[ISIS PHARMACEUTICALS LOGO]

==========

1999 ANNUAL REPORT

[ISIS PHARMACEUTICALS LOGO]

==========

To our Stockholders:

Since Isis' inception, our goal has been to discover and develop important new drugs to treat disease and improve the lives of patients through the creation of new RNA-based drug discovery technologies. Our technologies are broadly enabling and can be used to improve the drug discovery capability not only of Isis but of the pharmaceutical industry as well. Over the last ten years we have made tremendous advances toward our goal. Isis has pioneered two proprietary, innovative drug discovery technologies: antisense technology - the creation of specific inhibitors to a targeted gene's RNA, which can be used as drugs or as genomics tools; and Ibis technology - the creation of small molecule drugs that bind to structured areas of RNA. We intend to fully exploit all of our innovations to maximize shareholder value.

Isis' technologies are focused on RNA, which is a rich target for drug discovery. RNA is universal to all living things. It is the fundamental molecule that transfers genetic instructions from DNA to the cell to produce proteins, the working molecules of the body. By interfering with RNA, either through antisense inhibitors or Ibis' small molecule drugs, each of our technologies is capable of stopping the production of proteins involved in specific disease processes.

RNA-based drug design is rational, in that we use genetic information directly to design our drugs. The genetic alphabet is comprised of only four chemical bases that must obey strict rules for binding, called base-pairing. The orderly nature of base-pairing makes the creation of drugs that bind a predictable and efficient process. Both our antisense and Ibis drug discovery technologies take advantage of the rationality of RNA. We use the gene sequence directly to make drugs in our antisense therapeutics program, to validate gene targets in our new GeneTrove division and to determine ideal binding sites for small molecule drugs in our Ibis Therapeutics division.

RNA is a very specific site for drug development. Since an antisense drug is made according to the base-pairing rules, it is likely to bind only to its intended target, which dramatically lowers the likelihood of unwanted side effects when used as a drug. In addition, the process of characterizing an RNA binding site for a small molecule drug, as in Ibis, can be much simpler than the same task in binding to a protein, as in traditional drug discovery, because RNA structures are composed of only four chemical bases as opposed to the 20 amino acids that make up proteins.

Finally, RNA is still an untapped target for drug discovery. Isis has applied its expertise in molecular and cellular biology, medicinal chemistry, pharmacology and bioinformatics to our RNA drug discovery efforts. This proficiency, combined with our broad patent estate, has positioned the company as the leader in both antisense and Ibis technologies.

We are leveraging our wealth of technology in numerous ways to create value. First, we are developing an exciting pipeline of antisense products to meet important medical needs with significant commercial potential. Second, we have organized a new division of Isis called GeneTrove, which is actively marketing our capabilities in genomics to additional industry partners. We believe that our GeneTrove gene functionalization and target validation program represents an important product offering in 2000 and beyond that will bring incremental revenue to the company. Third, our Ibis technology has matured sufficiently to be attractive to industry partners that are seeking innovative drug discovery solutions. We are hoping to initiate research and development partnerships with major pharmaceutical companies based on this exciting platform. Finally, we are leveraging our antisense patent estate by exploiting the RNase H1 patent that issued recently. This fundamental antisense patent, along with related patents, has the potential to generate licensing revenues for Isis. In the following paragraphs I will provide additional detail about each of these immediate value drivers.

Antisense Research and Product Pipeline

Antisense is the most direct route from gene to drug because we use the gene sequence information directly to make an antisense inhibitor to a gene. Antisense drugs are more specific than traditional small molecule drugs and therefore have the potential to offer efficacy with an improved safety profile. The efficiency and specificity of antisense make it a rapid, highly productive approach to drug discovery. Our ongoing research efforts encompass a broad range of therapeutic areas, including liver diseases, metabolic diseases such as diabetes, inflammatory diseases, cancer and dermatology. We have discovered, through continued development of both first and second generation chemistries, that antisense is a versatile technology that can be delivered in a variety of ways to enhance patient convenience. Administration is feasible by topical cream, inhalation, enema, subcutaneous injection and, perhaps most significantly, orally. Many of these advances are reflected in the products currently in our development pipeline.

Before addressing our robust product pipeline, I will discuss the status of ISIS 2302 in Crohn's disease. We were very surprised and disappointed at the end of 1999 when we learned that the pivotal clinical trial of ISIS 2302 in Crohn's disease had failed. We responded to this disappointment with a substantial restructuring of the company in order to conserve resources and to focus our efforts on drug development programs with the greatest potential for adding near-term value. We are continuing to evaluate the data from the Crohn's disease trial.

