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Regulus Therapeutics Exclusively Licenses Intellectual Property from Stanford University

CAMBRIDGE, Mass. and CARLSBAD, Calif., May 6, 2008 – Regulus Therapeutics LLC, a joint venture between Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY) and Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) formed to discover, develop, and commercialize microRNA (miRNA) therapeutics, announced today that it has obtained exclusive rights from Stanford University to worldwide patent applications covering methods and compositions for antagonizing miR-181a to regulate immune responses. Changes in miR-181a levels have been shown to modify the response of immune cells such as T lymphocytes to specific stimuli and its antagonism could lead to a new way to treat inflammatory diseases.

“We are excited about obtaining exclusive rights to this intellectual property, as it is another step in Regulus’ overall strategy to build a broad and leading platform of technology and intellectual property for the development of miRNA therapeutics, and adds to our already dominant patent position,” said Kleanthis G. Xanthopoulos, Ph.D., President and Chief Executive Officer of Regulus. “At Regulus, we are aggressively exploring a variety of therapeutic areas including viral, metabolic, and inflammatory diseases. Access to this intellectual property allows us to apply our expertise in the biology and potential therapeutic uses of miRNAs to develop novel treatments for inflammatory diseases.

” Data published in 2007 by scientists at Stanford University and Alnylam in the journal *Cell* (Li *et al*. (2007) *Cell* 129, 147-161) demonstrated that modulation of miR-181a levels in an immune cell modified the sensitivity of the cell to specific stimuli. Researchers found that by increasing expression of miR-181a, an increase in the immune cell’s response to an inflammatory stimulus occurred. Conversely, decreasing levels of miR-181a in the immune cell led to a diminution in the cell’s response to an inflammatory stimulus, thereby de-sensitizing the cell to the stimulus. Using a selective miRNA antagonist to inhibit miR-181a function resulted in efficient reduction in the immune cell’s response to a stimulus. These data suggest that controlling miR-181a levels with selective antagonists may lead to a novel approach to treating inflammatory diseases.

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 believed to be over 250 confirmed miRNA genes in the human genome and there are many other predicted miRNAs. miRNAs 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, including cancer and viral infections.

About Regulus Regulus Therapeutics LLC is a biopharmaceutical company formed to discover, develop and commercialize miRNA therapeutics. Regulus aspires to successfully translate one of the most important new properties in biology into a novel new approach for innovative medicine and to build the leading microRNA company. 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 miRNA 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 (IP) for the development and commercialization of miRNA therapeutics. This IP estate includes over 900 patents and patent applications, including 600 issued patents, owned by Isis and Alnylam and pertaining to chemical modification of oligonucleotides for therapeutic applications. In addition, Regulus has collaborations with more than 60 academic researchers to build on the company’s understanding of microRNAs and recently formed a major alliance with GlaxoSmithKline to explore new therapeutic areas for microRNA therapeutics. Regulus, founded in September 2007, maintains facilities in Carlsbad, California. For more information, visit www.regulusrx.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 19 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. Ibis Biosciences, Inc., Isis’ majority-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 miRNA 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.

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 a wide range of disease areas, including hypercholesterolemia, liver cancers, and Huntington's disease. 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. To reflect its outlook for key scientific, clinical, and business initiatives, Alnylam has established "*RNAi 2010*" which includes the company's plan to significantly expand the scope of delivery solutions for RNAi therapeutics, have four or more programs in clinical development, and to form four or more new major business collaborations, all by the end of 2010. Alnylam is a joint owner of Regulus Therapeutics LLC, a joint venture focused on the discovery, development, and commercialization of miRNA therapeutics. Founded in 2002, Alnylam maintains headquarters in Cambridge, Massachusetts. For more information, visit www.alnylam.com.

Forward-Looking Statement This press release includes forward-looking statements regarding the future therapeutic and commercial potential of Isis', Alnylam's and Regulus' business plans, technologies and intellectual property related to microRNA therapeutics being discovered and developed by Regulus, including statements regarding Regulus' patent licensing agreement with Stanford University and the potential to develop microRNA antagonists to miR-181a. Any statement describing Isis', Alnylam's or Regulus' 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 such parties' 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. Such parties' forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause their results to differ materially from those expressed or implied by such forward-looking statements. Although these forward-looking statements reflect the good faith judgment of the management of each such party, these statements are based only on facts and factors currently known by Isis, Alnylam or Regulus, as the case may be. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis', Alnylam's and Regulus' programs are described in additional detail in Isis' annual report on Form 10-K for the year ended December 31, 2007 and in Alnylam's annual report on Form 10-K for the year ended December 31, 2007, which are on file with the SEC. Copies of these and other documents are available from Isis or Alnylam.