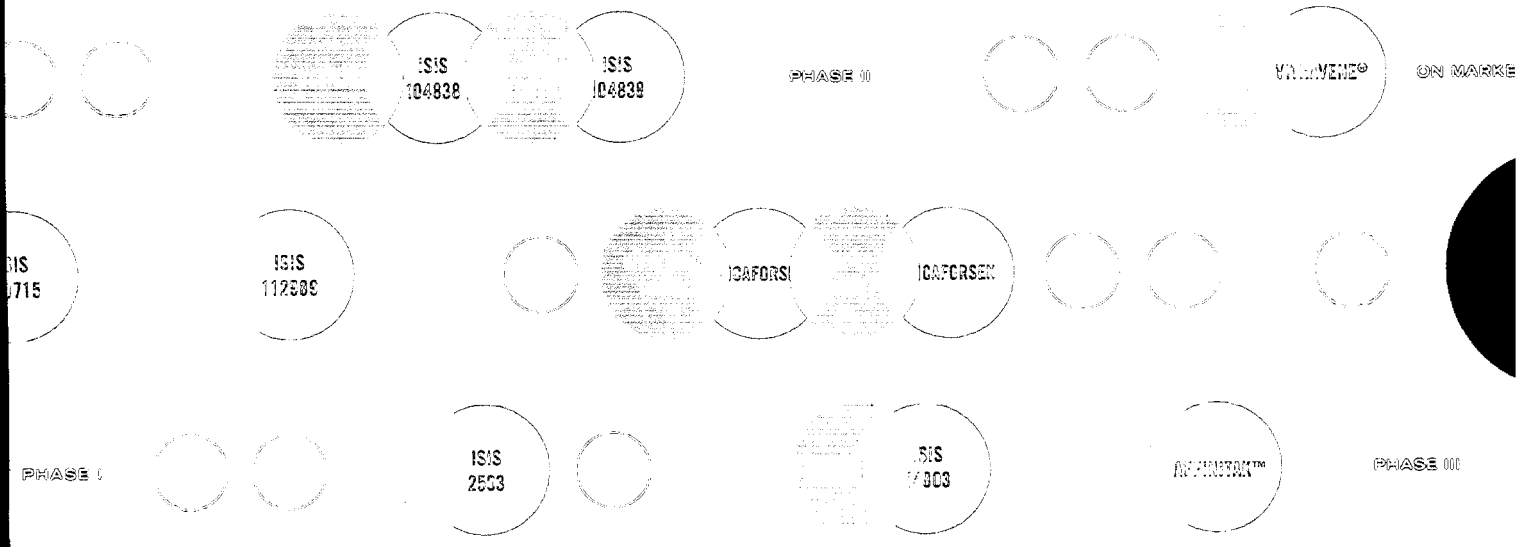
EXPANDING AND RENEWABLE PIPELINE



ISIS PHARMACEUTICALS *Annual Report 2002*

2002

STRENGTH IN PIPELINE

Eisai Pharmaceuticals

Isis is well positioned to create a new sector of the pharmaceutical industry based on antisense drugs.

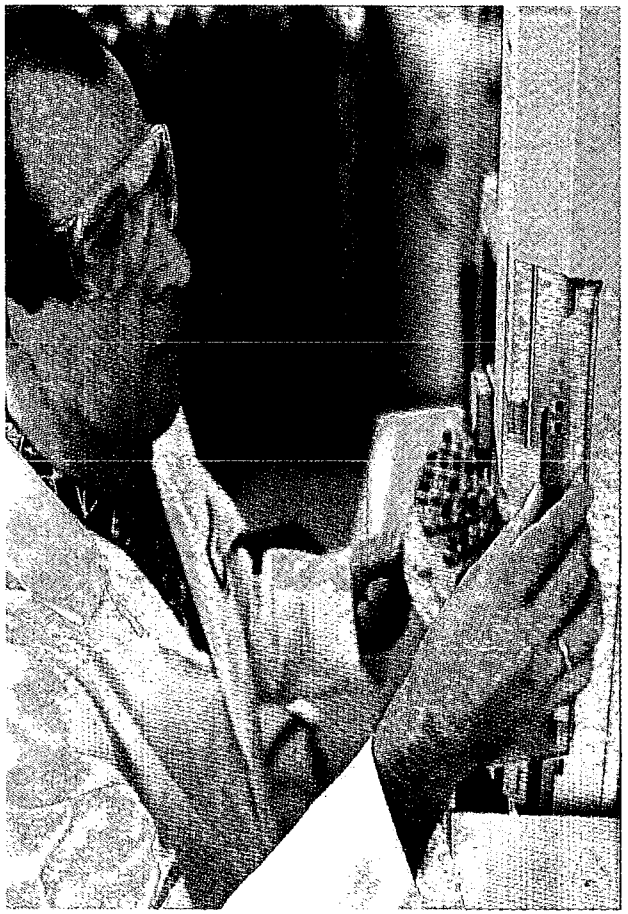
Isis has a leadership position in antisense, a broadly applicable drug discovery and development technology platform. With one drug already on the market, Isis is the owner of the world's largest and most diverse antisense-based product pipeline.

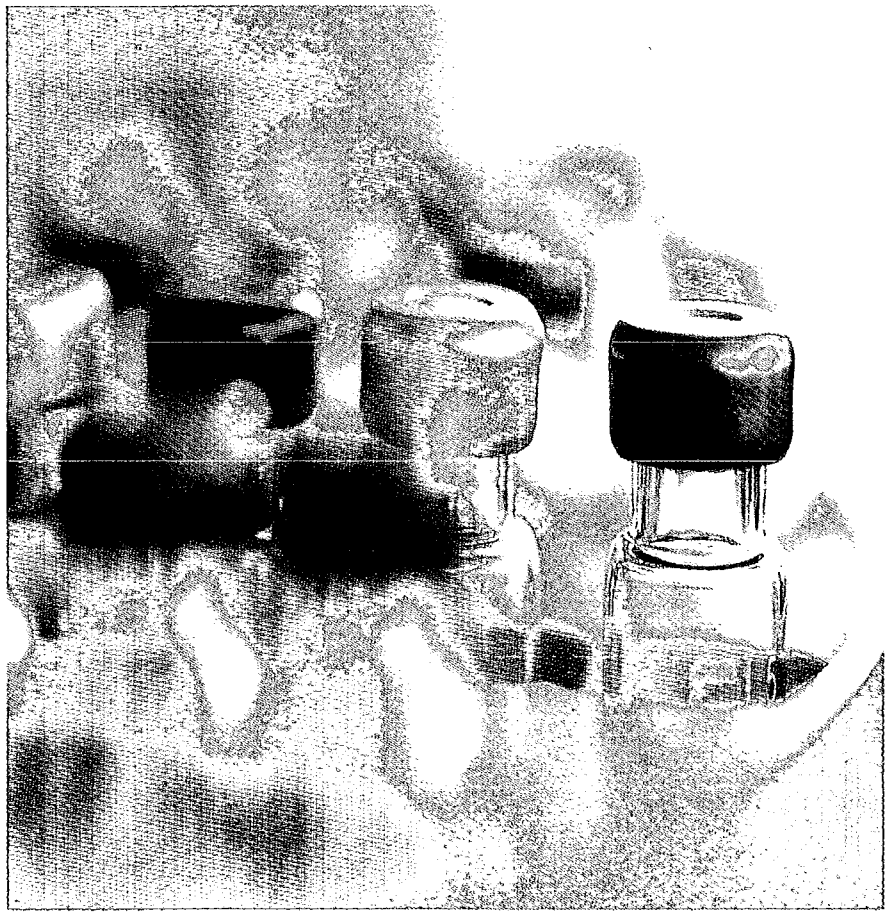
The company's late-stage pipeline consists of:

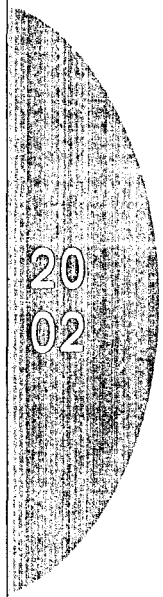
- two drugs in Phase III clinical trials for inflammatory disease and cancer
- five Phase II product opportunities in infectious and inflammatory diseases and cancer
- several drugs in, or advancing rapidly toward, Phase I trials in the areas of diabetes, cancer and multiple sclerosis
- additional early stage product opportunities in the areas of cardiovascular and metabolic diseases and cancer

Isis is a company rich with commercial prospects and opportunities to generate shareholder value. Isis enters 2003 with the resources to move its deep product pipeline forward to meaningful near term milestones.

