Isis Pharmaceuticals and Ercole Biotech Initiate Collaboration to Create Antisense Drugs Which Control Alternative Splicing

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CARLSBAD, Calif., and CHAPEL HILL, N.C., May 19 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) and Ercole Biotech, Inc., announced today the companies have initiated a multi-year collaboration to discover antisense drugs that regulate alternative RNA splicing. Through this collaboration, the companies will focus their complementary expertise in alternative splicing and leverage Isis' antisense technology to expand the potential of antisense drugs in treating disease. Specific financial terms of the deal were not disclosed.

Alternative splicing is largely responsible for the proteomic complexity of the approximately 30,000-40,000 genes in the human genome; 40-60 percent of human genes have alternative splice forms. Defects in the splicing process play a central role in many human diseases. Antisense is the only drug discovery technology able to target a gene's messenger RNA in a sequence- specific fashion, and thus regulate alternative splicing. This technology benefit makes antisense a unique and valuable approach to altering gene expression, and potentially controlling disease.

"Alternative splicing opens the door to thousands of new drug targets for the pharmaceutical industry, and we believe antisense is the technology poised to take advantage of this new biology. We are pleased to initiate our first corporate partnership with Isis, the leader in antisense technology," said Athanasios Maroglou, Ph.D., President of Ercole Biotech. "We will initially explore alternative splicing for new agents to treat prostate cancer, breast cancer, psoriasis, cardiovascular disorders and genetic diseases. We believe we will have our first product IND within 18 months and a pipeline of candidates against known and novel targets."

In the partnership, Isis and Ercole will engage in a drug discovery collaboration and cross-license splicing-related intellectual property. Ercole will also receive a license to certain Isis antisense chemistry patents. Isis and Ercole will work together to discover new antisense drugs, based on the RNA splice variant research conducted. Each company will pay the other for key preclinical, clinical and commercial achievements as well as royalties. Additionally, Ercole will receive a license to Isis' Bcl-x preclinical antisense drug. This antisense drug inhibits the production of splice variants of the Bcl-x gene, which is involved in the regulation of apoptosis, or programmed cell death. Ercole will undertake future clinical development and commercialization of the compound, and pay Isis milestones and additional royalty payments as they are achieved.

Under the agreement, Isis will take an equity ownership position in Ercole. The equity funding will be initially in the form of convertible debt, which the companies anticipate will convert into the securities Ercole issues at the time of the company's next venture capital financing. Isis also has the option to make an additional equity investment in Ercole. Isis' Vice President of Antisense Research, C. Frank Bennett, Ph.D., will serve as a member of Ercole's Scientific Advisory Board.

"Our partnership with Ercole is consistent with Isis' business strategy of leveraging antisense technology and expertise with high quality partners who have complementary expertise and focus. This allows us to expand our pipeline and participate in the upside of additional commercial opportunities," said Dr. Bennett of Isis.

ABOUT ALTERNATIVE SPLICING

Alternative splicing is an emerging area of research catalyzed by the completion of the sequencing of the human genome. Alternative splicing is a natural process in which a single gene can encode multiple related, yet distinct, protein products. During RNA splicing, most mammalian genes are interrupted by pieces of DNA, called introns, which are selectively removed during the maturation of RNA transcribed from a gene. Cells may remove and splice together different segments of RNA from the same gene, resulting in alternatively spliced gene products. In many cases, the alternative spliced products can have very different biological effects, with one form contributing to human disease and another form preventing human disease.

ABOUT ERCOLE BIOTECH, INC.

Ercole BioTech, Inc is a biopharmaceutical company focused on delivering RNA-based drug discovery technologies to identify and commercialize novel drugs to treat such important diseases as prostate cancer, breast cancer, psoriasis, cardiovascular disorders and genetic diseases. Ercole was founded in 2002 with technology licensed from The University of North Carolina at Chapel Hill, discovered by Dr. Ryszard Kole, a Professor in the Department of Pharmacology and the Lineberger Comprehensive Cancer Center at the University of North Carolina. Additional information about Ercole BioTech Inc. is available at www.ercolebiotech.com .

ABOUT ISIS PHARMACEUTICALS, INC.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs. The company has commercialized its first product, Vitravene® (fomivirsen), to treat CMV-induced retinitis in AIDS patients. In addition, Isis has 13 antisense products in its development pipeline, with two in late-stage development and five in Phase II human clinical trials. Affinitak™ (formerly called LY900003 and ISIS 3521), an inhibitor of PKC-alpha, is in Phase III development for non-small cell lung cancer, and alicaforsen (ISIS 2302), an ICAM-1 inhibitor, is in Phase III human clinical trials for Crohn's disease. Isis has a broad patent estate, as the owner or exclusive licensee of more than 1,200 issued patents worldwide. Isis' GeneTrove™ division uses antisense to assist pharmaceutical industry partners in validating and prioritizing potential gene targets through customized services. Ibis Therapeutics™ is a division focused on the diagnosis of infectious organisms and the discovery of small molecule drugs that bind to RNA. Additional information about Isis is available at www.isispharm.com .

This press release contains forward-looking statements concerning the potential of Isis Pharmaceuticals, antisense technology as a drug discovery and development platform for alternative splicing, Isis' Bcl-x preclinical drug candidate and Isis' drug discovery and cross-licensing patent collaboration with Ercole. Any statement describing a goal, expectation, intention or belief of Isis is a forward-looking 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 financing such activities. Actual results could differ materially from those projected in this release. As a result, you are cautioned not to rely on these forward-looking statements. These and other risks concerning Isis research and development programs are described in additional detail in Isis' Annual Report on Form 10- K and quarterly report on Form 10-Q for the periods ended December 31, 2002 and March 31, 2003, respectively, which are on file with the U.S. Securities and Exchange Commission, copies of which are available from the company.

Vitravene ® is a registered trademark of Novartis AG.
GeneTrove™ and Ibis Therapeutics™ are trademarks of Isis Pharmaceuticals, Inc.
Affinitak™, a trademark of Eli Lilly and Company, is an investigational cancer compound being developed through an alliance between Lilly and Isis Pharmaceuticals, Inc. and marketed globally by Lilly.

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