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Alnylam and Isis License Intellectual Property for MicroRNA Gene Involved in Hepatitis C Viral Infection

Role of MicroRNA-122 in Hepatitis C Infection Published in Science

CAMBRIDGE, Mass. & CARLSBAD, Calif.—(BUSINESS WIRE)—Sept. 13, 2005—Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY) and Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today a co-exclusive license agreement with Stanford University related to the discovery and development of therapeutic products for hepatitis C virus (HCV) infection by inhibiting a liver-specific microRNA. Data published on September 2, 2005 by Jopling et al. in the journal *Science* demonstrate that the microRNA known as miR-122 is required for HCV replication in mammalian cells. This study is the first to link endogenous expression of a specific microRNA with a major infectious disease, and suggests that antagonism of miR-122 may comprise a novel therapeutic strategy against HCV.

“The recent discoveries that over 250 human genes encode microRNAs and that these microRNAs may control gene expression for as much as one-third of the genome suggests that this part of the RNAi pathway plays a major role in human health and disease,” said John Maraganore, Ph.D., President and Chief Executive Officer of Alnylam Pharmaceuticals. “As part of our March 2004 agreement with Isis, we are together actively engaged in consolidating intellectual property in the microRNA field, and researchers at both companies are working to identify novel therapeutic opportunities.”

“The identification of miR-122 as a critical host factor for HCV infection is a remarkable finding that has implications for the discovery and development of novel anti-HCV therapeutics. These exciting results further validate that inhibiting or antagonizing microRNAs using antisense oligonucleotides has the potential to lead to exciting new therapeutics for diseases with unmet medical needs,” said C. Frank Bennett, Ph.D., Vice President, Antisense Research of Isis Pharmaceuticals. “Together with Alnylam, we continue to believe that approaches to antagonize or possibly replace microRNA function with traditional antisense oligonucleotides or with siRNA will represent an important new therapeutic strategy for the future.”

MiR-122 is specifically expressed and is highly abundant in the human liver. The study by Jopling et al. from the laboratory of Peter Sarnow, Ph.D. at Stanford University demonstrates that miR-122 interacts directly with a specific 5' noncoding sequence of the HCV genome leading to increased abundance of the viral mRNA. Antagonism of miR-122 function using an antisense oligonucleotide resulted in a dramatic decrease of viral RNA.

About RNA Interference (RNAi) RNA interference, or RNAi, is a naturally occurring mechanism within cells for selectively silencing and regulating 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. RNAi is induced by small, double-stranded RNA molecules. One method to activate RNAi is with chemically synthesized small interfering RNAs, or siRNAs, which are double-stranded RNAs that are targeted to a specific disease-associated gene. The siRNA molecules are used by the natural RNAi machinery in cells to cause highly targeted gene silencing.

About MicroRNA (miRNA) RNAi can also be induced by microRNAs, or miRNAs, that occur naturally within all mammalian cells. The miRNA molecules are encoded by the cell's own genes, giving rise to small RNA molecules that are similar in structure to siRNAs. There are at least 250 confirmed miRNA genes in the human genome and there are many other predicted miRNAs. MicroRNAs are thought to work through RNAi to regulate the activity of an estimated one-third of genes in the genome. The inappropriate absence or presence of specific miRNA molecules in various cells has been shown to be associated with specific human diseases.

About Antisense An antisense oligonucleotide hybridizes with a complementary target RNA to form a duplex. The formation of this duplex prevents the target RNA from functioning normally. Antisense drugs are short, chemically-modified RNA-like and DNA-like molecules that scientists design to complement a small, specific segment of messenger RNA, or mRNA. To date, there are at least 12 known antisense mechanisms, including RNase H, RNAi and alternative splicing. Each of these mechanisms has expanded the opportunities in which antisense drugs may be successful.

About Hepatitis C Hepatitis C is a viral infection of the liver that is a major cause of acute hepatitis and chronic liver disease, including cirrhosis and liver cancer. According to the World Health Organization, an estimated 170 million persons worldwide are chronically infected with HCV and 3 to 4 million persons are newly infected each year. No vaccine is currently available to prevent hepatitis C and treatment for chronic hepatitis C is too costly for most persons in developing countries to afford.

About Alnylam Alnylam is a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi.

The company is applying its therapeutic expertise in RNAi to address significant medical needs, many of which cannot effectively be addressed with small molecules or antibodies, the current major classes of drugs. Alnylam is building a pipeline of RNAi therapeutics; its lead program is in Phase I human clinical trials for the treatment of respiratory syncytial virus (RSV) infection. RSV infects nearly every child at least once by the age of two and accounts for more than 100,000 hospitalizations annually in the U.S. pediatric population. RSV infection also poses a great risk to the elderly and other adults with compromised immune systems. The company's leadership position in fundamental patents, technology, and know-how relating to RNAi has enabled it to form major alliances with leading companies including Merck, Medtronic, Novartis, and Biogen Idec. The company, founded in 2002, maintains global headquarters in Cambridge, Massachusetts, and has an additional operating unit in Kulmbach, Germany. For more information, visit www.alnylam.com.

About Isis Pharmaceuticals Isis is exploiting its expertise in RNA to discover and develop novel drugs for its product pipeline and for its partners. Isis has successfully commercialized the world's first antisense drug and has 15 drugs in development. Isis' drug development programs are aimed at treating cardiovascular, metabolic and inflammatory diseases. Isis' partners are focused in disease areas such as ocular, viral and neurodegenerative diseases, and cancer. Isis Biosciences, Inc., Isis' wholly owned subsidiary, is developing and commercializing the Isis T5000 Biosensor System, a revolutionary system to identify infectious organisms. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of approximately 1,500 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

Alnylam Forward-Looking Statements Various statements in this release concerning our future expectations, plans and prospects, including without limitation statements related to the potential for miR-181a and other microRNAs, constitute forward-looking statements for the purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors, including risks related to: Alnylam's approach to discover and develop novel drugs, which is unproven and may never lead to marketable products; Alnylam's ability to fund and the results of further pre-clinical and clinical trials; obtaining, maintaining and protecting intellectual property utilized by Alnylam's products; Alnylam's ability to enforce its patents against infringers and to defend its patent portfolio against challenges from third parties; Alnylam's ability to obtain additional funding to support its business activities; Alnylam's dependence on third parties for development, manufacture, marketing, sales, and distribution of products; the successful development of Alnylam's product candidates, all of which are in early stages of development; obtaining regulatory approval for products; competition from others using technology similar to Alnylam's and others developing products for similar uses; Alnylam's dependence on collaborators; and its short operating history; as well as those risks more fully discussed in the "Risk Factors" section of Alnylam's most recent report on Form 10-K on file with the Securities and Exchange Commission. In addition, any forward-looking statements represent Alnylam's views only as of today and should not be relied upon as representing its views as of any subsequent date. Alnylam does not assume any obligation to update any forward-looking statements.

Isis Forward-Looking Statements This press release includes forward-looking statements regarding Isis Pharmaceuticals' business, its intellectual property portfolio, and the therapeutic and commercial potential of molecules complementary to microRNAs. Any statement describing Isis' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such products. Isis' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause its results to differ materially from those expressed or implied by such forward-looking statements. Although Isis' forward-looking statements reflect the good faith judgment of its management, these statements are based only on facts and factors currently known by Isis. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2005, and its quarterly report on Form 10-Q for the quarter ended September 30, 2006, which are on file with the SEC. Copies of these and other documents are available from the Company.