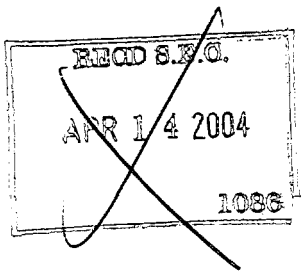
Realizing value from innovation



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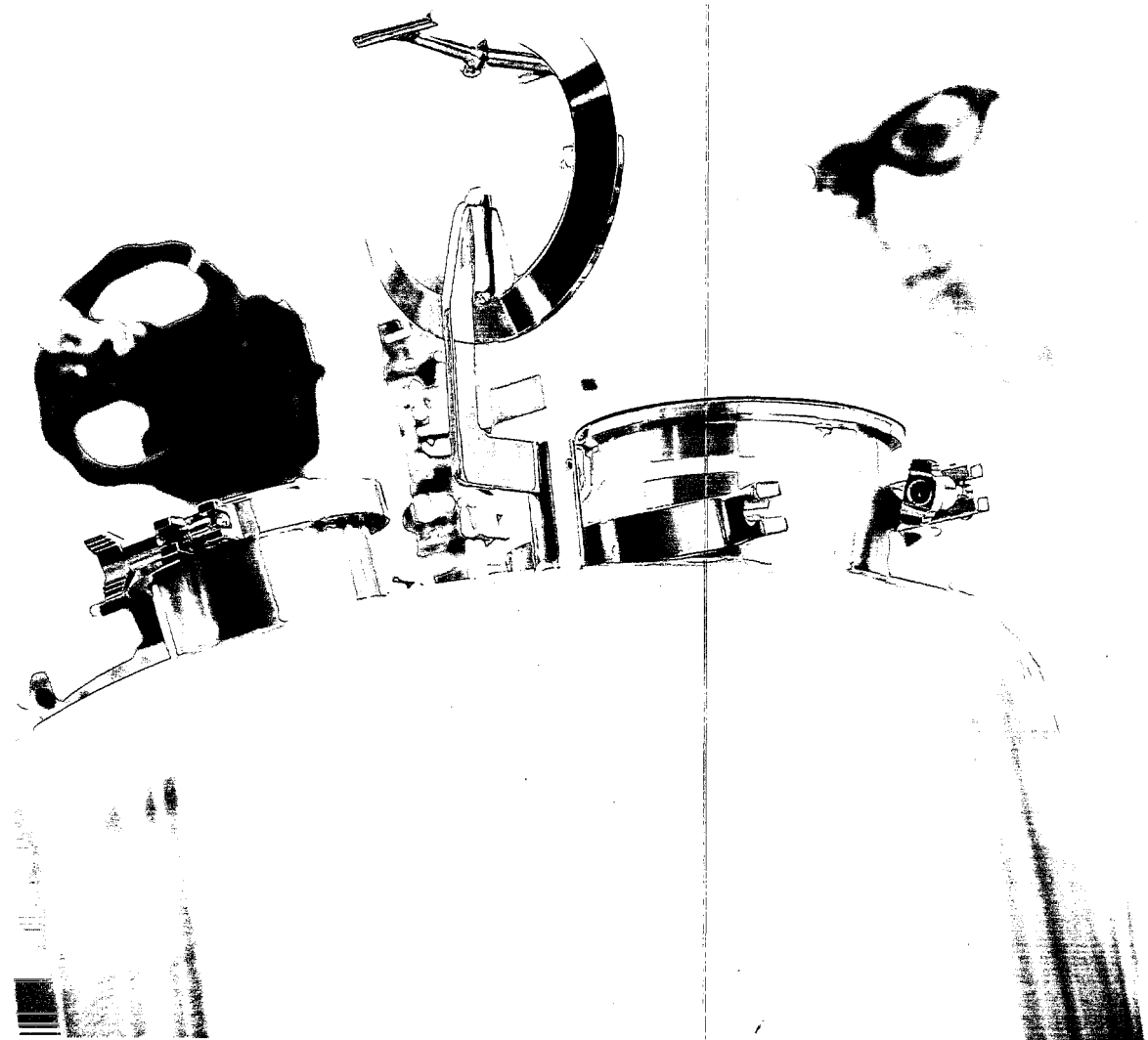
Isis Pharmaceuticals
2003 Annual Report

INC

Company profile

Isis Pharmaceuticals, Inc. is a leading drug discovery and development company focused on the therapeutic target, RNA.

The goal of the people who work at Isis is to create technology platforms that yield products to benefit patients and that represent significant commercial **opportunity.** The company has made tremendous **advancements** toward this goal, as evidenced by its portfolio of 11 antisense drugs in **development** to treat a wide range of diseases. Expanding on its novel **innovations,** Isis also has designed a new biosensor with the potential to revolutionize the identification of infectious disease. The company has led the way in RNA-based drug **discovery** and that leadership is reflected in its intellectual property position of more than 1,300 issued patents. With an **experienced** management team, Isis is moving these assets forward to bring value to shareholders.



