Regulus Therapeutics and Collaborators Publish New Pre-Clinical Data on microRNA-33 Demonstrating Key Role in Cholesterol Homeostasis and Fatty Acid Metabolism

- New publication in Nature shows therapeutic silencing of microRNA-33a/b for atherosclerosis -
- Company to host webinar on October 26, 2011 to discuss findings -

LA JOLLA, Calif., Oct. 20, 2011 /PRNewswire/ -- Regulus Therapeutics Inc., a biopharmaceutical company leading the discovery and development of innovative medicines targeting microRNAs, and collaborators at NYU Langone Medical Center and Wake Forest Baptist Medical Center today announced the publication of new pre-clinical research findings in the journal *Nature* (Rayner *et al., Nature*, October 20, 2011). The new data show the first demonstration of marked increases in high density lipoprotein cholesterol (HDL-C), the 'good' cholesterol, and suppression of plasma triglyceride levels in non-human primates through inhibition of both microRNA-33a and microRNA-33b (miR-33a/b) with proprietary chemically modified anti-miR oligonucleotides. A webinar to discuss the new data will be hosted by Regulus and features Kathryn Moore, Ph.D., associate professor in the Department of Medicine at NYU Langone Medical Center and Regulus scientists (11:00am EDT, October 26, 2011).

"In addition to atherosclerotic plaque regression and enhanced reverse cholesterol transport that we previously observed in rodents with our collaborators at NYU Langone Medical Center, anti-miR-33 treatment is now shown to increase HDL cholesterol and lower triglycerides in non-human primates," said Hubert C. Chen, M.D., Vice President of Translational Medicine at Regulus. "These combined data sets provide strong evidence that an anti-miR-33 therapeutic approach can offer multiple mechanisms to benefit patients with atherosclerosis. Anti-miR-33a/b is one of several microRNA therapeutic programs we are advancing toward clinical development."

Dr. Moore said, "The current study is the first to demonstrate in non-human primates that inhibition of miR-33a/b can both increase circulating levels of HDL-C and suppress plasma triglyceride levels. This study highlights the benefits of modulating miR-33a/b and their downstream metabolic pathways."

The *Nature* paper, "Inhibition of miR-33a/b in non-human primates raises plasma HDL cholesterol and reduces VLDL triglycerides," showed that systemic delivery of an anti-miR targeting both miR-33a and miR-33b in non-human primates increased hepatic miR-33 target gene expression and induced a sustained increase in plasma HDL-C over the 12-week study. In the study protocol, six animals per group received anti-miR-33 via subcutaneous injection at a clinically relevant dose of five mg/kg or a mismatch control. The anti-miR or control were formulated in saline, and administered twice weekly for the first two weeks, and then weekly for the remainder of the 12-week study. Results showed a maximal HDL-C increase of 50% after eight weeks that was sustained throughout the remainder of the study. Anti-miR-33a/b treatment in this model also increased the expression of miR-33 target genes involved in fatty acid oxidation resulting in suppressed triglyceride levels, a finding not previously observed in mice. The decrease in triglycerides was apparent after four weeks and reached a maximum reduction of 50%. This pre-clinical study was the first to demonstrate that inhibiting miR-33a/b has a profound and sustained effect on both circulating HDL-C and plasma triglyceride levels.

Ryan Temel, Ph.D., assistant professor at Wake Forest Baptist Medical Center, said, "anti-miR-33a/b has the potential to treat multiple aspects of metabolic syndrome which is a group of risk factors that increase the risk for coronary artery disease, stroke, and type 2 diabetes."

Multiple studies have demonstrated that miR-33a/b strongly represses the cholesterol transporter ABCA1, resulting in decreased generation of HDL-C and reverse cholesterol transport (Rayner *et al.*, *J Clin Invest.* 2011) as well as key enzymes involved in the oxidation of fatty acid resulting in the accumulation of triglycerides (Davalos *et al.*, *PNAS.* 2011). These findings indicate that miR-33a and miR-33b are key regulators of cholesterol and fatty acid metabolism, and that an anti-miR-33 approach can directly impact atherosclerosis, as well as address important cardiovascular risk factors such as obesity, insulin resistance, and hypertriglyceridemia.

Regulus is developing microRNA therapeutic s targeting miR-33a/b. The company controls fundamental patent rights related to miR-33a/b, including the miR-33a/b sequence and complementary sequences covered in the Tuschl III patent series. Additional Regulus patent rights include compositions of matter for various chemically modified anti-miR-33a/b compounds and methods of use for the treatment of cardiovascular diseases with anti-miR-33a/b.

Webinar to be held on October 26, 2011

Dr. Moore and Regulus scientists, Drs. Neil Gibson, Ph.D., Chief Scientific Officer, Hubert Chen, M.D., and

Christine Esau, Ph.D., Associate Director Metabolic Disease, will present the data published in *Nature* and discuss the data's implications in a webinar scheduled for 11:00am EDT on October 26, 2011. To participate in the webinar, register at http://www.videonewswire.com/event.asp?id=82015. Please connect to the webinar several minutes prior to the start time to ensure adequate time for any software download that may be necessary. Questions for the panelists may be submitted during the live event through the web portal. The webinar will be available for replay on the Regulus website at http://www.regulusrx.com.

About microRNA-33a/b

microRNA-33a and b (miR-33a/b), which differ by only two nucleotides, are intronic microRNAs located within the sterol response element binding protein genes *SREBF2* and *SREBF1*, respectively, which code for transcription factors that regulate cholesterol homeostasis and fatty acid metabolism. Recent studies have shown that miR-33a/b regulates the cholesterol and fatty acid pathways in a negative feedback loop. miR-33a/b represses the cholesterol transporter ABCA1 in hepatocytes and macrophages resulting in decreased cellular cholesterol efflux to apoA1, a key step in the generation of HDL-C and reverse cholesterol transport. Inhibition of miR-33 in mice, which only have miR-33a, resulted in an increase in expression of ABCA1 protein and increase in cholesterol efflux resulting in a reduction of atherosclerotic plaques (Rayner *et al.*, *J Clin Invest.* 2011). In addition, miR-33a/b suppresses key enzymes involved in the oxidation of fatty acids resulting in the accumulation of triglyceride. Inhibition of miR-33a/b increases fatty acid oxidation and insulin signaling (Davalos *et al.*, *PNAS*. 2011). These studies suggest that an anti-miR33a/b oligonucleotide treatment may be a promising strategy to treat atherosclerosis.

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 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. The company 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 toward clinical development in several areas, including fibrosis, hepatitis C, immuno-inflammatory diseases, metabolic diseases and oncology. 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 with an initial focus on fibrosis. For more information, please visit http://www.regulusrx.com.

Click here to view video segments about microRNA therapeutics and Regulus featuring the company's executives http://www.youtube.com/user/RegulusRx#p/f

Click here to follow Regulus on Twitter at www.twitter.com/regulusrx .

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-33a/b. 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.

SOURCE Regulus Therapeutics Inc.

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