

Regulus Therapeutics and Collaborators Discover Role of Viral microRNAs in Cancer and Identify First-Ever Example of a Viral microRNA Oncogene

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- New Findings Published in Nature Point to Potential Role for microRNA Therapeutics in the Treatment of Certain Cancers -

CAMBRIDGE, Mass. & CARLSBAD, Calif., Dec 12, 2007 (BUSINESS WIRE) -- Regulus Therapeutics, a joint venture between Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY) and Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) formed to discover, develop, and commercialize microRNA therapeutics, announced today the publication of new research in the journal *Nature*. The new study, performed in collaboration with scientists from Duke University, shows that a virally derived microRNA mimics the gene expression control by an endogenous host microRNA that has previously been implicated in human cancer. Evidence from the study suggests that the viral microRNA, which is encoded by the Kaposi's Sarcoma Associated Herpesvirus, or KSHV, may represent the first example of a viral microRNA oncogene, termed an "oncomir."

"We are very excited by these new data which suggest a key regulatory role of viral microRNAs in certain cancers that could lead to the application of microRNA therapeutics for the treatment of cancer, including lymphoma and leukemia," said Kleanthis G. Xanthopoulos, Ph.D., President and Chief Executive Officer of Regulus. "Our work with Duke and the publication of these new results is representative of Regulus' strategy to collaborate with leading academic groups to expand our identification and understanding of microRNA biology. We are also pleased that these findings add to a growing body of data that emphasizes the potential for microRNA therapeutics to generate high-impact new drugs for the treatment of serious diseases."

The newly published data (Gottwein et al. *Nature* 450, 1096-1099 (13 December 2007)) show that a viral microRNA (miR-K12-11), which is encoded by KSHV, functions as a mimic of the host cell microRNA known as miR-155. Expression of physiological levels of miR-K12-11 or miR-155 was found to result in the down-regulation of an extensive set of common mRNA and protein targets, including genes with known roles in cell growth regulation. Given the known important role of miR-155 in cancer and B-cell function and the association of KSHV infection with B-cell lymphomas and Kaposi's sarcoma, miR-K12-11 may represent the first example of a viral "oncomir."

Finally, analysis of currently known viral microRNAs reveals that the sequence and functional homology relationship observed between miR-K12-11 and miR-155 is likely not unique, as several other viral microRNAs appear to display this kind of homology to cellular microRNAs.

"These results demonstrate another major step forward in understanding what we believe are the broad biological roles for microRNAs in health and disease, and points to the significant applications for microRNA therapeutics," said Juergen Soutschek, Ph.D., Senior Director of Scientific Development for Regulus. "In addition to the exciting implications for B-cell related cancers, the observations related to homologous relationships of certain microRNAs raise the possibility that the similar activity noted for host cell miR-155 and viral miR-K12-11 is only the first example of a more general phenomenon of how viruses exploit the host's microRNA system to their advantage by molecular mimicry."

About microRNAs

microRNAs are a recently discovered class of genetically encoded small RNAs, approximately 20 nucleotides in length, and are believed to regulate the expression of a large number of human genes. microRNA therapeutics represent a new approach for the treatment of a wide range of human diseases. The inappropriate absence or presence of specific microRNAs in various cells has been shown to be associated with specific human diseases including cancer, viral infection, and metabolic disorders. Targeting microRNAs with novel therapeutic agents could result in high-impact and broadly acting treatments for human diseases.

About Regulus

Regulus Therapeutics LLC is a biopharmaceutical company formed to discover, develop and commercialize microRNA therapeutics. Regulus was created as a joint venture between Alnylam Pharmaceuticals, a leader in RNAi therapeutics, and Isis Pharmaceuticals, a leader in antisense technologies and therapeutics. Isis and Alnylam scientists and collaborators were the first to discover microRNA antagonist strategies that work in vivo in animal studies (Krutzfeldt et al. *Nature* 438, 685-689 (2005); Esau et al. *Cell Metab.*, 3, 87-98 (2006)). Isis and Alnylam have also created and consolidated key intellectual property for the development and commercialization of microRNA therapeutics. Regulus, founded in 2007, maintains facilities in Carlsbad, California. For more information, visit www.regulusrx.com.

About Alnylam Pharmaceuticals

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 leading the translation of RNAi as a new class of innovative medicines with peer-reviewed research efforts published in the world's top scientific journals including *Nature*, *Nature Medicine*, and *Cell*. The company is leveraging these capabilities to build a broad pipeline of RNAi therapeutics; its most advanced program is in Phase II human clinical trials for the treatment of respiratory syncytial virus (RSV) infection. In addition, the company is developing RNAi therapeutics for the treatment of influenza, hypercholesterolemia, and liver cancers, among other diseases. 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 Medtronic, Novartis, Biogen Idec, and Roche. The company, founded in 2002, maintains headquarters in Cambridge, Massachusetts. For more information, visit www.alnylam.com.

About Isis Pharmaceuticals, Inc.

Isis 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 18 drugs in development. Isis' drug development programs are focused on treating cardiovascular and metabolic diseases. Isis' partners are developing antisense drugs invented by Isis to treat a wide variety of diseases. Isis

Biosciences, Inc., Isis' wholly owned subsidiary, is developing and commercializing the Ibis T5000™ Biosensor System, a revolutionary system to identify infectious organisms. Isis is a joint owner of Regulus Therapeutics LLC, a joint venture focused on the discovery, development and commercialization of microRNA therapeutics. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of over 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 Alnylam's future expectations, plans and prospects, including statements concerning the potential of microRNA therapeutics and the importance of Alnylam's intellectual property, know-how, and other technology in the discovery, development and commercialization of microRNA therapeutics, 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; obtaining, maintaining and protecting intellectual property; 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; 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 Alnylam's short operating history; as well as those risks more fully discussed in the "Risk Factors" section of its most recent quarterly report on Form 10-Q 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 the future therapeutic and commercial potential of Isis' technologies and intellectual property related to microRNA therapeutics being discovered and developed by Regulus. 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, 2006, and its quarterly report on Form 10-Q for the quarter ended September 30, 2007, which are on file with the SEC. Copies of these and other documents are available from the Company.

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