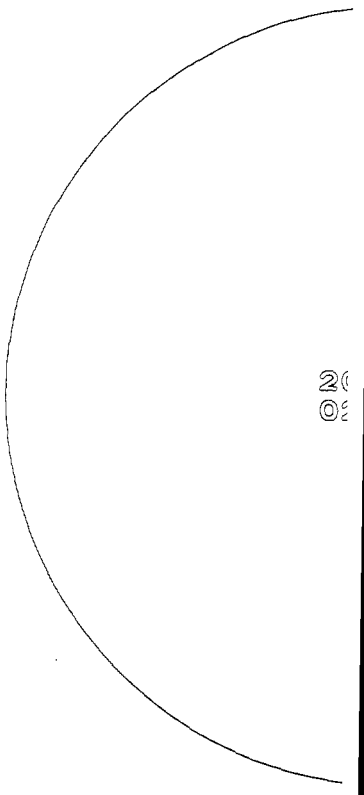
INDUSTRY LEADING ANTISENSE PIPELINE FORMIDABLE PATENT ESTATE VALUABLE GENOMICS SERVICES INNOVATIVE DIAGNOSTIC TECHNOLOGY PLATFORM







Isis Pharmaceuticals' pipeline of 13 products provides numerous opportunities to improve patients' lives and generate value for shareholders. The company's strong financial position, backed by nearly $300 million dollars in cash, provides the resources to achieve these goals.



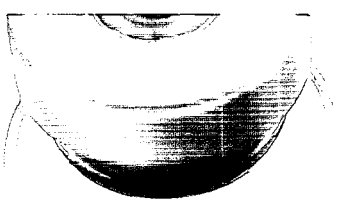
RNA-BASED DRUG DISCOVERY

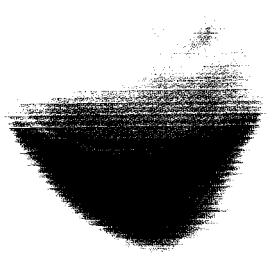
fig 1 **ISIS PIPELINE AT-A-GLANCE**

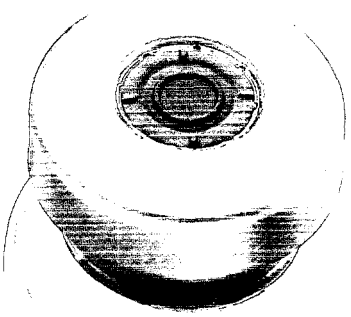
FIRST-GENERATION CHEMISTRY SECOND-GENERATION CHEMISTRY

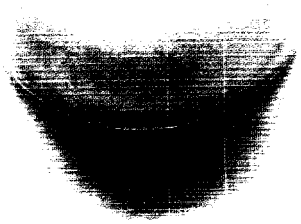
PRODUCT	LEAD INDICATION	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	ON MARKET
Vitravene® (i)	*CMV Retinitis*					
Affinitak™ (ISIS 3521) (p)	*Cancer - NSCLC, Others*					
Alicaforsen (ISIS 2302) (p)	*Crohn's Disease*					
Alicaforsen (ISIS 2302) (e)	*Ulcerative Colitis*					
ISIS 14803 (p)	*Hepatitis C*					
ISIS 2503 (p)	*Cancer - Pancreatic, Others*					
ISIS 104838 (p, o)	*Rheumatoid Arthritis*					
ISIS 104838 (t)	*Psoriasis*					
ISIS 112989 (OGX-011) (p)	*Cancer - Prostate, Others*					
ISIS 113715 (p)	*Diabetes*					
ISIS 13650 (i)	*Diabetic Retinopathy, Others*					
ISIS 107248 (ATL-1102) (p)	*Multiple Sclerosis*					
ISIS 23722 (p)	*Cancer*					
ISIS 301012 (p)	*Cardiovascular*					

i = INTRAVITREAL
p = PARENTERAL
e = ENEMA
t = TOPICAL
o = ORAL









Isis Pharmaceuticals, Inc. is a leading genomics-based drug discovery and development company focused on the untapped therapeutic target, RNA. The goal of the people who work at Isis is to develop new medicines that will improve patients' lives. The company accomplishes this by creating drugs based on the technologies it has invented. Isis also uses its novel approaches to enhance the drug discovery productivity of its pharmaceutical partners.

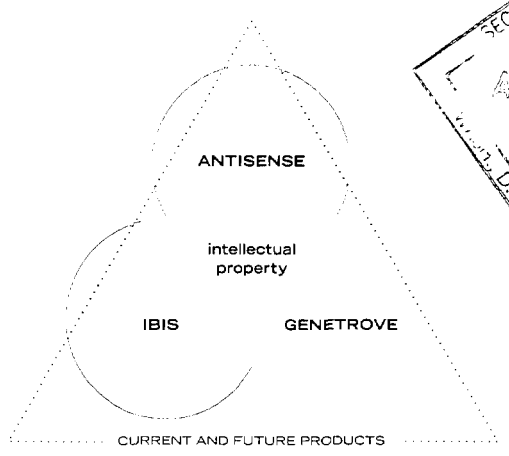


fig 2 ISIS BUSINESS AT-A-GLANCE

ANTISENSE DRUG DISCOVERY AND DEVELOPMENT

Isis' innovative antisense technology platform provides the company with a continually expanding and renewable pipeline. Isis has successfully commercialized the world's first antisense drug and currently has a development pipeline of 13 antisense product opportunities. This antisense-based pipeline, the industry's largest, is the company's most valuable asset.

Antisense drugs are designed to treat a wide range of conditions, including inflammatory, metabolic, dermatologic and hepatic diseases and cancer. Over the past decade, Isis scientists have made great advances in biology, antisense medicinal chemistry and drug delivery. These advancements continue to expand the range of diseases that may be treated with this unique technology.

Antisense is the first class of drugs to control expression of genes through interaction with RNA. Antisense drugs are designed to bind (hybridize) to a segment of a specific messenger RNA (mRNA), the molecule that encodes information to make a disease-causing protein. The cell recognizes an antisense drug hybridized to mRNA and dispatches a natural enzyme to destroy the mRNA, thereby inhibiting production of the disease-causing protein. Due to their high degree of specificity, antisense drugs may be more effective and less toxic than traditional drugs.

BUSINESS DIVISIONS

GeneTrove™ uses the company's antisense technology as a functional genomics tool for determining the biological roles of genes and the value of each gene as a drug target. GeneTrove serves as the engine to direct Isis' drug discovery efforts. Its efficiency provides Isis with a steady stream of drug candidates. The division also monetizes the front end of Isis' drug discovery process by offering functional genomics services to industry partners.