Chairman's letter

Dear Shareholders,

At Isis, we are pursuing an exhilarating, challenging mission: to invent a ground-breaking technology platform for drug discovery and development, and use it to create a new sector of the industry. In this letter, I will provide my perspective on Isis' progress in the realization of this goal by reviewing our business strategies and describing our near- and long-term approach to generating shareholder value.

Our strategies to achieve this mission are clear and focused:

1. Invest in basic research to create broadly-enabling RNA-based technologies and use them to develop drugs and products.

We now know how to exploit RNA for drug discovery. We can rapidly create an antisense inhibitor to any gene target and then use that inhibitor as a drug. Through our core research and clinical development programs, we have built a deep understanding of the characteristics of these drugs, which guides our development. We understand where these drugs distribute in the body, how they get there, how long they stay there, and how the body clears them. Further, we have established the safety profile of these drugs, and have created the world's largest safety database of antisense drugs in man.

Our leadership in RNA-based drug discovery is unmatched, and we have numerous research programs that continue to enhance the technology and the properties of our drugs. Our ongoing antisense mechanisms initiative, for instance, is a program of great interest. We have identified many mechanisms by which antisense drugs work, including RNase H, splicing and RNAi. Our recently initiated alliance with RNAi leader, Alnylam Pharmaceuticals, Inc., to discover and develop RNAi drugs is an example of how we are using our expertise to continually expand the therapeutic potential of antisense drugs.

2. Develop and commercialize a large pipeline of drugs.

Fundamental to our strategy is the construction of a large pipeline of drugs with significant market potential. Our 11 drugs in development give us many opportunities for clinical and commercial successes. Simultaneously moving numerous drugs forward in development allows us to better manage the risks inherent in clinical development, and expands our prospects for accomplishing our mission.

2004 will be another year of clinical momentum as we will reach a number of key clinical milestones with our first- and second-generation drugs that provide multiple opportunities to advance this pipeline. We already have been successful with our first-generation drugs, as shown by our commercialization of the first antisense drug, Vitravene®. This year, we expect to announce data from late-stage trials of our first-generation drugs in inflammatory bowel diseases, hepatitis C and cancer. Our first-generation drugs are well-suited for the treatment of these severe conditions.

2004
Upcoming clinical milestones

- Report performance of alicaforsen in Phase 3 Crohn's disease studies
- Report performance of alicaforsen in Phase 2 studies in ulcerative colitis
- Report results of Phase 3 Affinitak™ study in NSCLC (Lilly)
- Report preliminary Phase 2 results of ISIS 14803 in combination with current HCV therapies
- Initiate additional Phase 2 trial of ISIS 104838 in rheumatoid arthritis to optimize dose and schedule

We also are advancing the clinical development of our proprietary second-generation drugs, and in 2004 we plan to report clinical data on these compounds. These drugs offer enhanced patient convenience with more patient-friendly routes of delivery, less frequent dosing, decreased cost of therapy, and reduced side effects compared to previous generations. We also are optimistic about our ability to convert these drugs into capsules and tablets for oral administration, which greatly enhances the competitive and commercial value of our drugs. We are filling our pipeline with these new, improved antisense drugs, marking an important transition for the technology and the company. This pipeline transition broadens our therapeutic focus and moves the technology into larger markets, such as metabolic and cardiovascular diseases.

We are studying our second-generation drugs against targets that allow us to conduct trials with crisp, clear clinical endpoints: lowering cholesterol and improving insulin sensitivity. We already have positive results from clinical trials that confirm our drugs are working as expected. We know they accumulate in target tissue and reduce both messenger RNA and protein levels, causing therapeutic benefit. With endpoints such as these, we believe we can better define the doses and schedules for our second-generation drugs as a class, which will improve the potential for success in future Phase 3 trials.

