



Multiple Second-Generation Antisense Drugs Effectively Inhibit Tumor Growth and Show Potential as New Anti-Cancer Drugs

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Isis Pharmaceuticals and Partners Present Preclinical Results From Broad

Oncology Antisense Drug Discovery Programs at AACR

CARLSBAD, Calif., April 21 /PRNewswire-FirstCall/ -- In multiple preclinical studies, second-generation antisense drugs selectively inhibited novel cancer targets and improved survival in cancer cell and animal models, according to data presented this week at the 96th Annual Meeting of the American Association for Cancer Research. Scientists from Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) and collaborators from academia and industry made numerous presentations that demonstrate effectiveness of second-generation antisense drugs and the power of antisense technology to identify, characterize, and validate new targets for the treatment of cancer.

"In aggregate, data presented at AACR continue to show the value of second-generation drugs in cancer and underscore the productivity of our technology," said C. Frank Bennett, Ph.D., Isis' Vice President of Antisense Research. "Antisense is unique in that it can selectively inhibit essentially any gene in cell culture and in animal models, which allows us and our partners to rapidly determine the potential of a gene as a drug target. Additionally, we can easily approach molecular targets that are not accessible with traditional drug discovery methods. This opens many doors for our technology in treating disease and provides us with a competitive advantage in the marketplace."

Highlighted AACR presentations demonstrating the ability of antisense to discover potential new cancer drugs:

*** Inhibition of Eg5 (kinesin-like 1) with Antisense Oligonucleotides Leads to Cell-cycle Arrest in G2/M and Anti-tumor Activity Against Xenograft Tumors**

Isis scientists have developed a screening method to identify genomic targets required for cancer cells to progress in the cell cycle and divide. Second-generation antisense inhibitors to approximately 1,500 different genes were quickly screened to identify genes required for cancer cells to divide and grow.

In this study, antisense inhibition of kinesin-like-1 (Eg5) was particularly effective in reducing tumor cell growth and division in animal models of human cancer. Eg5, a novel gene target, is a member of a multi-gene family known to be involved in organizing chromosomes and enabling cell division.

*** Cell Type and Gene-specific Contributions of hypoxia-inducible factors (HIFs) to the Regulation of Transcriptional Responses under Hypoxia in Human Cancer Cells**

Isis and scientists from Eli Lilly and Company evaluated members of a complex multi-gene family, called hypoxia-inducible factors or HIFs, to define the role each gene may play in causing cancer, and that may be an exciting target for cancer therapy. This family of genes is induced by stress and thought to be genes cancer cells use to survive.

HIF family members HIF-1 alpha and HIF-2 alpha were shown to be very intricate and subtle regulators of the stress response. In contrast, HIF-1 beta was shown to be more broadly involved.

*** The Comparison of aurora A and aurora B as Therapeutic Targets Using Antisense Oligonucleotides**

Isis scientists and academic collaborators evaluated members of a multi-gene family that phosphorylate proteins (kinases) to determine which member of the family demonstrates the best anti-cancer activity.

Antisense inhibition of either aurora A or aurora B resulted in significant effects on pancreatic cancer cells. Inhibition of aurora A caused tumor cell death, and inhibition of aurora B resulted in abnormal cell division. Antisense inhibition of both targets produced

more profound effects on the tumor cells.

Highlighted AACR presentations demonstrating the value of selective inhibition of specific genes to create safer and more effective anti-cancer agents:

*** Synergistic Anti-tumor Activity of mcl-1 Antisense Oligonucleotides and Docetaxel in Gastric Cancer Cells**

The gene mcl-1 is a member of the bcl-2 family of genes. The bcl-2 family is the best characterized family of proteins involved in the regulation of apoptotic cell death, consisting of anti-apoptotic and pro-apoptotic members. mcl-1 is a gene believed to be involved in drug resistance in cancer. In gastric cancer, mcl-1 is found in up to 75% of all cases. However, the clear biological role of mcl-1 in gastric cancer is not yet known.

An antisense inhibitor to mcl-1 decreased the levels of this protein by up to 70% in a dose-dependent manner in cells. Further, this inhibition significantly reduced gastric cancer cell growth. Scientists also evaluated the effects of adding the mcl-1 antisense inhibitor to docetaxel or cisplatin, which resulted in increased tumor sensitivity to the chemotherapy drugs.