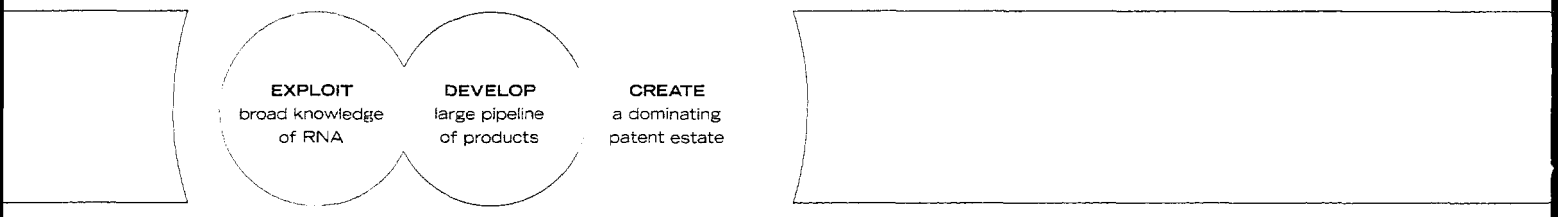
Ibis Therapeutics™ expands on Isis' RNA-based drug discovery and development expertise in order to revolutionize the detection and treatment of infectious diseases. With funding support from the U.S. Department of Defense, Ibis is creating a sensor to detect biological agents and developing small-molecule antibacterial and antiviral drugs that bind to RNA. This technology represents a second drug discovery platform invented by Isis.

INTELLECTUAL PROPERTY

To protect shareholders' investment in antisense and Ibis technologies, Isis has created a broad patent estate of nearly 1,200 issued or licensed patents worldwide. Isis is continually extracting value from its inventions by actively licensing select components of this estate to industry collaborators.

Isis believes that its pipeline, two business divisions, extensive patent estate and expertise in RNA-based drug discovery and development form the foundation for a bright future.

fig 1 KEY STRATEGIES IN ACHIEVING OUR VISION



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

Assessing our progress

LOOKING AHEAD

Dear Shareholders:

2002 was a year of steady and exciting progress in the development of our broad pipeline of antisense drugs and in the strengthening of our business. In the clinic, positive results from five Phase II clinical trials highlighted the year. Our key business achievements included progress in partnerships and improvement of our balance sheet. We ended the year with nearly $300 million in cash.

In March 2003, we and our partner, Eli Lilly and Company, experienced a disappointment. The results of the first Phase III trial of Affinitak™ in patients with non-small cell lung cancer (NSCLC) failed to show statistically significant improvement in median survival in this difficult-to-treat disease. We view this outcome as a temporary setback. Our conclusion is based on overwhelming data from multiple clinical trials, which demonstrate that antisense technology works and is capable of producing a stream of drugs with the potential to form a new sector of the pharmaceutical industry.

In this letter, I will review our assessment of the Affinitak Phase III data, our exciting portfolio of products and upcoming key development milestones, our appraisal of antisense technology and the prospects for our business in 2003 and beyond.

AFFINITAK DATA ASSESSMENT

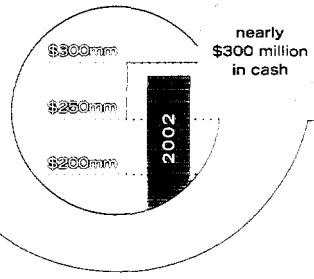
While we did not meet the primary endpoint in the Phase III study of Affinitak in NSCLC, we did observe a clear suggestion of the drug's activity in a more detailed statistical analysis of the data. We will further investigate these data, as well as data from Lilly's Phase III trial of Affinitak. The observations that we make will provide insight into the treatment of NSCLC, where there have been no new first-line treatments in nearly a decade.

It is important to keep the outcome of this Phase III trial in perspective. It is the first of two Phase III trials evaluating Affinitak in NSCLC. Lilly's trial of Affinitak, in combination with the chemotherapy regimen Gemzar™ and cisplatin, provides an opportunity to further evaluate the activity of Affinitak in the near term. As we proceed with these evaluations, Lilly and we will make decisions about the future development of Affinitak. Lilly's commitment to antisense remains strong and we look forward to updating you on the progress of the drug and our ongoing antisense drug discovery collaboration.

CLINICAL MOMENTUM

With 13 antisense products in development, we have a very strong pipeline, evident in its size, advanced stages and therapeutic diversity. At present, we have seven antisense products in either Phase II or Phase III development. We are evaluating these drugs to treat a broad range of diseases that represent important market opportunities, including cancers, Crohn's disease, ulcerative colitis, hepatitis C and rheumatoid arthritis. The diversity of our product portfolio gives us multiple

fig 2 ISIS FINANCIAL STRENGTH



opportunities for success, which helps to offset the inherent risk in the drug development process.

Our pipeline is our most important asset. Looking ahead, we expect 2003 to be another year of clinical momentum as several of our products are approaching major development milestones. Here is a partial list by year:

- '03 Report Phase II results of ISIS 104838, an antisense inhibitor of TNF-alpha, in rheumatoid arthritis
- '03 Initiate human clinical trials of ISIS 113715 in Type 2 diabetes
- '04 Report results of two Phase III trials of alicaforsen (ISIS 2302) in Crohn's disease and refine new drug application (NDA) submission strategy
- '04 Report results of alicaforsen Phase II enema trials in ulcerative colitis and define NDA submission strategy
- '04 Initiate Phase II studies of first oral drug
- '04 /'05 Report results of Lilly's Phase III NSCLC trial of Affinitak in combination with Gemzar and cisplatin

The advances in the clinic are mirrored by progress in drug discovery. We continue to expand our pipeline into new therapeutic areas such as cardiovascular disease.

ANTISENSE TECHNOLOGY APPRAISAL

Our confidence in the potential of antisense technology remains as strong as ever. We have conducted thousands of research experiments and generated significant clinical data that, in aggregate, indicate the tremendous potential of antisense technology. The following points summarize key highlights of this work:

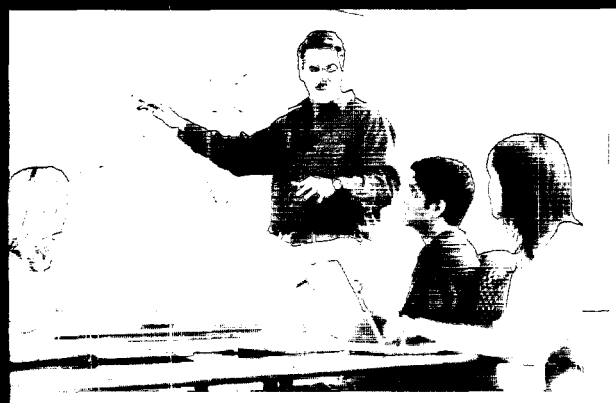
- **Extensive clinical experience with antisense drugs**
  With 13 products in development, we have substantial experience with antisense drugs in the clinic. We have treated approximately 3,000 patients. We have solid evidence of clinical activity and safety, with nine positive Phase II results in the past two years alone.

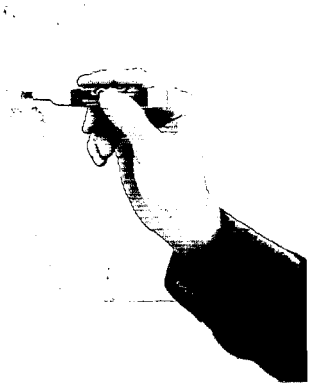
  We are exploiting our first-generation antisense drugs for the treatment of severe diseases and bringing forward our more potent and stable second-generation antisense drugs for the treatment of chronic illnesses. In 2002, we reported positive Phase I results with the first solid oral form in humans, demonstrating that we are likely to be successful in making antisense drugs in "pill" form.