3. Protect our inventions through patenting and exploit our IP to generate licensing revenue.

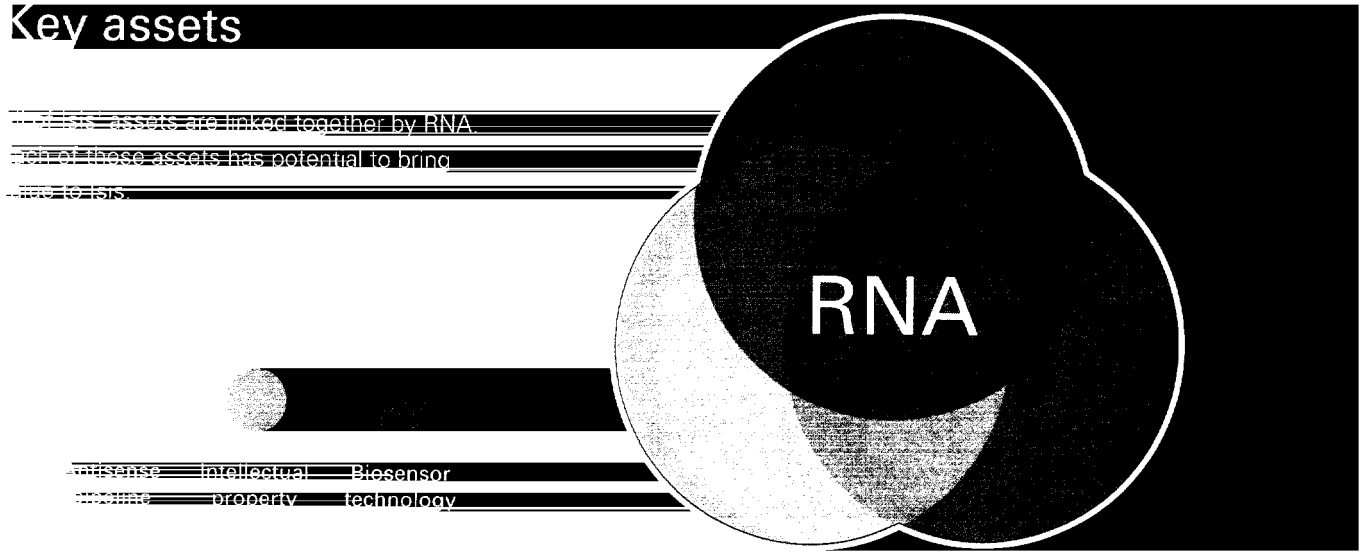
Through our investment in creating new technology platforms, we have established a preeminent position in RNA-based drug discovery and development. Today, our more than 1,300 issued patents give us influence over how the platform is and can be used. We have generated more than $40 million from licenses granted to various companies in the antisense and related fields. We are focused on using our intellectual property (IP) position to generate licensing revenue and to attract new collaborators.

4. Use a combination of equity and corporate partnering to add relevant expertise to our programs and manage risk.

We have been very successful in balancing our use of equity and corporate partnerships as sources of funding. Through partnering, our plan is to create a large portfolio of drugs, retain substantial ownership of some, and hold varying levels of ownership in many more. This strategy allows us to broadly participate in an array of potential antisense successes. Partnering will continue to be a key business strategy as we move ahead.

Our numerous corporate partnerships are strategically important as they provide scientific and therapeutic expertise in addition to financial resources, which help us manage and reduce risk in clinical development. We are pleased by the pharmaceutical industry's interest in RNA-based drugs and the progress we have made in our antisense drug discovery collaborations with Eli Lilly and Company and Amgen. We also have enjoyed success with our additional 20 corporate and government partners.

Key assets



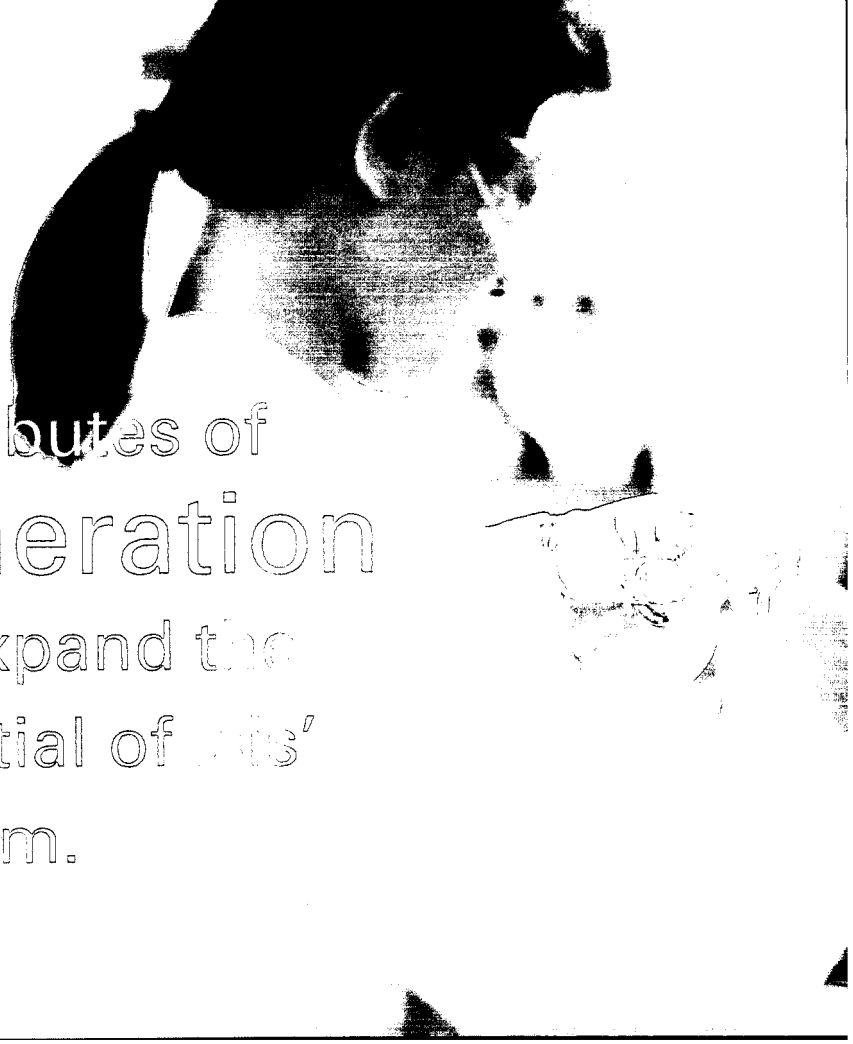
Isis' assets are linked together by RNA.
Each of these assets has potential to bring
value to Isis.