While we may never fully understand why the results of the second half of the trial completely reversed the positive results that were achieved in the first half, we believe that there are trends within subgroups of the patients that support activity of the drug. At the present time, we have not determined whether we will pursue further development of ISIS 2302 in this disease. While this event was a setback for Isis, it represented a single disappointment in a single indication of a single product. The

totality of the data convince us that antisense technology is capable of producing important drugs, and we have proof of principle with the successful commercialization of the first antisense drug, Vitravene(TM), for treatment of CMV retinitis. We are committed to our goal of bringing novel drugs to patients through innovative RNA-based drug development technologies that we create and are therefore very excited about the pipeline of drugs currently in development.

Isis' product pipeline consists of five drugs in Phase II development and two drugs in preclinical development. These products focus on diseases with substantial unmet medical need: cancer, psoriasis, hepatitis C and inflammatory diseases.

Cancer: We have three anti-cancer drugs in the clinic, each being studied in multiple tumor types. In 2000, we plan to advance our lead anti-cancer compound, ISIS 3521 in non small cell lung cancer (NSCLC), into Phase III clinical trials. ISIS 3521 is a potent, selective inhibitor of protein kinase C-alpha. We are very pleased with the performance of ISIS 3521 in combination with standard chemotherapy in improving the average survival rate of NSCLC patients that we have seen to date in our ongoing Phase II trial. Additionally, results to date in the Phase II single agent trial of ISIS 3521 in non-Hodgkin's lymphoma are encouraging, and we are aggressively expanding this program. Our other two anti-cancer drugs, ISIS 5132 and ISIS 2503, are progressing through Phase II trials. These drugs target C-raf kinase and Ha-ras, respectively. We expect to have sufficient data to evaluate these drugs later in 2000.

Psoriasis: In 1999, we initiated Phase II trials of a topical cream formulation of ISIS 2302, an inhibitor of ICAM-1, in plaque psoriasis. We are very enthusiastic about the potential for this indication, as the market potential for psoriasis drugs is vast and our topical formulation would offer a competitive dosing advantage over other intravenous drugs in development. We expect analysis of this trial in the late 2000/early 2001 timeframe.

Hepatitis C: ISIS 14803 is currently being studied in a Phase I/II trial of patients chronically infected with the Hepatitis C virus under HepaSense, a joint venture formed with Elan Corporation, plc. (Elan). The drug is being administered intravenously in this first trial, and with positive results, additional trials using subcutaneous delivery and using Elan's MEDIPAD microinfusion pump will be initiated. The potential of a new treatment in a convenient MEDIPAD delivery system is very exciting, as Hepatitis C is a rapidly growing health concern with currently limited options for treatment. Results of the initial clinical trial are expected in the late 2000/early 2001 timeframe.

Inflammatory Diseases: In 1999 we formed a partnership with Elan, called Orasense, to pursue oral formulation of antisense drugs, with ISIS 104838 as the lead product. ISIS 140838 is an inhibitor of TNF-alpha, which is a validated target involved in diseases such as rheumatoid arthritis and Crohn's disease. Our second drug for inflammatory disease is ISIS 107248, which is an inhibitor of CD49d for the treatment of multiple sclerosis. An important distinction of our two drugs in preclinical development for inflammatory diseases is that they are second-generation antisense chemistry products rather than first-generation chemistry, and therefore have the potential to be even more potent, to have fewer side effects and to be formulated orally. We believe that the therapies we are creating are exciting and

important to the medical community and patients. We also believe that as we have success in the clinic, our pipeline will increase in value for our shareholders.

GeneTrove - Gene Function and Target Validation Program

At Isis we are using antisense technology to answer the most fundamental question of the genomics revolution: Which genes make the best targets for drug discovery? As the sequences of all 100,000 human genes become available, the answer to this question is of utmost value to pharmaceutical companies focused on drug discovery. To pursue the wrong gene would mean tremendous waste of resources and reduced competitiveness in the marketplace. Antisense inhibitors are ideal tools for understanding what genes do, in what cellular pathways they reside, how they are regulated and whether they are important in disease.

With the proprietary, automated systems that we have developed for our own use to create antisense drugs, we generate solutions to genomic questions very rapidly and efficiently. To determine if a gene is important in a disease, for example, we start with the sequence of a target gene, which is provided by our partners or is available to Isis through our research. Using our proprietary High-Throughput Screening process, our computer designs antisense inhibitors and tests them to find inhibitors that bind to the RNA of the gene. We then select the best inhibitor candidates and perform tests in an animal model cell culture. These in vitro tests enable us to verify that the inhibitor is acting specifically and selectively; it is stopping the expression of the targeted gene in cells in a test tube. At this point we have a lead inhibitor of the gene, and it has taken about one week to do the work described thus far. The final step is to stop the production of the gene in vivo, in a living animal, to see if inhibition of the gene can protect the animal from contracting the disease we are studying. The results of this last step tell us clearly whether or not the gene target is important in the disease of interest and whether or not we, in our own research, or our partner should focus resources on developing a drug to this gene. The beauty of the antisense process that I've just described is that we can "multiplex", or run multiple tests of multiple inhibitors on multiple genes simultaneously and provide information about complex biological pathways very rapidly.

