Regulus Therapeutics to Present New In Vivo Data for microRNA-21 in Kidney Fibrosis

-Regulus Scientists to Provide Update on Lead Therapeutic Program at American Society of Nephrology Meeting-

LA JOLLA, Calif., Nov. 8, 2011 /PRNewswire/ -- Regulus Therapeutics Inc., a biopharmaceutical company leading the discovery and development of innovative medicines targeting microRNAs, today announced presentations on its preclinical programs for the treatment of fibrosis at the American Association of Nephrology "Kidney Week" Annual Meeting held Nov. 8–13, 2011, in Philadelphia. New data will be presented demonstrating that microRNA-21 (miR-21) is upregulated in human patients and animal models with kidney injury and fibrosis. In preclinical models, genetic deletion of miR-21 or pharmacologic inhibition using proprietary anti-miR oligonucleotides decreased fibrotic gene expression and improved kidney fibrosis. These new data demonstrate that miR-21 contributes to fibrosis and epithelial injury in the kidney, and supports the development of anti-miR-21 oligonucleotides as a therapeutic approach for treating chronic kidney disease.

"In collaboration with Dr. Jeremy S. Duffield, M.D., Ph.D., University of Washington, we have shown that inhibition of miR-21 with our proprietary anti-miR oligonucleotides is effective at preventing kidney fibrosis in animal models. We are working with our partners at Sanofi to select optimal anti-miR-21 oligonucleotides to move forward into clinical development," said Neil W. Gibson, Ph.D. Chief Scientific Officer of Regulus Therapeutics. "Fibrosis is a key contributor to several disease conditions having limited treatment options, and anti-miR oligonucleotides targeting miR-21 provide a promising innovative approach to this significant unmet medical need."

"The kidney acts as the body's natural filter of blood, removing waste products, toxins and producing urine. As such, the kidney is particularly susceptible to fibrosis because of its highly unusual vascular bed and susceptibility to tissue ischemia. The causes of kidney fibrosis are many including diabetes and hypertension, as well as acute injuries to the kidney such as IgA nephropathy, a common form of inflammation of the glomeruli, or as the result of organ transplant," said Dr. Duffield, M.D., Ph.D. Associate Professor of Medicine, in the Division of Nephrology, at the University of Washington. "In our work with Regulus, we have identified microRNA signatures in kidney injury and fibrosis in both animal models and human disease. Our results strongly suggest that miR-21 contributes to the pathogenesis of kidney injury and fibrosis, and inhibition with anti-miR-21 oligonucleotides may be useful as a treatment of chronic kidney diseases in humans."

Regulus controls fundamental patent rights related to miR-21, including compositions of matter for the miR-21 sequence and complement covered in the Tuschl III patent series. Additional Regulus patent rights include compositions of matter for various chemically modified anti-miR-21 oligonucleotides and methods of use for the treatment of fibrosis with anti-miR-21.

Regulus is advancing multiple microRNA therapeutic programs to the clinic in the areas of fibrosis, HCV infection, immuno-inflammatory disease, metabolic disease, and oncology. The miR-21 program is partnered with Sanofi and together we are advancing anti-miR-21 toward the clinic.

Regulus will have two oral presentations at Kidney Week:

1. B. Nelson Chau, Ph.D. Associate Director at Regulus will be giving the lecture "microRNA Therapeutics" on November 9th, 2011 at 3:00pm as part of a focused Early Session: Advances in Research Conference: MicroRNA.

2. Deidre MacKenna, Ph.D. Director at Regulus will be giving an oral presentation entitled: "Inhibition of microRNA-21 as a Therapeutic Strategy for Kidney Fibrosis" on November 12th, 2011 at 4:30pm as part of the session on "Tubular Injury and Fibrosis: Starting and Stopping".

Data that will be presented include the demonstration that miR-21 is upregulated in kidney injury and fibrosis in both preclinical mouse models and human patients. Regulus and collaborators used two well-characterized preclinical mouse models of kidney damage: unilateral ureteral obstruction (UUO) and unilateral ischemia reperfusion injury (IRI) models. miR-21 was highly expressed in normal kidney and was further induced in response to either UUO or IRI. In humans, miR-21 was upregulated in biopsies from kidney transplant patients with histological markers of acute kidney injury (AKI) and chronic allograft nephropathy (CAN). To further understand the role of miR-21 in the preclinical models, miR-21 deficient mice were characterized and found to be healthy, fertile, and have normal body weight. Additionally, these mice were resistant to fibrosis induced in either the UUO or IRI models. The results were recapitulated in the UUO model using anti-miR-21 oligonucleotides administered prophylactically. The mice treated with anti-miR-21 had improved fibrosis as judged both by histology or fibrotic gene expression. Gene expression data from kidneys of wildtype and miR-21

knockout mice identified about 700 genes that appear to be regulated by miR-21, including genes involved in metabolic pathways such as PPARa (peroxisome proliferator-activated receptor alpha). PPARa is a central transcription factor that regulates a number of lipid oxidation and metabolism pathways. Genetic manipulation of PPARa expression further validated the role of miR-21 in UUO induced fibrosis. Mice lacking PPARa were not protected by anti-miR-21 treatment, while those that expressed PPARa specifically in the proximal tubule epithelium were protected. Induction of PPARa appears to participate in the protective effects of anti-miR-21 treatment, potentially through protection of the epithelial tubule injury and repair processes. These studies demonstrate that miR-21 contributes to fibrogenesis and epithelial injury in the kidney, and is a candidate target for anti-fibrotic therapy.

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.

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. Regulus is also on YouTube at http://www.youtube.com/user/RegulusRx and 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-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.

For further information: Regulus Therapeutics, Zachary Zimmerman, Ph.D., busdev@regulusrx.com, +1-858-202-6300; or Russo Partners, David Schull, david.schull@russopartnersllc.com, +1-212-845-4271
