Regulus Therapeutics to Present New Advancements in microRNA Therapeutics for Treatment of Metabolic Diseases and Cancer

-Regulus Chief Scientific Officer to Provide Updates on Lead Therapeutic Programs Targeting microRNA-33 and microRNA-21 at Oligonucleotide Therapeutics Society Meeting-

LA JOLLA, Calif., Sept. 8, 2011 /PRNewswire/ -- Regulus Therapeutics Inc., a biopharmaceutical company leading the discovery and development of innovative medicines targeting microRNAs, today announced the presentation of recent advances in its microRNA therapeutic preclinical programs for the treatment of metabolic diseases and cancer. Specifically, Neil W. Gibson, Ph.D., Regulus' chief scientific officer will provide updates on the company's programs targeting microRNA-33 and microRNA-21 at the 7th Annual Meeting of the Oligonucleotide Therapeutics Society held Sept. 8–10, 2011, in Copenhagen, Denmark. In a talk titled "Therapeutic Targeting of microRNAs," Dr. Gibson will present new data demonstrating that the inhibition of microRNA-33 with proprietary oligonucleotide anti-miRs in animal models increased levels of HDL-cholesterol (the 'good' cholesterol) and reduced levels of triglycerides. Additional preclinical data presented by Regulus confirmed that microRNA-21 is upregulated in human cancers and that microRNA-21 inhibition impacts tumor burden and significantly increases survival in preclinical models of hepatocellular carcinoma.

"Our exciting data show that inhibiting dysregulated microRNAs with our proprietary anti-miR oligonucleotides are effective at altering disease pathogenesis in animal models and provide us confidence to move these programs forward into clinical development," said Dr. Gibson. "Indeed, anti-miRs targeting miR-33 show promise as a novel strategy for treatment of cardiovascular disease and metabolic syndrome while anti-miRs targeting miR-21 demonstrate robust efficacy in pre-clinical tumor models."

Data updates will be made on the following programs:

miR-33. Regulus is developing microRNA therapeutics targeting miR-33 using proprietary chemically modified anti-miR oligonucleotides delivered systemically. 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 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-33/b represses the cholesterol transporter ABCA1 resulting in decreased cellular cholesterol efflux to HDL-C and reverse cholesterol transport. Inhibition of miR-33 in mice, which only have miR-33a, resulted in enhanced cholesterol transport and reduction of atherosclerotic plaques (Rayner *et al.*, *J Clin Invest* doi:10.1172/JCI57275). miR-33a/b also suppresses key enzymes involved in the oxidation of fatty acids resulting in the accumulation of triglycerides. Inhibition of miR-33a/b increases fatty acid oxidation and insulin signaling (Davalos *et al.*, *PNAS* doi:10.1073/pnas.1102281108). These studies suggest that an anti-miR33a/b oligonucleotide treatment may be a promising strategy to treat metabolic disease.

miR-21. Regulus is developing microRNA therapeutics targeting miR-21 using proprietary chemically modified anti-miR oligonucleotides delivered systemically. Recent studies have demonstrated that miR-21 is overexpressed in many cancer types (Volinia *et al., PNAS*. 2006) and can promote tumor progression and metastasis (Medina *et al., Nature*. 2010). Regulus data has shown that miR-21 is upregulated in patients with hepatocellular carcinoma (HCC). In preclinical models of HCC, short term treatment (2-3 weeks) with anti-miR-21 inhibited miR-21 in the liver and reduced liver tumor formation. Longer term treatment (17 weeks) with anti-miR-21 resulted in a significant survival advantage ($p<0.0001$) over saline and control anti-miR treated mice. These findings suggest that miR-21 is a promising target for cancer.

In addition, Regulus collaborators Markus Stoffel, Ph.D., M.D. of ETH Zurich will be chairing a session titled "Targeting microRNA," and Thomas Thum, M.D., Ph.D. of Medical School Hannover, Germany will be presenting a talk on "Therapeutic targeting of individual cardiac cell types by microRNA antagonists."

Regulus is advancing multiple microRNA therapeutic programs to the clinic in the areas of fibrosis, immuno-inflammatory disease, metabolic disease, and oncology.

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 and miR-21. 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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