Antisense
Medicine

Intellectual
property

Biosensor
technology

sis is rich with assets that have
the potential to bring near– and
long–term value to patients and
shareholders.

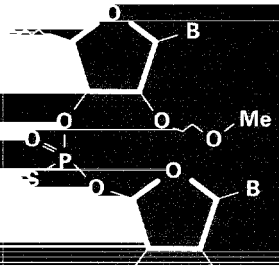


The improved attributes of

second-generation

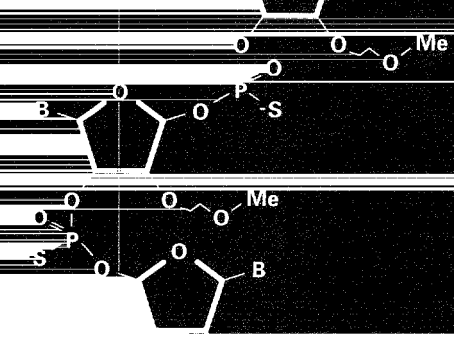
antisense drugs expand the commercial potential of Isis' technology platform.

Antisense advancements



Attributes:

[illegible] making thousands of chemical [illegible] Isis scientists have developed second generation [illegible] activity that is several times more potent than the previous generation. [illegible] properties of these advanced [illegible] provide the company with [illegible] therapeutic opportunities.

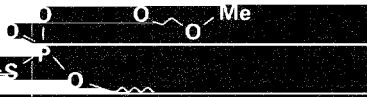


→ Increased potency

→ More convenient, less frequent dosing regimens

→ More favorable routes of administration

→ Reduction in side effects



→ Decrease in cost of goods, which reduces overall cost of therapy

P = Phosphate

Me = Methyl

B = Base

O = Oxygen

S = Sulfur

Report Phase 2 study results of ISIS 113715 in type 2 diabetes (late 2004/ early 2005)	Report Phase 1 results of ISIS 301012 for cardiovascular disease	Report results of Phase 1/2 studies of ISIS 112989 in prostate cancer and other solid tumors (OncoGenex)	Report Phase 1 results of ISIS 107248 Initiate Phase 2 trial in multiple sclerosis (ATL)	Initiate clinical trials of LY2181308 for cancer (Lilly)

5. Take advantage of opportunities that arise from our innovation to create new assets.

From our expertise in RNA, we have created exciting new opportunities for our shareholders. In our Ibis program, we have developed a pathogen and infectious disease biosensor system called TIGER, which has the potential to revolutionize the identification of infectious disease. We are moving this biosensor system toward commercialization. The Ibis program also is focused on the discovery of small molecule drugs that bind to RNA. Both of these programs have been funded by the federal government, which is interested in our technology as a defense against biological terrorism. This government funding has allowed us to build an important asset that is rich with opportunities.

In conclusion, we have an exhilarating vision coupled with prudent and well-executed business strategies that are bearing fruit. Our financial position is strong, and we are focused on taking advantage of the many assets we have created. These assets are described in greater detail on the following pages of this annual report.

As we move forward, our tasks are clear:

- We plan to bring our late-stage product opportunities to the marketplace.
- We will continue to fill our pipeline with new second-generation antisense drugs.
- We and our partners plan to advance the clinical development of numerous antisense drugs and move them into the commercial markets.
- We intend to continue to enforce and derive value from our patents.
- We plan to advance our TIGER biosensor towards commercial reality.
- We are committed to our leadership role in RNA-based drug discovery and its successful exploitation.