- **Defined behavior of antisense drugs**
  We know antisense drugs distribute to a wide range of organs, including liver, kidney, spleen, bone marrow and fat cells and we know they can be administered through a variety of routes. We believe this breadth of utility provides antisense drugs an even larger therapeutic opportunity than can be approached by protein-based drugs such as monoclonal antibodies.

  We have also learned that antisense drugs within a given chemical class behave in the body similarly from drug to drug, regardless of therapeutic target. Their consistency of behavior allows us to apply what we learn from one drug to future drugs, thus reducing the potential for failure in the early stages of development and creating opportunity for significant competitive advantage.

- **Evidence of antisense inhibition**
  We have inhibited the expression of thousands of genes *in vitro* in a highly specific manner and we have demonstrated that antisense is the most likely mechanism for the effect. We have performed the same experiments for numerous gene targets in multiple animal models of disease. These





experiments demonstrate the specificity of antisense drugs. Specificity is a primary objective of drug discovery. The more specifically a drug binds (hybridizes) to its target, the less likely it is to produce unwanted side effects.

- **Efficiency of production**
  We understand the rules for making antisense drugs, so their design is both rational and rapid. This efficiency vastly speeds and simplifies the identification of a drug that can enter clinical trials.

  We can further leverage the uniformity of antisense drugs in the area of manufacturing. The large-scale synthesis of antisense molecules is a straightforward process, relative to other classes of drugs, so initial start-up costs are significantly less. We believe our advances in manufacturing will make antisense drugs cost competitive with other therapies.

POSITIVE BUSINESS OUTLOOK

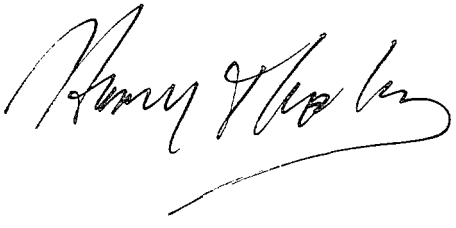
We are pleased with the strength of the company in all areas of the business. Our products in development are maturing and will achieve meaningful milestones in the near term.

We are financially strong. In 2002, we generated record revenue of more than $80 million, strengthened our balance sheet by retiring high-priced debt and ended the year with nearly $400 million in cash and committed cash. Our financial resources enable us to continue to aggressively advance the development of our pipeline.

Our divisions, GeneTrove and Ibis are strategic assets of the company. GeneTrove is a powerful engine for Isis' drug discovery efforts. We added several new target validation partnerships in 2002, which generate revenue for the company. The Ibis group is making tremendous progress on behalf of the U.S. Department of Defense in biological warfare defense research. Ibis' efforts are essentially fully funded by the government.

We hold nearly 1,200 issued patents worldwide. This intellectual property bears on all aspects of RNA-based drug discovery, development and manufacturing. We believe our patent estate gives us a controlling position in antisense as a technology platform.

Based on the cumulative data, antisense has the potential to revolutionize the pharmaceutical industry and Isis holds the keys. The incomparable specificity, opportunity for enhanced safety, breadth of utility and tremendous efficiencies are attributes that establish antisense as a valuable drug discovery platform. With substantial financial resources to support us, we are continuing the steady advancement of our pipeline in order to realize our vision. We appreciate the continued support and confidence of our shareholders and we look forward to a very productive year.



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

Clinical Momentum

2002 marked a year of clinical momentum for a number of Isis' development programs. The company initiated five new studies and reported data from five Phase II programs in the areas of non-small cell lung cancer (NSCLC) and pancreatic cancer, Crohn's disease, hepatitis C and psoriasis. While the company encountered a setback with Affinitak™, the 13 drugs in Isis' pipeline provide the company with multiple opportunities for success.

phase III

PHASE III

AFFINITAK

Isis and its partner, Eli Lilly and Company, announced the results of an open-label, randomized, 616-patient Phase III clinical trial of Affinitak in combination with chemotherapy for the treatment of NSCLC. In the study, no difference was observed in a primary analysis of the overall survival of the two groups. Survival was the primary endpoint of the study.

Upon completion of additional analyses of the trial data, Isis observed evidence of activity of Affinitak that suggests continued evaluation of the drug in NSCLC is merited. For example, in a more detailed statistical analysis, survival of Affinitak-treated patients was greater than that of patients who received chemotherapy alone. This result was statistically significant and suggests Affinitak is active.

In addition, a survival analysis of the 256 patients who completed six cycles of chemotherapy showed a median survival of 17.3 months for Affinitak-treated patients compared to 14.4 months for patients who received chemotherapy alone. This result suggests that duration of treatment with Affinitak may contribute to improved survival. In this subset, results also favored the Affinitak-treated group across multiple secondary endpoints.

The addition of Affinitak to the chemotherapy regimen was well tolerated. There were no increases in severe toxicities or toxicity-related deaths in patients receiving Affinitak, compared to those receiving chemotherapy alone.

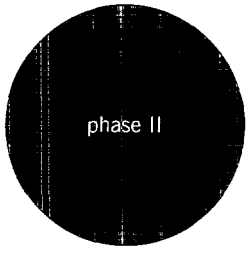
Lilly and Isis plan to evaluate Affinitak's performance in an ongoing Phase III trial, which is studying Affinitak in combination with Gemzar® and cisplatin. As the partners proceed with these evaluations, the companies will make decisions about the future development of Affinitak.

ALICAFORSEN (ISIS 2302)

Alicaforsen, Isis' second most advanced antisense drug, is in two Phase III studies for the treatment of Crohn's disease. One is enrolling patients in the U.S. and the other in Europe. The trials are evaluating the safety and efficacy of alicaforsen at doses higher than previously studied in controlled trials. Isis expects to complete enrollment of both studies in early 2004. Based on previous Phase II trial experience, the company is optimistic about the potential of this drug to reduce symptoms of Crohn's disease.

PHASE II

Alicaforsen produced improvement in Disease Activity Index (DAI) and Clinical Activity Index (CAI) scores in patients with ulcerative colitis (UC), according to results of an initial Phase II study. DAI and CAI are common clinical index scoring systems for the severity of symptoms and quality of life for patients with UC. Based on these results, Isis has initiated two Phase II trials with this drug. The first is a 170-patient study which compares



the safety and efficacy of an enema formulation of alicaforsen to a mesalamine enema, a widely used medication for UC. The second is a 100-patient placebo controlled study evaluating the safety and efficacy of multiple dosing regimens of alicaforsen in patients with UC.

ISIS 14803

ISIS 14803 has the potential to be an important new agent for the treatment of the hepatitis C virus (HCV). In November 2002, Isis presented data from two Phase II studies that showed ISIS 14803 is active in drug-resistant, genotype 1 HCV patients, the most difficult-to-treat segment of the HCV patient population. The drug demonstrated promising antiviral activity by producing up to 3.8 log reductions in viral titer, or a 6,300-fold decrease in viral load, in patients with the disease. Final results of an ongoing Phase II trial will be reported in 2003. The company plans to initiate additional Phase II studies of ISIS 14803 in combination with currently used HCV treatments.

The commercial potential of ISIS 14803 was enhanced for Isis in 2002. Elan Corporation, plc, concluded its participation in the HepaSense™ joint venture. As a result, Isis regained full rights to ISIS 14803.

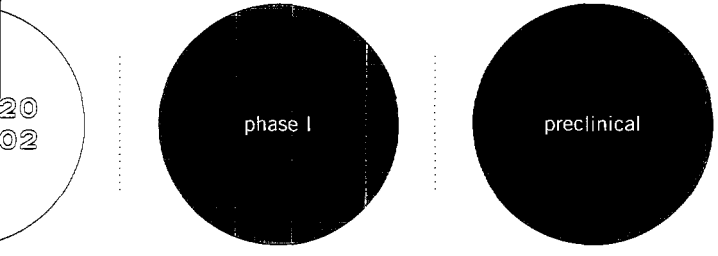
ISIS 2503

ISIS 2503 is in Phase II development for the treatment of pancreatic, breast and NSCLC cancers. Final results of a Phase II study in pancreatic cancer demonstrated that 57.5 percent of 48 patients who received ISIS 2503 plus Gemzar survived six months or longer. Based on these data, Isis is considering various strategies, including partnering, for the further development of this compound in pancreatic cancer. Results from studies of the drug in pancreatic, breast and NSCLC cancers are expected to be reported in 2003.