*** Depleting eIF4E Expression with a Novel eIF4E Targeted Antisense Oligonucleotide Suppresses eIF4E Expression and Human Xenograft Tumor Growth without Overt Toxicity**

Eukaryotic initiation factor-4E (eIF-4E) is a protein that is upregulated or overexpressed in a variety of cancers, including breast, head and neck, prostate, lung, bladder, colon, thyroid and non-Hodgkin's lymphomas. The protein facilitates the synthesis of tumor angiogenic factors (factors that facilitate the growth of new blood vessels to support the development and progression of tumors), growth factors and survival factors by selectively enhancing their translation. Based on scientific literature, there is a strong indication that eIF-4E may act as a critical "switch" in cancer progression.

In this study, scientists from Isis and Lilly demonstrated that an antisense drug targeting eIF-4E significantly reduced levels of the target and several survival proteins as predicted. Further, the drug appeared to be highly effective in animal models of cancer.

In September 2004, Lilly licensed LY2275796, a second-generation antisense drug candidate targeting eIF-4E, from Isis for clinical development.

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 and inflammatory diseases, and cancer. Through its Ibis division, Isis is developing a system to identify infectious organisms. As an innovator in RNA-based drug discovery and development, Isis is the owner or exclusive licensee of more than 1,500 issued patents worldwide. Additional information about Isis is available at <http://www.isispharm.com>.

This press release includes forward-looking statements regarding antisense technology, the development and therapeutic potential of antisense drugs to specific cancer targets, and the success of Isis and its partners' anti-cancer antisense drug discovery programs. 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 discovering, developing and commercializing drugs that are safe and effective for use as human therapeutics, in developing and commercializing technology and systems used to identify infectious agents, and in the endeavor of building a business around such products and services. Our forward-looking statements also involve assumptions that, if they never materialize or prove correct, could cause our results to differ materially from those expressed or implied by such forward-looking statements. Although our forward-looking statements reflect the good faith judgment of our management, these statements are based only on facts and factors currently known by us. As a result, you are cautioned not to rely on these forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in Isis' Annual Report on Form 10-K for the year ended December 31, 2004, which is on file with the U.S. Securities and Exchange Commission (SEC), and available from the Company.

Bibliography and Additional Abstracts Presented at AACR

Inhibition of Eg5 (kinesin-like 1) with Antisense Oligonucleotides leads to cell-cycle arrest in G2/M and antitumor activity against xenograft tumors

Stephanie S. Propp, Erich Koller, Ming Yi Chang, Robert I. Glazer, Scott Hirsch, Peter Shepard, Seongjoon Koo, Cain Murphy,

Nicholas Dean. ISIS Pharmaceuticals, Carlsbad, CA and Georgetown University, Washington, DC.

Cell type and gene-specific contributions of hypoxia-inducible factors (HIFs) to the regulation of transcriptional responses under hypoxia in human cancer cells

Youngsoo Kim, Eric G. Marcusson, Thomas M. Vincent, Grace Mao, Kerry L. Blanchard, Nicholas M. Dean. ISIS Pharmaceuticals, Inc., Carlsbad, CA and Eli Lilly and Company, Indianapolis, IN.

The comparison of aurora A and aurora B as therapeutic targets using antisense oligonucleotides

Steven L. Warner, Ruben M. Munoz, Erich Koller, Laurence H. Hurley, Daniel D. Von Hoff, Haiyong Han. College of Pharmacy, University of Arizona, Tucson, AZ, Translational Genomics Research Institute, Phoenix, AZ, Isis Pharmaceuticals, Carlsbad, CA.

Synergistic anti-tumor activity of Mcl-1 antisense oligonucleotides and docetaxel in gastric cancer cells

Volker Wacheck, Daniel Cejka, Wolfgang Sieghart, Doris Losert, Sabine Strommer, Brett P. Monia, Burkhard Jansen. Medical University Vienna, Vienna, Austria and ISIS Pharmaceuticals, Carlsbad, CA.

Depleting eIF4E expression with a novel eIF4E targeted antisense oligonucleotide suppresses eIF4E expression and human xenograft tumor growth without overt toxicity

Jeremy R. Graff, Bruce W. Konicek, Rebecca L. Lynch, Thomas M. Vincent, Spring N. Bailey, Phil Schwier, Drew Capen, Robin Goode, Sean Sissons, Karen Cox, Ann M. McNulty, Tao Wang, Lillian Sams, Sandaruwan Geeganage, Larry E. Douglass, Julia H. Carter, Eric G. Marcusson. Eli Lilly & Co., Indianapolis, IN, Isis Pharmaceuticals, Carlsbad, CA, Wood Hudson Cancer Research Labs., Newport, KY.

SOURCE Isis Pharmaceuticals, Inc.
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