We are realizing the extraordinary value of our innovations, and appreciate your support.

Sincerely,

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

Clinical pipeline

Isis' portfolio of 11 antisense drugs in development and its first marketed product are the company's most valuable assets.

	PRODUCT NAME	TARGET	PARTNER	LEAD INDICATION
First – generation chemistry	Vitravene® I	CMV	Novartis	CMV retinitis
	Affinitak™ P	PKC-alpha	Lilly	Cancer-NSCLC
	Alicaforsen (ISIS 2302) P	ICAM-1	Isis	Crohn's disease
	Alicaforsen (ISIS 2302) E	ICAM-1	Isis	Ulcerative colitis
	ISIS 14803 P	HCV	Isis	Hepatitis C
Second – generation chemistry	ISIS 104838 P,O	TNF-alpha	Isis	Rheumatoid arthritis
	ISIS 104838 P,T	TNF-alpha	Isis	Psoriasis
	ISIS 113715 P	PTP-1B	Isis	Type 2 diabetes
	OGX-011 (ISIS 112989) P	Clusterin	OncoGenex	Cancer-solid tumors
	ATL-1102 (ISIS 107248) P	VLA-4	ATL	Multiple sclerosis
	ISIS 301012 P	apoB-100	Isis	Cardiovascular disease
	LY2181308 P	Survivin	Lilly	Cancer

I = INTRAVITREAL E = ENEMA
P = PARENTERAL T = TOPICAL
O = ORAL

Isis commercialized the world's first antisense drug, Vitravene.

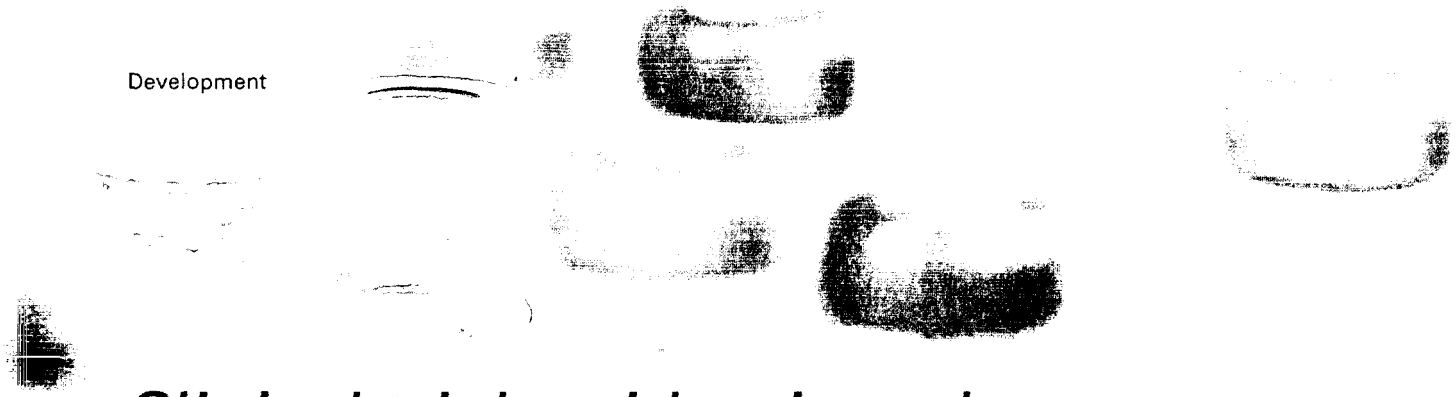
Vitravene

LEAD INDICATION: CMV retinitis PHASE: Marketed PARTNER: Novartis

Vitravene is the first antisense drug to achieve marketing clearance. Vitravene treats a condition called cytomegalovirus (CMV) retinitis in people with AIDS. Isis developed the drug and licensed worldwide commercial rights to Novartis.

Vitravene's approval was important to Isis and antisense technology, as it demonstrated that antisense drugs:

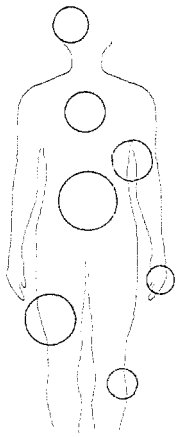
- Can be effective in the treatment of local disease
- Can meet regulatory requirements for marketing approval by the U.S. Food and Drug Administration and agencies around the world
- Can be manufactured for commercial use



Clinical trials with crisp, clear endpoints demonstrate that these drugs are working as expected and have the potential to increase the success rate of late-stage development.

Routes of administration

Isis is enhancing the scope of antisense technology by developing numerous routes of administration and researching multiple therapeutic areas.



