entered into a product alliance with Kyowa Hakko Kirin for the development and commercialization of ALN-RSV in territories not covered by the Cubist agreement, which include Japan and other markets in Asia. We also have discovery and development alliances with Isis, Novartis and Biogen Idec.

We also seek opportunities to form new ventures in areas outside our core strategic focus. For example, during 2009, we established Alnylam Biotherapeutics, an internal effort regarding the application of RNAi technology to improve the manufacturing processes for biologics, which is comprised of recombinant proteins, monoclonal antibodies and vaccines. This initiative has the potential to create new business opportunities. In addition, during 2007, we formed Regulus, together with Isis, to capitalize on our technology and intellectual property in the field of microRNA-based therapeutics. Given the broad applications for RNAi technology, we believe additional opportunities exist for new ventures.

To generate revenues from our intellectual property rights, we grant licenses to biotechnology companies under our InterfeRx program for the development and commercialization of RNAi therapeutics for specified targets in which we

have no direct strategic interest. We also license key aspects of our intellectual property to companies active in the research products and services market, which includes the manufacture and sale of reagents. Our InterfeRx and research product licenses aim to generate modest near-term revenues that we can re-invest in the development of our proprietary RNAi therapeutics pipeline. As of January 31, 2010, we had granted such licenses, on both an exclusive and non-exclusive basis, to approximately 20 companies.

Since delivery of RNAi therapeutics remains a major objective of our research activities, we also look to form collaboration and licensing agreements with other companies and academic institutions to gain access to delivery

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technologies. For example, we have entered into agreements with Tekmira, MIT, UBC and AICana, among others, to focus on various delivery strategies. We have also entered into license agreements with Isis, Max-Planck-Innovation GmbH, Tekmira and MIT, as well as a number of other entities, to obtain rights to important intellectual property in the field of RNAi. In April 2009, we established a new collaboration with Isis to focus on the development of ssRNAi technology.

Finally, we seek funding for the development of our proprietary RNAi therapeutics pipeline from the government and foundations. In 2006, NIAID awarded us a contract to advance the development of a broad spectrum RNAi anti-viral therapeutic against hemorrhagic fever virus, including the Ebola virus. In 2007, the Defense Threat Reduction Agency, or DTRA, an agency of the United States Department of Defense, awarded us a contract to advance the development of a broad spectrum RNAi anti-viral therapeutic for hemorrhagic fever virus, which contract ended in February 2009. In addition, we have obtained funding for pre-clinical discovery programs from organizations such as The Michael J. Fox Foundation.

***Strategic Alliances***

We have formed, and intend to continue to form, strategic alliances to gain access to the financial, technical, clinical and commercial resources necessary to develop and market RNAi therapeutics. W