ISIS 104838

ISIS 104838 is an antisense inhibitor of TNF-alpha, a molecule known to be involved in inflammatory diseases. ISIS 104838 is being evaluated in Phase II trials for the treatment of rheumatoid arthritis (RA) and psoriasis. In RA, Phase II studies are evaluating the efficacy of ISIS 104838 and its ability to reduce TNF-alpha levels in tissue and blood. A topical cream formulation of ISIS 104838 is being evaluated in a Phase II study in patients with moderate to severe psoriasis. Results from all three trials are expected in late 2003.

ISIS 104838 is the first second-generation antisense compound to advance into Phase II development. This proprietary chemistry has the potential to provide safety, efficacy and cost advantages compared to protein inhibitors, including those that inhibit TNF-alpha.



PHASE I

ISIS 104838

To further enhance the commercial competitiveness of antisense drugs, Isis is developing an oral delivery platform for the company's second-generation compounds. Isis announced favorable Phase I data from the first solid oral formulation studies in man in 2002 with ISIS 104838. Data from this trial demonstrated that antisense drugs can be delivered in an oral capsule form and achieve bioavailability levels sufficient to be commercially viable. The best performing formulation achieved a predicted average tissue bioavailability of 10%-15%. Bioavailability refers to the percentage of ingested drug that is actually absorbed into the bloodstream and then tissues. Based on these findings, the company has selected a lead solid oral formulation for further optimization and advancement into Phase II trials.

ISIS 112989 / OGX-011

Isis' partner OncoGenex Technologies, Inc. initiated a Phase I program of ISIS 112989 in patients with cancer. ISIS 112989, a second-generation antisense drug, is being developed to decrease tumor resistance to existing treatments, such as chemotherapy, hormone ablation therapy and radiation therapy. The first Phase I trial is evaluating ISIS 112989 in combination with hormone therapy prior to surgical removal of the prostate. In 2003, the partnership initiated a second Phase I study which is evaluating ISIS 112989 in combination with Taxotere® in various solid tumors. ISIS 112989 is Isis' third anti-cancer drug currently in human clinical trials and the first second-generation compound to be tested in patients with cancer.

ISIS 107248 / ATL1102

Through a partnership with Antisense Therapeutics Limited (ATL), ISIS 107248 is advancing into Phase I human clinical trials. The first trial, scheduled to begin by mid-year, will evaluate the pharmacokinetic and safety profile of the drug in approximately 40 volunteers. ISIS 107248 is an antisense inhibitor to CD49d, a sub-unit of VLA-4 (Very Late Antigen-4). Inhibition of VLA-4 has been shown to have positive effects in animal models of a number of inflammatory diseases, including the autoimmune disease multiple sclerosis.

PRECLINICAL

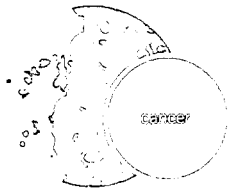
Isis has several second-generation antisense compounds in preclinical development for the treatment of cancer and metabolic and cardiovascular diseases. Most recently, the company added the cardiovascular agent ISIS 301012 to its pipeline, further expanding the technology's therapeutic potential.

Isis licensed its exciting preclinical anticancer candidate ISIS 23722 to Lilly in 2002, as part of the companies' expanded research collaboration in cancer. ISIS 23722 targets survivin, a protein that has been shown to play a role in preventing cancer cell death.

Isis plans to initiate human clinical trials of ISIS 113715 for the treatment of Type 2 diabetes. In preclinical studies, ISIS 113715 improved the regulation of blood sugar levels in animal models of Type 2 diabetes.

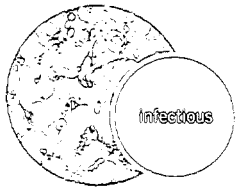
With a robust antisense pipeline of drugs, Isis is well poised to advance the technology to benefit the patient, medical and investment communities.

CLINICAL PIPELINES BY THERAPEUTIC AREA

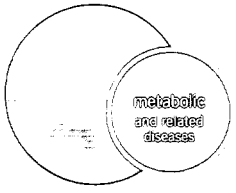


	TARGET	LEAD INDICATION	PARTNER	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	ON MARKET
Affinitak™	*PKC-alpha*	*Cancer - NSCLC, Others*	*Lilly*					
ISIS 2503	*H-ras*	*Cancer - Pancreatic, Others*	*Isis*					
ISIS 112989 (OGX-011)	*Clusterin*	*Cancer - Prostate, Others*	*OncoGenex*					
ISIS 23722	*Survivin*	*Cancer*	*Lilly*					

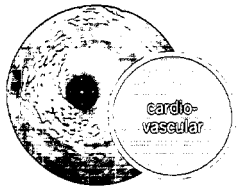
	TARGET	LEAD INDICATION	PARTNER	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	ON MARKET
Alicaforsen	*ICAM-1*	*Crohn's Disease*	*Isis*					
Alicaforsen	*ICAM-1*	*Ulcerative Colitis*	*Isis*					
ISIS 104838	*TNF-alpha*	*Rheumatoid Arthritis*	*Isis*					
ISIS 104838	*TNF-alpha*	*Psoriasis, Others*	*Isis*					
ISIS 107248 (ATL-1102)	*VLA-4*	*Multiple Sclerosis*	*ATL*					



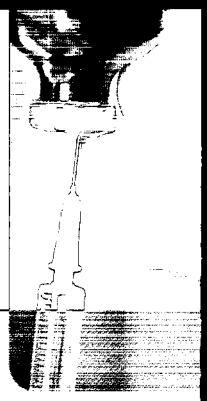
	TARGET	LEAD INDICATION	PARTNER	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	ON MARKET
Vitravene®	*Antiviral*	*CMV Retinitis*	*Novartis*					
ISIS 14803	*HCV*	*Hepatitis C*	*Isis*					



	TARGET	LEAD INDICATION	PARTNER	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	ON MARKET
ISIS 113715	*PTP-1B*	*Diabetes*	*Isis*					
ISIS 13650	*c-raf*	*Diabetic Retinopathy, Others*	*Isis*					



	TARGET	LEAD INDICATION	PARTNER	PRECLINICAL	PHASE 1	PHASE 2	PHASE 3	ON MARKET
ISIS 301012	*apoB-100*	*Cardiovascular*	*Isis*					



Capitalizing on CORE RESEARCH

Isis has maintained its strong track record of "firsts" in antisense research. The company's commitment to and investment in core antisense research is unparalleled in the industry and its scientists have contributed significantly to the industry's major scientific breakthroughs in the technology. In 2002, Isis' research yielded exciting results in a new therapeutic area, in drug delivery and formulations and in the area of intellectual property.

NEW THERAPEUTIC OPPORTUNITY

Isis entered the cardiovascular disease arena with the identification of its first preclinical drug candidate. ISIS 301012 targets apoB-100, a protein that plays a pivotal role in the production of low-density lipoprotein (LDL), the "bad" cholesterol. It has proven difficult to design small molecule drugs to target the apoB-100 protein since this target is neither an enzyme nor a receptor. However, ISIS 301012 selectively binds (hybridizes) to the target RNA sequence that encodes for the apoB-100 protein, rather than to the protein itself.