- Intravitreal
- Intravenous infusion
- Subcutaneous injection
- Topical cream
- Enema
- Inhalation
- Oral (capsules or tablets)

Therapeutic areas of research

(Isis division of resources)

Inflammatory

Cancer

Bone

Other

Cardiovascular

Metabolic

Company scientists have systematically advanced antisense technology to create fundamentally new treatments for patients. Isis' development programs are strategically focused on therapeutic areas where the competitive advantages of its antisense drugs are significant. Furthermore, this pipeline reflects the technology's unique capability to pursue therapeutic targets that are unapproachable with traditional drug discovery platforms, yet are considered to be potentially critical in treating disease.

The company is developing drugs for the treatment of metabolic, inflammatory, cardiovascular and viral diseases, as well as cancer. Each of these drugs has a compelling product profile, as described on the following pages.

First-generation drugs

WELL-ADVANCED IN DEVELOPMENT

Alicaforsen (ISIS 2302)

LEAD INDICATION: Crohn's disease PHASE: 3

Potential for prolonged remissions, an important benefit for the one million people worldwide with Crohn's disease

In Phase 2 clinical studies, alicaforsen produced long-lasting clinical remissions in patients with Crohn's disease. This antisense drug is designed to reduce the production of ICAM-1 (Intercellular Adhesion Molecule-1), a protein that plays an important role in inflammation. People with Crohn's and other inflammatory bowel diseases, including ulcerative colitis, tend to have an increased amount of ICAM-1 in their diseased tissue.

Results from two Phase 3 trials are expected in the second half of 2004.

Alicaforsen (ISIS 2302)

LEAD INDICATION: Ulcerative colitis PHASE: 2

Enema treatment may produce durable responses for the one million people worldwide with ulcerative colitis (UC)

Alicaforsen has produced durable disease responses of up to six months in patients with active distal UC. Patients in a Phase 2 study who received the highest dose of alicaforsen did not need additional treatments during the entire trial period. Further, Phase 2 trials in pouchitis, a UC-related condition, provided additional evidence of response durability with alicaforsen. In these pouchitis studies, patients treated with alicaforsen enema experienced sustained improvement for six to nine months with a decreased need for supplemental treatment, based on endoscopic scores.

The company plans to have results from two Phase 2 UC trials in the second half of 2004.

Second-generation drugs

EXPAND THE MARKET POTENTIAL OF ANTISENSE TECHNOLOGY

ISIS 104838

LEAD INDICATION: Rheumatoid arthritis/psoriasis PHASE: 2

An innovative approach to targeting TNF-alpha for rheumatoid arthritis (RA), a chronic condition affecting 2.1 million Americans

ISIS 104838, an inhibitor of TNF-alpha, may offer RA patients a potentially oral, less costly treatment option with fewer side effects than current protein-based therapies. Based on results of further dose optimization studies and the potential for oral administration, ISIS 104838 may be highly competitive in the RA marketplace.

In an earlier Phase 2 study, RA patients that received ISIS 104838 experienced improved responses compared to patients receiving placebo. In a biomarker study, the drug accumulated in patients' diseased joints in a dose-dependent manner, reducing TNF-alpha mRNA levels in inflamed tissue.

Isis plans to initiate a Phase 2 trial during 2004 to further optimize dose and schedule for ISIS 104838 in RA. The company is also planning a Phase 2 trial of systemically delivered ISIS 104838 for psoriasis.

ISIS 113715

LEAD INDICATION: Type 2 diabetes PHASE: 2

Potential new insulin sensitizer for the 17 million people with type 2 diabetes

ISIS 113715 illustrates Isis' development strategy of pursuing targets inaccessible with other drug discovery approaches. An antisense inhibitor of PTP-1B, ISIS 113715 may provide an improved treatment option for type 2 diabetes patients, particularly those who inadequately respond to available oral therapies. In preclinical studies, this novel drug did not cause hypoglycemia or weight gain, effects commonly observed with other diabetes therapies.

In a Phase 1 study in normal volunteers, ISIS 113715 enhanced insulin's ability to normalize glucose levels as measured by a glucose tolerance test. Inefficient use of insulin is a primary characteristic of type 2 diabetes. Isis plans to initiate enrollment of a Phase 2 clinical trial in diabetic patients by mid-year 2004, and report results in late 2004 or early 2005.

The inhibition of PTP-1B may cause insulin receptors to stay active longer. This allows for more sugar uptake into cells, and thereby reduces sugar levels in the bloodstream. The pharmaceutical industry has used traditional drug discovery methods to target PTP-1B, but lack of specificity has prevented success with these approaches. According to preclinical data, ISIS 113715 selectively inhibits this gene without affecting other members of the phosphatase family.

