Nature Article Implicates microRNAs in the Pathogenesis of Obesity and Type 2 Diabetes

- Work of scientists with Regulus, Alnylam and ETH Zurich shows microRNAs 103/107 are upregulated in mouse models of obesity; targeting with anti-miRs improves glucose homeostasis and insulin sensitivity -

LA JOLLA, Calif., and CAMBRIDGE, Mass., June 8, 2011 /PRNewswire/ -- Regulus Therapeutics Inc., a biopharmaceutical company leading the discovery and development of innovative medicines targeting microRNAs, and Alnylam Pharmaceuticals, Inc. (Nasdaq: ALNY), a leading RNAi therapeutics company, today announced the publication in *Nature* of new pre-clinical data in mice about the antagonism of microRNA-103 and microRNA-107 (miR-103/107). Data from a collaborative study performed by Regulus, Alnylam and ETH Zurich demonstrated that antagonism of miR-103/107 with proprietary chemically modified anti-miR oligonucleotides could promote insulin signaling in both liver and adipose tissue. Silencing miR-103/107 in animal models of obesity improved glucose homeostasis, suggesting that these microRNAs are potential targets for the treatment of diabetes.

Defects in insulin signaling are among the most common and earliest defects that predispose an individual to the development of type 2 diabetes. The new findings demonstrated that miR-103/107 are upregulated in obese mice, and silencing with anti-miRs could improve glucose homeostasis and insulin sensitivity, while gain of function in liver or fat caused impaired glucose homeostasis. Direct targets of miR-103/107 identified include caveolin-1, a critical regulator of the insulin receptor. Upon miR-103/107 inactivation, caveolin-1 is upregulated, resulting in stabilization of the insulin receptor, enhanced insulin signaling, decreased adipocyte size and enhanced insulin-stimulated glucose uptake.

"microRNAs are a new class of regulatory molecules that influence many biological functions, including metabolism. These studies suggest that antagonizing miR-103/107 with therapeutic anti-miR oligonucleotides can regulate insulin sensitivity in mouse models of obesity and diabetes," said Neil W. Gibson, Ph.D., chief scientific officer at Regulus. "This new paper, and others we have published recently on miR-33, supports the development of anti-miRs as potential therapeutics for metabolic diseases. This is one of the many exciting exploratory opportunities we are evaluating."

Prof. Markus Stoffel with the Institute for Molecular Systems Biology, ETH Zurich, and member of Regulus' scientific advisory board, said: "Our studies with Regulus and Alnylam show the importance of miR-103/107 to insulin sensitivity. The data establish miR-103/107 as a potential therapeutic target for the treatment of type 2 diabetes and obesity."

About microRNAs

The discovery of microRNA in humans during the last decade is one of the most exciting scientific breakthroughs in recent history. microRNAs are small RNA molecules, typically 20 to 25 nucleotides in length, that do not encode proteins but instead regulate gene expression. More than 700 microRNAs have been identified in the human genome, and over one-third of all human genes are believed to be regulated by microRNAs. A single microRNA can regulate entire networks of genes. As such, these molecules are considered master regulators of the human genome. microRNAs have been shown to play an integral role in numerous biological processes, including the immune response, cell-cycle control, metabolism, viral replication, stem cell differentiation and human development. Most microRNAs are conserved across multiple species, indicating the evolutionary importance of these molecules as modulators of critical biological pathways. Indeed, microRNA expression, or function, has been shown to be significantly altered in many disease states, including cancer, heart failure and viral infections. Targeting microRNAs with anti-miRs, antisense oligonucleotide inhibitors of microRNAs, or miR-mimics, double-stranded oligonucleotides to replace microRNA function opens potential for a novel class of therapeutics and offers a unique approach to treating disease by modulating entire biological pathways. To learn more about microRNAs, please visit http://www.regulusrx.com/microrna/microrna-explained.php.

About RNA Interference (RNAi)

RNAi (RNA interference) is a revolution in biology, representing a breakthrough in understanding how genes are turned on and off in cells, and a completely new approach to drug discovery and development. Its discovery has been heralded as "a major scientific breakthrough that happens once every decade or so," and represents one of the most promising and rapidly advancing frontiers in biology and drug discovery today which was awarded the 2006 Nobel Prize for Physiology or Medicine. RNAi is a natural process of gene silencing that occurs in organisms ranging from plants to mammals. By harnessing the natural biological process of RNAi occurring in our cells, the creation of a major new class of medicines, known as RNAi therapeutics, is on the

horizon. Small interfering RNAs (siRNAs), the molecules that mediate RNAi and comprise Alnylam's RNAi therapeutic platform, target the cause of diseases by potently silencing specific mRNAs, thereby preventing disease-causing proteins from being made. RNAi therapeutics have the potential to treat disease and help patients in a fundamentally new way.