In preclinical studies, an Isis apoB-100 inhibitor reduced total cholesterol, specifically LDL, very low-density lipoproteins (VLDL) and triglyceride levels, all of which are keys to managing heart disease. With more than 100 million American adults living with excessively high cholesterol levels, new therapies are needed for this widespread condition. Isis plans to expeditiously advance the development of ISIS 301012.

ORAL DELIVERY OF ANTISENSE DRUGS

Isis continues to enhance the commercial potential of antisense drugs by increasing the number of routes by which these drugs can be administered to patients. One of the most important achievements of 2002 was demonstration of the feasibility of solid oral dosing of antisense drugs in humans, using Isis' second-generation chemistry.

Isis' antisense drugs are currently delivered by enema, topical cream, intravenous infusion, subcutaneous injection and intravitreal injection formulations. Additionally, Isis has demonstrated the potential for pharmacological activity of aerosol administered drugs in asthma models.

Isis' work on the oral delivery of antisense drugs began in 1996 and its scientists have systematically generated a comprehensive body of data in support of this platform-enhancing goal. The timeline below outlines research achievements that laid the

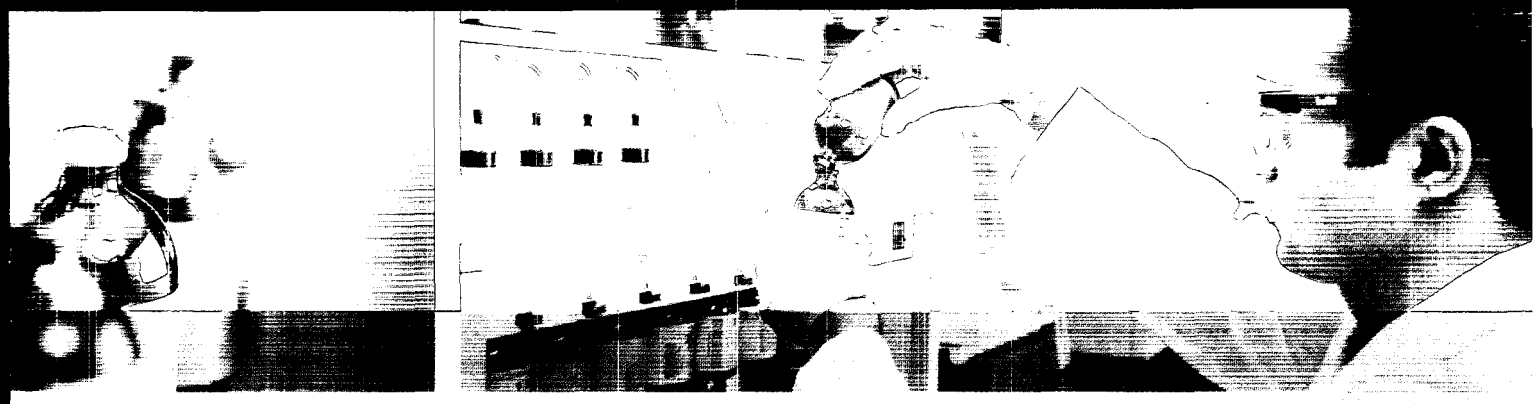
fig.1 **ORAL DELIVERY RESEARCH - systematic steps to address the challenge**

Created animal models to assess the percentage of antisense drug absorbed into the bloodstream.

Demonstrated Isis' second-generation (2'-MOE) chemistry increased drug absorption 5-10 fold over first-generation chemistry.

Identified penetration enhancing chemicals to increase the intestine's natural ability to absorb the drug into the bloodstream.

Invented novel oral formulation that contained both antisense drug and penetration enhancer.



RESEARCH SCALE SYNTHESIS OF ANTISENSE DRUGS

foundation for the past year's clinical success in oral antisense delivery.

The potential of oral administration greatly enhances patient convenience and expands the range of conditions that can be treated with antisense. Isis' cutting-edge research in oral development strengthens the commercial potential of second-generation antisense drugs.

PROTECTING INNOVATION

In 2002, Isis celebrated the issuance of its 1000th patent. Isis has created a formidable intellectual property position in RNA-based drug discovery. This patent estate, an important asset to the company, is a product of its extensive research and innovation. The company's strong patent position protects the investments it has made in creating antisense technology, encourages partnerships with pharmaceutical companies interested in utilizing its technologies and generates near term revenue through licensing.

The company continues to enhance its intellectual property position and capitalize on its core research, while improving antisense technology. Several key patents were awarded to Isis this year, including an important set covering second-generation antisense chemistries. Specifically, Isis' proprietary, second-generation chemistry, 2'-O-methoxyethyl (2'-MOE), increases the stability and potency of Isis' antisense drugs. Additionally, 2'-MOE chemistry enhances safety and the potential for oral bioavailability of antisense drugs. Isis also strengthened its ownership and license positions in what many in the industry consider to be the "next generation" of antisense therapeutics – peptide nucleic acid (PNA) drugs – with the issuance of new PNA patents.

SUCCESS IN RESEARCH PARTNERSHIPS

Isis has continued to advance its broad antisense drug discovery program with Eli Lilly and Company. Isis has delivered antisense inhibitors to more than 225 different gene targets, several of which have been validated as drug targets by the partnership. These targets, which span multiple therapeutic areas, have advanced into antisense drug discovery.

Isis also made rapid progress in its drug discovery collaboration with Amgen Inc. In less than 18 months since initiation of this partnership, Isis achieved two research milestones. Additionally, Merck & Co., Inc. and Isis extended their hepatitis C drug discovery collaboration for a second time.

Isis' commitment to its comprehensive core research program has led to successful partnerships that contribute to the advancement of antisense technology and to the broadening of Isis' pipeline.

1999

Established joint venture with Elan Corporation, plc, a leader in drug delivery, to gain expertise and secure funding to develop solid formulation for human dosing.

2000

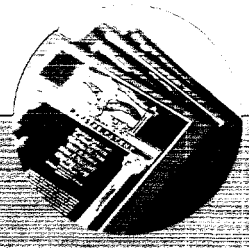
Dosed humans with first-generation antisense drug in a liquid formulation. These studies demonstrated initial proof-of-concept.

2001

Dosed humans with a second-generation antisense drug in a liquid formulation. Results yielded acceptable absorption levels into the bloodstream and supported further studies.

2002

Dosed humans with solid forms of ISIS 104838, a second-generation antisense drug.



GeneTrove and Ibis Therapeutics

LEVERAGING TECHNOLOGY PLATFORMS

ANTISENSE-BASED FUNCTIONAL GENOMICS

GENETROVE™ A DIVISION OF ISIS PHARMACEUTICALS, INC.

Gene functionalization and target validation are the first steps in drug discovery. Gene functionalization is the identification of the role a particular gene plays in disease. Target validation is the determination of a gene's value as a drug target. In Isis' GeneTrove™ division, the company uses optimized, target-specific antisense inhibitors to generate this critical information. The resulting insights direct the drug discovery research of Isis and its antisense drug discovery partners, Lilly and Amgen.

Isis is capitalizing on its antisense-based functional genomics expertise and proprietary high-throughput process by offering functional genomics services to industry partners though GeneTrove. Specifically, the division provides two main product offerings to partners: Custom Target Validation collaborations and intellectual property licenses.

In its Custom Target Validation collaborations, the company works with partners to identify the biological role of specific genes and determine the suitability of those targets for drug discovery. The information generated from these studies is then used to enhance and expedite partners' drug discovery decisions. These services are generally conducted on a non-exclusive basis, which allows Isis to retain rights to develop antisense drugs to the genes evaluated.

GeneTrove also licenses its antisense-based functional genomics patents to partners. Through these agreements, GeneTrove collaborators gain access to Isis' functional genomics expertise for use in their internal genomics programs.