ISIS 301012

LEAD INDICATION: Cardiovascular disease PHASE: 1

Isis' first antisense drug to treat heart disease; high cholesterol affects more than 100 million Americans

Lowering cholesterol levels is a key component of heart disease management. ISIS 301012 has the potential to offer a new treatment option for patients whose cholesterol levels are not effectively managed with current drugs.

ISIS 301012 safely lowered cholesterol in numerous well-accepted animal models of cardiovascular disease. This drug inhibits apoB-100, a target long considered "undruggable" by other drug discovery methods. apoB-100 is critical for the production and transport of low density lipoprotein (LDL), the "bad" cholesterol that contributes to heart disease. ISIS 301012 is the company's first cardiovascular drug to enter the clinic.

The company plans to report Phase 1 trial results in the second half of 2004.

Affinitak™

LEAD INDICATION: Cancer PHASE: 3 PARTNER: Lilly

Evaluating a treatment strategy for non-small cell lung cancer; 174,000 people expected to be diagnosed with NSCLC in 2004

Lilly is evaluating Affinitak in combination with Gemzar® and cisplatin in patients with NSCLC. This is the second of two Phase 3 studies to test the antisense drug in combination with standard chemotherapy regimens. The results of an initial 600-patient Phase 3 study concluded in March 2003 were not sufficient to support a single-study new drug application (NDA).

Results from Lilly's ongoing Phase 3 trial are likely in the second half of 2004.

ISIS 14803

LEAD INDICATION: Hepatitis C PHASE: 2

Active drug in treatment-resistant hepatitis C patients; new hope for the millions of Americans with this condition

Approximately 35% of patients with the hepatitis C virus (HCV) do not achieve a viral response with the current standard of care, interferon and ribivirin. These patients have essentially no treatment options. Isis is evaluating ISIS 14803, an antisense inhibitor of HCV viral replication, in this patient population in combination with current therapies. Isis plans to announce initial results from this trial in the second half of 2004.

In earlier Phase 2 single-agent studies, ISIS 14803 demonstrated promising antiviral activity by producing up to 3.8 log dose-dependent reductions in plasma virus levels in HCV patients. The majority of patients participating in the studies had HCV genotype 1, the most common and difficult-to-treat form of the disease, and previously had failed treatment with interferon-based therapies.

Partnered second-generation antisense drugs in development

An advantage of the antisense platform is its ability to generate far more drugs than Isis can afford to develop on its own. Isis' business strategy is to engage in antisense drug discovery and development partnerships to increase the use of the technology within the industry and participate in the commercial upside of multiple antisense drugs. These partnerships provide Isis with potential licensing fees, development and regulatory milestone payments and royalties.

OGX-011 (ISIS 112989)

LEAD INDICATION: Cancer PHASE: 1/2 PARTNER: OncoGenex

Approximately 230,000 men are diagnosed with prostate cancer every year in the U.S., and new treatment alternatives that enhance or replace current therapies are needed. Canada-based OncoGenex Technologies, Inc is conducting Phase 1/2 studies of OGX-011 for the treatment of prostate cancer and other solid tumor types. This antisense drug is an inhibitor of clusterin, a cell-survival protein that becomes over-expressed in many human malignancies as a result of tumor-killing strategies, such as chemotherapy, hormone ablation and radiation therapy.

Data from these studies are expected in the first half of 2004.

ATL-1102 (ISIS 107248)

LEAD INDICATION: Multiple sclerosis PHASE: 1 PARTNER: ATL

Two million people worldwide have multiple sclerosis (MS), which is an inadequately treated condition. ISIS 107248 inhibits CD 49d, a sub-unit of VLA-4 (Very Late Antigen-4). Inhibition of VLA-4 has demonstrated positive effects in animal models of a number of inflammatory diseases, such as MS.

Australia-based Antisense Therapeutics Limited (ATL) has completed Phase 1 development of ISIS 107248. Final results from this Phase 1 study are expected mid-year 2004. ATL plans to initiate Phase 2 studies in patients with MS by the end of 2004.

LY2181308 (ISIS 23722)

LEAD INDICATION: Cancer PHASE: Preclinical PARTNER: Lilly

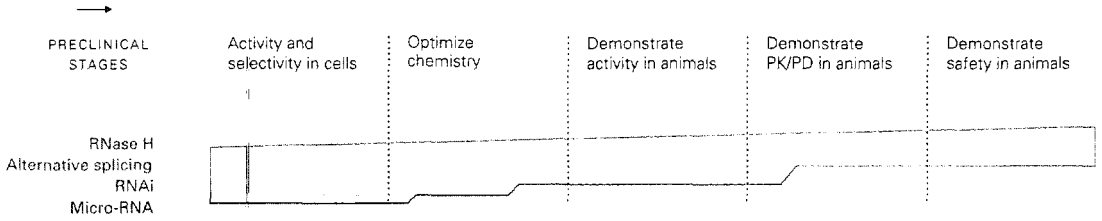
LY2181308 is an inhibitor of survivin, a leading cancer target. Survivin is a molecule that allows survival of cells that would normally undergo programmed cell death. When cancer cells grow, they appear to need the help of survivin. The molecule is abundant in many types of cancers, including colon, brain, lung, skin and others, but nearly nonexistent in normal cells.

