



Alnylam and Isis License Intellectual Property for MicroRNA Gene Involved in Hepatitis C Virus 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 seeking to develop and commercialize novel therapeutics based on RNA interference, or RNAi. Growing from its foundation as the world's first company focused on RNAi therapeutics, the company's leadership in the field of RNAi is supported by its preeminent founders and advisors and its strengths in fundamental patents, technology, and know-how that underlie the commercialization of RNAi therapeutics. Alnylam is developing a pipeline of RNAi products using Direct RNAi™ to treat ocular, central nervous system, and respiratory diseases and Systemic RNAi™ to treat a broad range of diseases, including oncology, metabolic, and autoimmune diseases. The company's global headquarters are in Cambridge, Massachusetts. For additional information, please visit www.alnylam.com.

About Isis Pharmaceuticals, Inc.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel drugs for its product pipeline and for its partners. The Company has successfully commercialized the world's first antisense drug and has 12 antisense drugs in development to treat metabolic, cardiovascular and inflammatory diseases, and cancer. In its Ibis division, Isis is developing and commercializing the TIGER 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 more than 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 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: our approach to discover and develop novel drugs, which is unproven and may never lead to marketable products; our ability to obtain additional funding to support our business activities; our dependence on third parties for development, manufacture, marketing, sales and distribution of our products; the successful development of products, all of which are in early stages of development; obtaining regulatory approval for products; competition from others using technology similar to ours and others developing products for similar uses; obtaining, maintaining and protecting intellectual property utilized by our products; and our short operating history; as well as those risks more fully discussed in the "Certain Factors That May Affect Future Results" section of our most recent Form 10-Q filed with the Securities and Exchange Commission. In addition, any forward-looking statements represent our views only as of today and should not be relied upon as representing our views as of any subsequent date. We do not assume any obligation to update any forward-looking statements.

Isis Forward-Looking Statements

This press release contains forward-looking statements concerning the discovery, development and therapeutic potential of RNA-based technology and drugs, the potential success of Isis' agreement with Alnylam and Stanford University and the potential of the Company's intellectual property position. Any statement describing Isis' goals, expectations, 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, 2004, and its quarterly report on Form 10-Q for the quarter ended June 30, 2005, which are on file with the SEC. Copies of these and other documents are available from the Company.

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