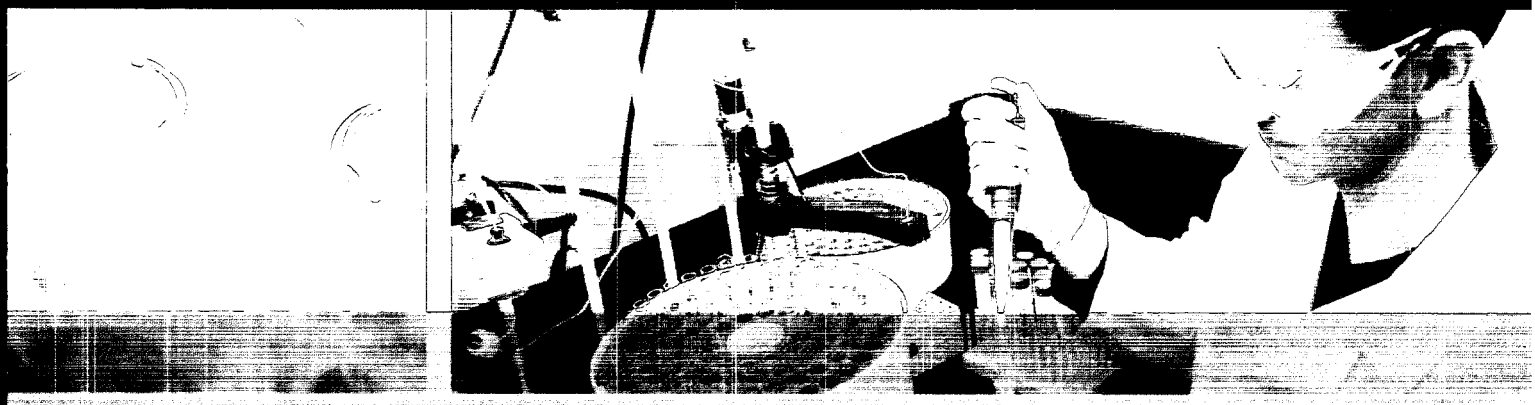
While advocating partnering whenever possible, Isis actively defends its intellectual property position and has made progress on this front. In 2002, the company reached a mutually agreeable business resolution to a patent infringement lawsuit with Sequitur, Inc. As a result, Isis granted Sequitur a license to certain Isis patents for target validation and functional genomics using first-generation antisense chemistry in exchange for licensing fees from Sequitur.

In response to changes in the genomics market in 2002, Isis discontinued its investment in the division's Human Gene Function Database product. This action further aligned GeneTrove's activities with the company's overall business strategy and with partners' immediate drug discovery needs.

GeneTrove's partnerships continue to contribute revenue to Isis, expand the number of companies utilizing Isis' antisense technology and create potential opportunities for new drug discovery and development collaborations.

GENETROVE partners and licensees

- Amgen Inc.
- atugen AG
- Celera Genomics
- Chiron Corporation
- Eli Lilly and Company
- GlaxoSmithKline
- Johnson & Johnson Pharmaceutical Research & Development, LLC
- Merck & Co., Inc.
- Pfizer, Inc.
- Pharmacia Corporation
- Sequitur, Inc.



SAMPLE PURIFICATION FOR ANTISENSE RESEARCH

RNA-BASED DIAGNOSTICS AND DRUG DISCOVERY

Ibis Therapeutics™ has expanded on Isis' RNA-based drug discovery and development expertise in order to revolutionize the detection and treatment of infectious diseases. The division's goals are to create a sensor to detect biological agents and to develop small molecule antibacterial and antiviral drugs that bind to RNA. To accomplish these tasks, Ibis scientists integrate functional genomics, bioinformatics and RNA-focused chemistry programs with novel high-throughput, mass spectrometry-based screening methods.

Ibis scientists are engaged in the development of a sensor designed to detect infectious organisms, including known, unknown, unculturable, or bioengineered elements that could be used in biological warfare attacks. The program, called the Triangulation Identification for Genetic Evaluation of Risks (TIGER), is underwritten by a $9 million contract from the Defense Advanced Research Projects Agency (DARPA). Ibis is working with San Diego-based Science Applications International Corporation (SAIC) on this program. The companies made significant research progress in the past year, as they successfully conducted proof-of-principle experiments and began testing field samples. Beyond government applications, the device may have future commercial potential in the public health arena as a tool to more rapidly and accurately diagnose infectious diseases.

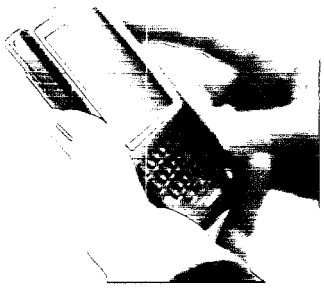
Ibis has also been working with the U.S. government over the past six years to identify and develop broad-spectrum anti-infective drugs that could be useful in national defense and beyond. Ibis continued its stream of funding from the Department of Defense with the receipt of a new three-year $2.4 million government contract to transition its drug discovery program to the U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID).

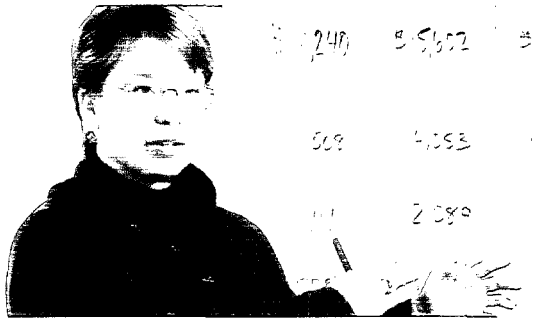
To protect its groundbreaking inventions, Ibis has created a significant intellectual property portfolio comprised of more than 120 applications and 10 issued patents. In 2002, several important patents were issued to Ibis pertaining to its proprietary computational genomics and high-throughput mass spectrometry-based screening methods for drug discovery.

The division reflects Isis' commitment to innovation and provides the company with additional product and partnership opportunities. Over the course of its history, Ibis has received government-funded grants and contracts totaling approximately $23 million. Beyond USAMRIID and DARPA, Ibis has research relationships with several other government entities including the United States Navy, the Federal Bureau of Investigation and the Centers for Disease Control and Prevention.

Financial STRENGTH

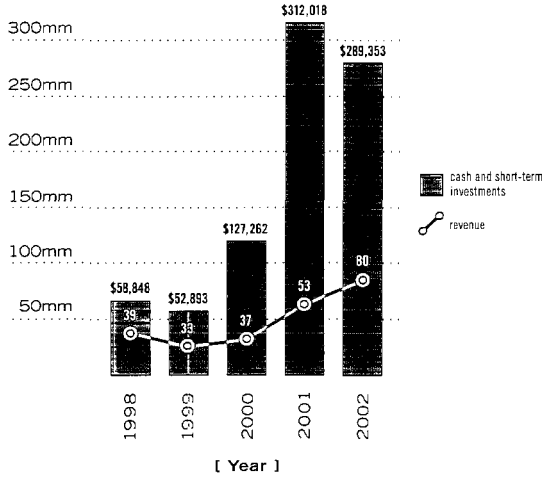
Isis has effectively managed its financial resources to aggressively advance its large pipeline and numerous research programs. In 2002, the company took several strategic measures to strengthen its financial position. Isis had nearly $300 million in cash and short-term investments at year-end. The improved balance sheet is a key asset for the company.