This important information is the product that Isis' GeneTrove division is offering to industry partners. In 1999, Abbott Laboratories and Aventis (formerly Rhone-Poulenc Rorer) initiated gene target validation collaborations with Isis. In January 2000, AstraZeneca became the third partner for Isis' genomics services. We are focused on growing the GeneTrove business and generating incremental revenue for Isis. We believe GeneTrove is highly competitive based on the proprietary technology we have developed and the fundamental antisense mechanism of action patent on RNase H1 that we've been issued. We are very excited about this business opportunity, as GeneTrove uniquely provides partners the vital information to maximize value from genomics.

Ibis Technology - Discovery of Small Molecule Drugs that Bind to RNA

Ibis technology uses genomic sequence data and expertise in RNA structure and function to discover new small molecule drugs that bind to novel targets. Ibis has developed proprietary methods and systems to rapidly identify critical structures in RNA, define the best sites for small molecule drugs to bind to the structure, and then create customized small molecule drugs that will bind specifically to the

intended site. Our innovative tools include comparative genomics, mass spectrometry screening and SAR (structural activity relationship) by mass spectrometry.

A key technological advance that Ibis has pioneered is the use of high resolution mass spectrometry and parallel high-throughput screening to identify small molecule drugs that bind to RNA targets. In this process, each drug and each target RNA is labeled by its exact molecular mass. Since every small molecule is labeled uniquely, a large mixture can be screened in the presence of several RNA targets simultaneously. The identity of the small molecule, the RNA target that it binds, its binding affinity and the location of the binding site on the RNA can be determined in one rapid set of experiments. Using this technology, we expect to be able to screen 10,000 compounds per day against 10 RNA targets.

Since 1997, Ibis has received over $10 million in funding by DARPA, the Defense Advanced Research Projects Agency, to focus on developing antibacterial drugs to protect against biological warfare. The technology is now sufficiently developed to be applied to a wide variety of therapeutic areas, including antibiotics, antivirals, anticancer and Hepatitis C drugs and has attracted the interest of major pharmaceutical companies. Our goal is to initiate at least one major pharmaceutical partnership for Ibis in 2000.

Patent Estate

We are very pleased that our investment in basic antisense research and our focused patenting strategy have yielded exactly what we hoped: a dominant position in both antisense technology and in small molecule drug discovery. Our efforts were recognized recently in the Wall Street Journal, where we were named among the top holders of gene-related patents in the U.S. In fact, we have filed over 800 patents worldwide and have had nearly 600 issued or allowed to date.

Antisense Patents: Our antisense patent estate is extremely broad and very valuable. It can be divided into three components: core antisense mechanisms and biology, core antisense chemistry and antisense inhibitors of genes.

- - Antisense Mechanisms of Action - We have recently added a very important patent to our patent estate covering one of the basic biological processes, or mechanisms, through which antisense inhibitors work. It is the patent on the RNase H1 mechanism. When a DNA-like antisense inhibitor binds to RNA, forming a DNA-RNA duplex, the cell recognizes the duplex as something foreign, or unusual. The enzyme RNase H1 is then activated and destroys the RNA portion of the duplex. The RNase H1 mechanism is a robust and potent antisense mechanism of action. It is a mechanism used by almost all antisense gene functionalization and target validation approaches, and it is the mechanism used by most of the antisense drugs in development. As we believe many pharmaceutical and genomics companies are using antisense technology to functionalize genes, this patent and the other members of this patent family have the potential to generate substantial licensing revenues for Isis.

  Additionally, we have patented the use of RNA-like antisense inhibitors to activate double strand RNase, another mechanism that causes RNA to be destroyed when antisense drugs bind to it. Double strand RNase is an enzyme that is mobilized when the cell recognizes foreign RNA-RNA

duplexes formed when an RNA-like antisense inhibitor binds to RNA. These patents are a part of a growing patent family that give us a dominant position in antisense. This is a very valuable position that we have gained by our innovation.

- - Antisense Medicinal Chemistry - At Isis we have invented many chemistries that can be used to make improved antisense drugs. Our patents cover both the basic building blocks of antisense inhibitors and their use in antisense drugs. These patents contribute to our dominance of antisense.

