Antisense Drug Targeting STAT-3 Demonstrates Significant Anti-Tumor Activity

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Isis Pharmaceuticals Adds Preclinical Compound to Development Pipeline

CARLSBAD, Calif., Sep 16, 2004 /PRNewswire-FirstCall via COMTEX/ -- Antisense inhibition of the drug target Signal Transducer and Activator of Transcription 3 (STAT-3), a protein that regulates cell division and growth, and prevents cell death, significantly delayed tumor growth and increased the rate of cancer cell death in multiple cell and animal models of cancer, according to data presented today at Advances in Cancer Therapies 2004 meeting in London, England. ISIS 345794 is a second-generation antisense drug that targets STAT-3, and based on these preclinical findings, Isis Pharmaceuticals (Nasdaq: ISIS) has selected ISIS 345794 for clinical development. Nicholas Dean, Ph.D., Isis Vice President, Functional Genomics, presented these data at the conference.

"STAT-3 is a compelling drug target in oncology as it is expressed and activated in a wide range of solid and hematological cancers, such as prostate, breast, lymphomas and multiple myeloma. There is a substantial amount of scientific data which demonstrate that activation of STAT-3 initiates a series of cellular events that eventually lead to malignancy," said Dr. Dean. "In our study, we observed that selective, dose-dependent inhibition of this target produces pro-apoptotic effects while slowing the rate of tumor growth, potentially delaying the progression of the disease for cancer patients. We intend to rapidly move ISIS 345794 into clinical development, and anticipate initiating clinical trials in patients with cancer in 2005."

In multiple in vitro and in vivo preclinical studies, antisense inhibition of STAT-3:

* Reduced both STAT-3 messenger RNA (mRNA) and protein by up to 95% in cells and in human xenograft models of cancer.
* Produced increased rates of cancer cell death in human multiple myeloma, breast, prostate and lung cancer cells.
* Demonstrated anti-tumor activity in a variety of human xenograft models of cancer, including prostate, lymphoma, multiple myeloma and melanoma cells. This anti-tumor activity was associated with the selective inhibition of STAT-3.
* Did not produce any serious dose-limiting toxicities.

ISIS' ANTI-CANCER DRUG DISCOVERY AND DEVELOPMENT PARTNERSHIPS

The addition of ISIS 345794 to Isis' development pipeline further strengthens the company's robust cancer franchise that is supported through both strategic partnerships and internal research and development. Isis has several ongoing collaborations that are focused on identifying new antisense drugs for the treatment of cancer. Isis is currently working with Eli Lilly and Company to discover antisense drugs targeting novel cancer targets. The companies' oncology collaboration, initiated in June 2002 and extended earlier this year, is part of a broad, strategic alliance to discover antisense drugs.

With Isis' assistance, OncoGenex Technologies is developing OGX-011, an inhibitor of clusterin. Clusterin is a cell survival protein that, when overproduced, prevents cancer cell death and counters the effectiveness of standard anti-tumor treatments.

OGX-011 is a second-generation antisense drug being developed to sensitize tumors resistant to existing treatments such as chemotherapy, hormone ablation therapy and radiation therapy. The companies recently reported results from a Phase I study showing that once weekly intravenous administration of OGX-011 is well tolerated, achieves excellent drug concentration in target tissue, and produces up to a 91% dose-dependent decrease of its target, clusterin, in prostate cancer.

In 2003, Isis and OncoGenex expanded their antisense drug development partnership to include the development of the second-generation antisense anti-cancer drug candidate, OGX-225. The compound is the first bi-specific antisense inhibitor, a single-stranded antisense drug designed to inhibit the production of two proteins simultaneously, to enter into preclinical development. OGX-225 targets both insulin-like growth factor binding protein-5 (IGFBP-5) and insulin-like growth factor binding protein-2 (IGFBP-2), two molecules involved in the development of metastatic disease in hormone-regulated tumors such as prostate and breast cancers.

Isis is also working with Ercole Biotech, a company focused on discovering antisense drugs that regulate alternative RNA splicing. Through this collaboration, Ercole received a license to Isis' Bcl-x preclinical antisense drug. This drug, currently in preclinical development, inhibits the production of splice variants of the Bcl-x gene, which is involved in the regulation of apoptosis, or programmed cell death.

ABOUT STAT-3

STAT-3 is a member of a multi-gene family called Signal Transducers and Activators of Transcription, which is involved in the regulation of cell growth. STAT-3 appears to play an important role in cell development and death, and is active in a wide range of cancers, including both solid and hematological cancers. Activated STAT-3 is present in numerous malignancies including head, neck, prostate, breast and lung cancers, and in multiple myeloma, anaplastic lymphoma, chronic myeloid leukemia and melanoma. The control of both the activation and inactivation of STAT-3 is equally important to maintain normal cell growth.

ABOUT ISIS PHARMACEUTICALS, INC.

Isis Pharmaceuticals, Inc. is exploiting its expertise in RNA to discover and develop novel human therapeutic drugs for its pipeline and for its partners. The company has successfully commercialized the world's first antisense drug and has 10 antisense products in development to treat metabolic, cardiovascular, inflammatory and viral diseases and cancer. Through its Ibis Therapeutics® program, Isis is developing a biosensor to identify infectious organisms, and discovering small molecule drugs that bind to RNA. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of more than 1,400 issued patents worldwide. Additional information about Isis is available at www.isispharm.com.

This press release includes forward-looking statements regarding Isis' collaborations with Eli Lilly and Company, OncoGenex Technologies and Ercole

Biotech and the development, therapeutic potential and safety of LY2181308, OGX-011, OGX-225 and ISIS 345794 in treating cancer. Any statement describing our goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement, including those statements that are described as Isis' clinical goals. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of developing technology and systems used to identify infectious agents, in discovering and commercializing drugs that are safe and effective for use as human therapeutics, and in the endeavor of building a business around such products and services. Actual results could differ materially from those discussed in this press 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 for the year ended December 31, 2003, and quarterly report on Form 10-Q for the quarter ended June 30, 2004, which are on file with the U.S. Securities and Exchange Commission. Copies of these and other documents are available from the company.

SOURCE Isis Pharmaceuticals, Inc.

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