

## Issuance of Pivotal Patent Provides Isis Pharmaceuticals Therapeutic Control Over Third-Generation Antisense Chemistry

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Isis Is Exclusive Therapeutic Licensee of PNA Chemistry

CARLSBAD, Calif., May 29 /PRNewswire-FirstCall/ -- Isis Pharmaceuticals, Inc. (Nasdaq: ISIS) announced today that the United States Patent and Trademark Office has issued U.S. Patent 6,395,474 to a group of inventors originally working at the University of Copenhagen, Denmark. As the exclusive licensee of therapeutic rights to this patent, Isis gains control over the usage of the antisense chemistry called Peptide Nucleic Acid, or PNA, for drug discovery and development. The issued patent covers the basic composition of matter for PNA, including its basic structure, as well as pharmaceuticals that contain PNA. PNAs represent a new chemical class of antisense drugs.

PNA drugs have physical and chemical properties that are very different from current antisense drugs, as they appear to distribute to tissues and cells not reached with other classes of antisense drugs. In addition, PNA drugs are very stable, enhancing the opportunity for oral delivery. These characteristics may allow Isis and its sublicensees to expand the therapeutic opportunity for antisense drugs. PNA is one of hundreds of chemistries included in Isis' antisense medicinal chemistry portfolio.

"PNA chemistry is strategically important to Isis, as we believe it has the potential to serve as the foundation for third-generation antisense drugs," said Richard Griffey, Ph.D., Isis' Vice President, Medicinal Chemistry. "Our goal is to maintain our leadership position in antisense technology through persistent innovation and acquisition. The creation of new classes of antisense drugs that have enhanced appeal to patients or broadened applications in disease is one key way to ensure our long-term leadership of this new platform for drug discovery."

Isis exclusively licensed therapeutic rights to PNA chemistry in 1991 from its Danish inventors. Isis has sublicensed rights to specific therapeutic applications of PNA to Pantheco, a Danish company that is focused on the development of PNA chemistry and drugs. Isis is working with Pantheco to determine the therapeutic potential of PNA. Isis has an equity position in Pantheco and the right to milestones and royalties on any PNA drugs. Pantheco is developing PNA-based antisense drugs to treat infectious disease and has rights to expand their development activities to metabolic and cardiovascular diseases.

Isis established its medicinal chemistry program in several sequential steps.

- First, the company has focused on exploiting first generation drugs for the diseases where their characteristics are commercially acceptable, as in cancer and severe inflammatory diseases.
- In parallel, Isis scientists have rigorously explored the chemical space available to antisense molecules and selected a proprietary second-generation chemistry that has the potential to broaden the usefulness of antisense drugs to chronic diseases such as diabetes and cardiovascular disease. Nearly half of the 13 products in Isis' development pipeline are second-generation drugs, and human clinical trials of second-generation drugs are in progress.
- Isis is continuing to push the boundaries of antisense technology to identify third generation chemistries, such as PNA.

Isis owns a broad intellectual property estate of more than 900 issued patents that covers RNA-based drug discovery and development. The patent portfolio covers the use of antisense inhibitors as drugs, including chemistries, antisense inhibitor designs called "motifs," methods of use of antisense inhibitors, and mechanisms of action by which antisense inhibitors inactivate an RNA target. Isis' patent estate also covers the use of antisense inhibitors as tools for gene functionalization and target validation. Isis builds its intellectual property position through internal scientific innovation and by in-licensing intellectual property from other companies.

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 six in Phase II human clinical trials. Affinitac™, an inhibitor of PKC-alpha, is in Phase III trials for non-small cell lung cancer, and alicaforsen (ISIS 2302), an ICAM-1 inhibitor, is in a Phase III trial in Crohn's disease. Isis has a broad patent estate as the owner or exclusive licensee of more than 900 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 discovery of small molecule drugs that bind to RNA. Additional information about Isis is available at [www.isispharm.com](http://www.isispharm.com).

This press release contains forward-looking statements concerning Isis Pharmaceuticals and the potential of the company's intellectual property position. Any statement describing a goal, expectation, intention or belief of the Company 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 financing such activities. Actual results could differ materially from those projected in this release. As a result, the reader is 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 the Company's Annual Report on Form 10K, for the period ended December 31, 2001, which is on file with the U.S. Securities and Exchange Commission, copies of which are available from the Company.

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