- - Antisense Inhibitors of Genes - We have over one hundred patents covering antisense inhibitors of genes. Again, this is a valuable patent position that protects the drugs we develop and provides barriers to entry for others to work on these genes.

Ibis Patents: We have pioneered small molecule-based drug discovery focused on creating drugs that bind to structural RNA. We are building a strong proprietary position for this technology.

Leveraging Our Assets to Generate Value

This is an important and exciting time in Isis' history. We are technology-rich. We plan to reap the rewards of our scientific efforts in new ways, by marketing our capabilities in genomics and Ibis small molecule discovery and leveraging our patent estate. These assets represent immediate revenue opportunities for the company and are in effect our products for 2000-2001.

We have a robust product pipeline. We will aggressively move our seven products through clinical development as rapidly as possible to bring new drugs to the market.

We are strong financially. We have raised a substantial amount of capital in the recent months and we will to use less cash in 2000 than in 1999. Based on cash on hand, committed funds and committed financing, we have well over three years of funding, which will enable us to aggressively pursue our research and development goals.

We believe we have in place key elements for success: innovative technologies, broad intellectual property, scientific expertise, therapeutically important products, financial and managerial resources and a vision to make a difference in the lives of patients. We are more enthusiastic than ever about the potential of Isis. We appreciate the support of our investors as we pursue our goals.

Sincerely,

/s/ STANLEY T. CROOKE

Stanley T. Crooke, M.D., Ph.D.
Chairman and CEO

ISIS PHARMACEUTICALS, INC.

FORM 10-K
(FOR THE FISCAL YEAR ENDED DECEMBER 31, 1999)

[INCORPORATED BY REFERENCE AND PREVIOUSLY FILED WITH THE SECURITIES AND EXCHANGE COMMISSION ON MARCH 28, 2000]

CORPORATE INFORMATION
ISIS PHARMACEUTICALS, INC.

EXECUTIVE OFFICERS

STANLEY T. CROOKE, M.D., PH.D.
Chairman of the Board and Chief Executive Officer

B. LYNNE PARSHALL, J.D.
Executive Vice President, Chief Financial Officer and Secretary

DEBBY JO BLANK, M.D.
Executive Vice President

C. FRANK BENNETT, PH.D.
Vice President, Biology

DAVID J. ECKER, PH.D.
Vice President, Managing Director
Ibis Therapeutics, a division of Isis Pharmaceuticals

PATRICIA LOWENSTAM
Vice President, Human Resources and Operations

BOARD OF DIRECTORS

STANLEY T. CROOKE, M.D., PH.D.
Chairman of the Board and Chief Executive Officer
Isis Pharmaceuticals, Inc.

CHRISTOPHER F.O. GABRIELI
General Partner
Bessemer Venture Partners

ALAN C. MENDELSON, J.D.
Senior Partner
Cooley Godward LLP

WILLIAM R. MILLER
Former Vice Chairman of the Board of Directors
Bristol-Myers Squibb Company

MARK SKALETSKY
President and Chief Executive Officer
GelTex Pharmaceuticals, Inc.

LARRY SOLL, PH.D.
Former Chairman and Chief Executive Officer
Synergen, Inc.

JOSEPH H. WENDER
Limited Partner
Goldman, Sachs & Company

CORPORATE HEADQUARTERS
Isis Pharmaceuticals, Inc.
Carlsbad Research Center
2292 Faraday Avenue
Carlsbad, CA 92008
(760) 931-9200
www.isip.com
info@isisph.com

TRANSFER AGENT
American Stock Transfer & Trust
40 Wall Street
New York, NY 10005

LEGAL COUNSEL
Cooley Godward LLP
4365 Executive Drive Suite 1200
San Diego, CA 92121

INDEPENDENT AUDITORS
Ernst & Young, LLP
501 West Broadway Suite 1100
San Diego, CA 92101

COMMON STOCK SYMBOL
NASDAQ: ISIP

This annual report contains forward-looking statements regarding the Company's business and the therapeutic and commercial potential of its technologies and products in development. Such statements are subject to certain risks and uncertainties, particularly those risks or uncertainties inherent in the process of discovering, developing and commercializing drugs that can be proven to be safe and effective for use as human therapeutics, and the endeavor of building a business around such potential products. Actual results could differ materially from those discussed in this annual report. 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, 1999, which is a part of this annual report and is on file with the U.S. Securities and Exchange Commission. As a result, the reader is cautioned not to rely on these forward-looking statements.

[ISIS PHARMACEUTICALS LOGO]

==========

2292 Faraday Avenue Carlsbad, CA 92009
Phone (760) 931-9200
www.isip.com