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

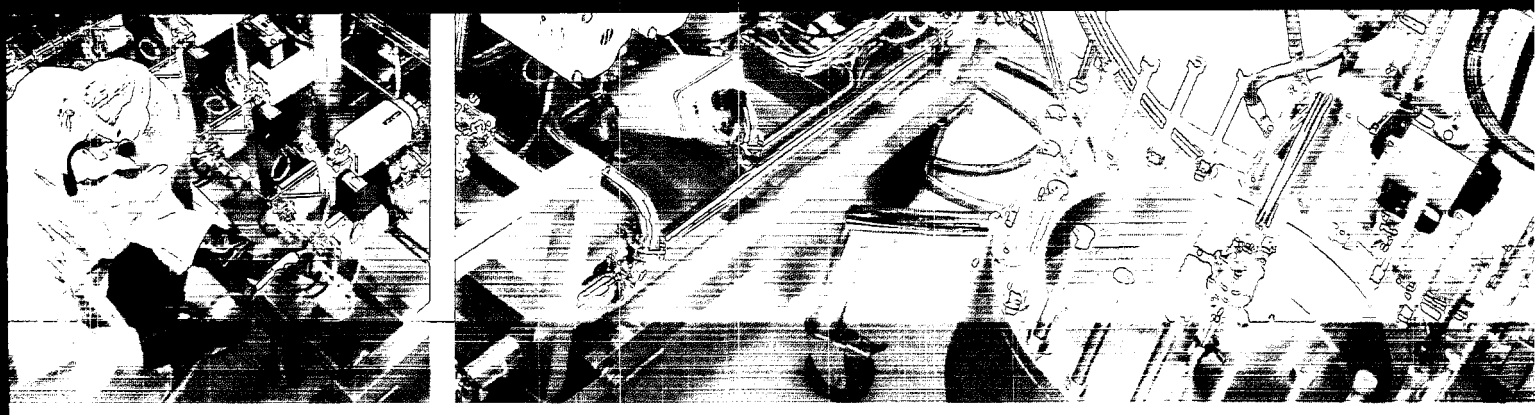
fig 1 REVENUE AND CASH BY YEAR



RECORD REVENUE

Isis reported record revenue of more than $80 million in 2002, exceeding the previous year's revenues by 51%. The company continues to benefit from numerous sources of revenue, including drug licenses, drug discovery partnerships, patent licenses, GeneTrove™ collaborations and government contracts. The company's collaboration with Eli Lilly and Company was the primary contributor to the revenue increase. More specifically, in 2002 Isis earned revenue from progress in a variety of existing relationships and from the creation of new partnerships:

- the Lilly Affinitak™ partnership
- the addition of cancer targets to the Lilly antisense drug discovery collaboration
- the achievement of a milestone from the antisense drug discovery collaboration with Amgen Inc.



COMMERCIAL SCALE SYNTHESIS OF ANTISENSE DRUGS

- the second extension of the hepatitis C drug discovery collaboration with Merck & Co., Inc.
- the addition of new GeneTrove collaborations with Amgen, Merck, Pharmacia Corporation and GlaxoSmithKline
- the receipt of a new government contract for Ibis' drug discovery program

Perhaps the most strategically significant partner transaction of 2002 was the expansion of the company's relationship with Lilly to include the manufacturing of Affinitak. This transaction enabled Isis to significantly upgrade and enlarge its own manufacturing suite and add a second suite dedicated to Affinitak. This facility is a key asset for Isis, since it will be available to support the company's development and commercialization of future antisense drugs.

Isis' ongoing corporate partnerships continue to provide the company with a strong financial foundation. For example, in early 2003 Isis achieved a second research milestone in its Amgen antisense drug discovery collaboration. The revenue generated by partner activities helps to offset the costs of the company's research activities and clinical development programs.

IMPROVED BALANCE SHEET

Isis took several strategic steps in 2002 to fortify its balance sheet through preservation of its cash balance and effective debt management. In addition to the nearly $300 million in cash at year-end, Isis has funding commitments from the Lilly research collaboration and other partners of approximately $100 million, bringing the total of cash and committed cash to nearly $400 million available to Isis through 2005. With this financial position, the company is well poised to advance its broad pipeline to many key clinical milestones.

This cash balance was sustained primarily through cash inflows from partnerships and the issuance of $125 million in 5.5% convertible notes. With the proceeds from the financing, Isis substantially improved the structure of its debt through two transactions:

1. The company prepaid $74 million in 14% senior subordinated notes.
2. The company prepaid, at a 25% discount, nearly $20 million in 12% convertible debt held by Elan Corporation, plc.

The early retirement of this high-interest debt resulted in net savings of approximately $40 million in total future interest payments. The financial flexibility gained through the convertible debt offering also produced working capital to use for clinical and preclinical development, the manufacturing of drugs and capital expenditures.

Isis' enhanced financial condition enabled the company to regain assets from the Elan joint ventures on favorable terms. Elan concluded its funding and scientific participation in both the HepaSense™ and Orasense™ joint ventures. Isis regained rights to an exciting drug for the treatment of hepatitis C, ISIS 14803 and to the oral formulation of ISIS 104838, which is in development for rheumatoid arthritis.

In April 2003, Isis implemented an operating plan to manage the company's expenses, while preserving research and clinical programs that provide multiple opportunities to move drugs toward commercialization. The company believes this operating plan, which included a modest reduction in its workforce, is the best strategy to advance its product pipeline to key value inflection points and gives Isis the opportunity to generate value for patients and shareholders.

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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. 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 annual report. 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, 2002, which accompanies this annual report and is on file with the U.S. Securities and Exchange Commission, copies of which are available from the company.

ACKNOWLEDGMENTS

cover insert: Hans Gaus, *Associate Director.* p05: Kumar Hari, *Scientist/Bio data analysis,* Helena Yang, *Senior Scientist,* Bridget Lollo, *Associate Director,* Scott Henry, *Executive Director.* p11: Gopal Inamati, *Research Associate.* p13: Eric Marcusson, *Associate Director.* p15: Demitrius Walcott, *Scientist*

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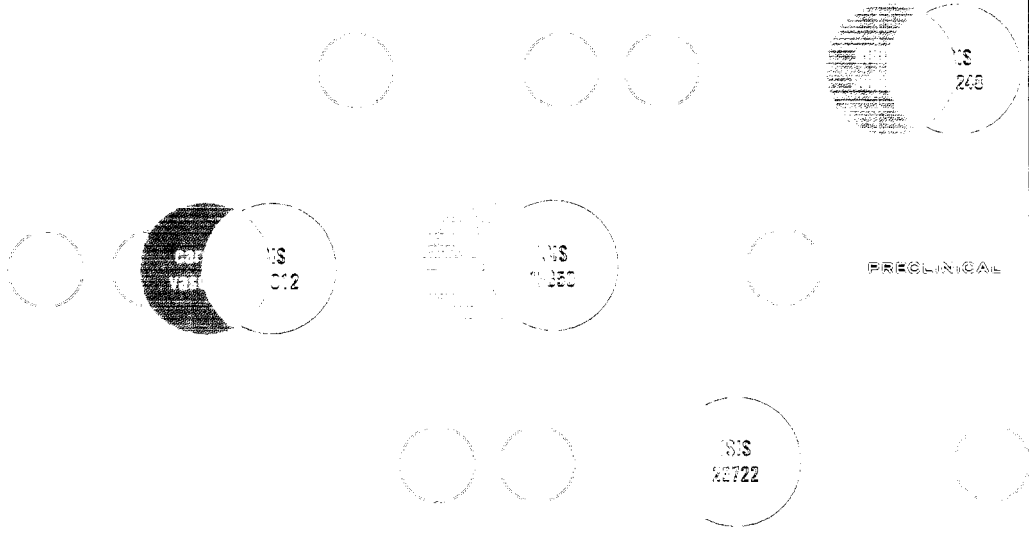

RNA-BASED
drug discovery

PRECLINICAL