About Regulus Therapeutics Inc.

Regulus Therapeutics is a biopharmaceutical company leading the discovery and development of innovative medicines targeting microRNAs. Regulus is using a mature therapeutic platform based on technology that has been developed over 20 years and tested in more than 5,000 humans. In addition, Regulus works with a broad network of academic collaborators and leverages the oligonucleotide drug discovery and development expertise of its founding companies, Alnylam Pharmaceuticals (*NASDAQ:ALNY*) and Isis Pharmaceuticals (*NASDAQ:ISIS*). Regulus is advancing microRNA therapeutics towards the clinic in several key areas including hepatitis C infection, immuno-inflammatory diseases, fibrosis, oncology, and cardiovascular/metabolic diseases. Regulus' intellectual property estate contains both the fundamental and core patents in the field and includes over 600 patents and more than 300 pending patent applications pertaining primarily to chemical modifications of oligonucleotides targeting microRNAs for therapeutic applications. In April 2008, Regulus formed a major alliance with GlaxoSmithKline to discover and develop microRNA therapeutics for immuno-inflammatory diseases. In February 2010, Regulus and GlaxoSmithKline entered into a new collaboration to develop and commercialize microRNA therapeutics targeting microRNA-122 for the treatment of hepatitis C infection. In June 2010, Regulus and sanofi-aventis entered into the largest-to-date strategic alliance for the development of microRNA therapeutics. This alliance is focused initially on fibrosis. For more information, please visit http://www.regulusrx.com.

About Alnylam Pharmaceuticals

Alnylam is a biopharmaceutical company developing novel therapeutics based on RNA interference, or RNAi. The company is leading the translation of RNAi as a new class of innovative medicines with a core focus on RNAi therapeutics for the treatment of genetically defined diseases, including ALN-TTR for the treatment of transthyretin-mediated amyloidosis (ATTR), ALN-PCS for the treatment of severe hypercholesterolemia, and ALN-HPN for the treatment of refractory anemia. As part of its "Alnylam 5x15TM" strategy, the company expects to have five RNAi therapeutic products for genetically defined diseases in advanced stages of clinical development by the end of 2015. Alnylam has additional partner-based programs in clinical or development stages, including ALN-RSV01 for the treatment of respiratory syncytial virus (RSV) infection, ALN-VSP for the treatment of liver cancers, and ALN-HTT for the treatment of Huntington's disease. The company's leadership position on RNAi therapeutics and intellectual property have enabled it to form major alliances with leading companies including Merck, Medtronic, Novartis, Biogen Idec, Roche, Takeda, Kyowa Hakko Kirin, and Cubist. In addition, Alnylam and Isis co-founded Regulus Therapeutics Inc., a company focused on discovery, development, and commercialization of microRNA therapeutics; Regulus has formed partnerships with GlaxoSmithKline and sanofi-aventis. Alnylam has also formed Alnylam Biotherapeutics, a division of the company focused on the development of RNAi technologies for application in biologics manufacturing, including recombinant proteins and monoclonal antibodies. Alnylam scientists and collaborators have published their research on RNAi therapeutics in over 100 peer-reviewed papers, including many in the world's top scientific journals such as Nature, Nature Medicine, Nature Biotechnology, and Cell. Founded in 2002, Alnylam maintains headquarters in Cambridge, Massachusetts. For more information, please visit www.alnylam.com.

Forward-Looking Statements

This press release includes forward-looking statements regarding the future therapeutic and commercial potential of Regulus' business plans, technologies and intellectual property related to microRNA therapeutics being discovered and developed by Regulus, including statements regarding the therapeutic potential of targeting miR-103/107. Any statement describing Regulus' goals, expectations, financial or other projections, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. 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 forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause the 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 Regulus' management, these statements are based only on facts and factors currently known by Regulus. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Regulus', Alnylam's, and Isis' programs are described in additional detail in Alnylam's and Isis' annual reports on Form 10-K for the year ended December 31, 2010 and its most recent quarterly report on Form 10-Q. Copies of these and other documents are available from Alnylam or Isis.

Alnylam Forward-Looking Statements

Various statements in this release concerning Alnylam's 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, 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.

SOURCE Regulus Therapeutics Inc.

For further information: Zachary Zimmerman, Ph.D. of Regulus Therapeutics, +1-858-202-6300, busdev@regulusrx.com, or David Schull of Russo Partners, +1-212-845-4271, david.schull@russopartnersllc.com, for Regulus Therapeutics; or Investors, Cynthia Clayton of Alnylam Pharmaceuticals, +1-617-551-8207, or Media, Amanda Sellers of Spectrum, +1-202-955-6222, ext. 2597, for Alnylam Pharmaceuticals

---