

Regulus Therapeutics and Collaborators from NYU Langone Medical Center Publish New Data Demonstrating Clearance of Cholesterol from Bloodstream and Reduction of Atherosclerotic Plaques through Inhibition of microRNA-33

- Paper published in Journal of Clinical Investigation supports development of anti-microRNA 33 as potential therapeutic for atherosclerosis and related metabolic diseases -

LA JOLLA, Calif., June 6, 2011 – [Regulus Therapeutics Inc.](#), a biopharmaceutical company leading the discovery and development of innovative medicines targeting microRNAs, today announced [publication](#) in the *Journal of Clinical Investigation* of new pre-clinical data in mice on the antagonism of microRNA-33 (miR-33). The study, performed with collaborators at NYU Langone Medical Center, demonstrated that antagonism of [miR-33](#) with [proprietary](#) chemically modified anti-miR oligonucleotides can promote clearance of excess cholesterol and statistically significant regression of atherosclerosis in mice with established atherosclerotic plaques.

Recent advances in lipid metabolism have identified miR-33 as a "master switch" of cholesterol transport genes, such as ATP-binding cassette transporter A1 (ABCA1), a regulator of high density lipoprotein cholesterol (HDL-C), or 'good' cholesterol. Inhibition of miR-33 results in increased ABCA1 expression and elevations in HDL-C, suggesting that miR-33 antagonism may be atheroprotective [Rayner *et al.* Science 328, 1570 (2010)]. In this new study, in collaboration with Kathryn Moore, Ph.D., associate professor in the Department of Medicine at NYU Langone Medical Center, the impact of miR-33 inhibition was assessed in mice with established atherosclerotic plaques. Treating mice with anti-miR-33 led to increased HDL-C, enhanced reverse cholesterol transport to the plasma, liver and feces, and reductions in plaque size and lipid content.

"We are encouraged by the continuing progress being made on our miR-33 program and the ongoing work done in collaboration with Dr. Moore's lab at NYU Langone," said Hubert Chen, M.D., vice president of translational medicine at Regulus. "These studies establish that antagonizing miR-33 with therapeutic anti-miR oligonucleotides can promote regression of atherosclerosis by increasing levels of HDL-C and promoting reverse cholesterol transport. This new paper, and others we have published recently, supports the development of anti-miR-33 as a potential new therapeutic for dyslipidemias, atherosclerosis, and other related metabolic diseases."

In the study, the impact of miR-33 inhibition was evaluated in low density lipoprotein cholesterol receptor deletion (LDLR-/-) hypercholesterolemic mice with already established atherosclerosis to more closely resemble patients in a clinical setting. The mice were treated weekly for four weeks with subcutaneous injections of 10 mg/kg of anti-miR-33 or control anti-miR oligonucleotides. Anti-miR-33 treatment increased HDL-C and enhanced cholesterol transport from peripheral cells to the liver for further excretion into bile and feces. In addition, anti-miR treated mice had a 35% reduction in lesion area of atherosclerotic plaques. Taken together, the results indicated that anti-miR-33 treatment supports the efflux of cholesterol from lesional macrophages and promotes regression of established atherosclerosis. Importantly, no elevations in serum hepatotoxicity markers, aspartate aminotransferase or alanine aminotransferase (AST/ALT) were observed.

"Our studies with Regulus show that miR-33 inhibition raises circulating HDL-C, promotes removal of excess cholesterol from atherosclerotic plaques, and favorably affects lesion pathology," said Dr. Moore of NYU Langone. "The data establish miR-33 as an attractive therapeutic target for the treatment of atherosclerotic disease."

Regulus controls fundamental patent rights related to miR-33, including the miR-33 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-33 compounds and methods of use for the treatment of metabolic diseases with anti-miR-33.

About miR-33

Cholesterol metabolism is tightly regulated at the cellular level, and recent discoveries have shown that miR-33 modulates genes involved in cellular cholesterol transport. Mice have a single copy of miR-33 but non-human primates and humans have two copies of miR-33 (miR-33a and miR-33b), and technologies developed at Regulus have been used to demonstrate ways to inhibit both. miR-33a and miR-33b are found in the introns of the SREBP-2 and SREBP-1 genes, transcriptional regulators of cholesterol and fatty acid synthesis. Inhibition of miR-33a and miR-33b increases cholesterol efflux in the liver and peripheral macrophages through upregulation of the target gene ABCA1. As a result, HDL cholesterol levels increase and reverse cholesterol transport is enhanced, making miR-33 a promising target for treatment of atherosclerosis. Additional targets of miR-33a and miR-33b in the fatty acid oxidation and insulin signaling pathways have also suggested that miR-33a and miR-33b inhibition will be beneficial for multiple aspects of metabolic syndrome.

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/microna/microna-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. 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>.

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-33. 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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