Preclinical results with LY2181308 are among the first to demonstrate antitumor activity *in vivo* with a drug that specifically inhibits survivin expression.

Lilly licensed this compound as part of its broad-based antisense drug discovery collaboration with Isis. Upon Lilly's selection of LY2181308 for clinical development in 2003, Isis achieved a $1.5 million milestone. Lilly's Phase 1 program is expected to begin during 2004.

Research

Turning antisense mechanisms into drugs:
Current stages in drug development



Isis has led the industry in basic and applied RNA-based drug discovery research. The company's innovations have been reported in hundreds of scientific publications and are the basis for one of the largest RNA patent estates in the industry.

Core research

An important area of Isis' basic research is to understand the molecular mechanisms of antisense. At least 12 known antisense mechanisms can be induced once an antisense drug binds to its target RNA. Isis has created proprietary chemical modifications to exploit many of these mechanisms for drug discovery. As its understanding of these mechanisms further improves, the company expects to develop antisense drugs with enhanced performance and for broader therapeutic applications.

An antisense mechanism is defined as the process in which an antisense inhibitor binds (hybridizes) to a target RNA to form a duplex. The formation of this duplex, or two-stranded molecule, prevents the RNA from functioning normally and from producing a protein product.

Progress in Isis' mechanism of action research program is illustrated by the company's accomplishments in understanding RNase H. The majority of late-stage antisense drugs in development bind to their target RNA forming a duplex, which activates a cellular enzyme called RNase H. This enzyme destroys the target RNA, inhibiting production of a specific protein. Isis has cloned and characterized human RNase H and has effectively used that information to design its proprietary second-generation drugs. The company expects to further improve its drugs, using its insights into the RNase H mechanism.

In addition to its RNase H expertise, Isis has made advancements in understanding and exploiting other antisense mechanisms.

RNA interference (dsRNase, siRNA and RNAi)
Antisense drugs can be designed to bind to their target RNAs and recruit a different class of enzymes, called double-stranded RNases (dsRNase), that cleave the target RNA. There are many dsRNases in the cell, making this a potentially attractive mechanism. Isis' research led to one of the first scientific publications and key issued patents that address this mechanism. siRNAi and RNAi, for example, are dsRNase mechanisms that have received much attention in the drug discovery community. Isis is making significant advances in understanding siRNA through SARS and Lilly research partnerships. Isis also recently announced a strategic collaboration with a leader in RNAi therapeutics, Alnylam Pharmaceuticals, Inc. This alliance will utilize each company's intellectual property and expertise to develop and commercialize RNAi therapeutics.

Alternative splicing
DNA is composed of chains of nucleotides (abbreviated as A, C, T and G) that encode for proteins, as well as regions that are unnecessary for making proteins. Both the coding and non-coding regions are "copied" from DNA to RNA. The non-coding regions, called introns, must be deleted from the RNA strand. The process that removes these regions and reforms the finished RNA is called splicing.

Alternative splicing has been shown to result in many diseases and accounts for most of the diversity in proteins. Alternative splicing is largely responsible for the functional complexity of the approximately 30,000-40,000 genes in the human genome; 40-60 percent of human genes have alternative splice forms.

From its research and innovation, Isis has created a valuable intellectual property position based on more than

1,300 issued patents.

Realizing value through intellectual property

Isis' portfolio of more than 1,300 issued patents and more than 1,700 active patent applications is an important asset. This patent estate protects the investments the company has made in creating antisense technology, supports partnerships with pharmaceutical companies interested in utilizing Isis' technologies, and generates near-term revenue through licensing.

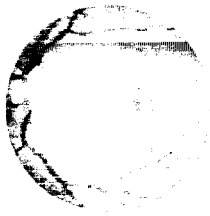
Eyetech licensing

In January 2002, Eyetech Pharmaceuticals, Inc., licensed specific Isis chemistry patents necessary for the company to develop, manufacture and commercialize Macugen™, its lead product for a form of age-related macular degeneration (AMD). Eyetech paid an upfront fee of $2 million and will pay Isis milestones and royalties on sales of the drug. Based on promising Phase 3 results, Eyetech has stated its intention to file a NDA and, with Pfizer, it will commercialize the drug in the 2004-2005 timeframe.

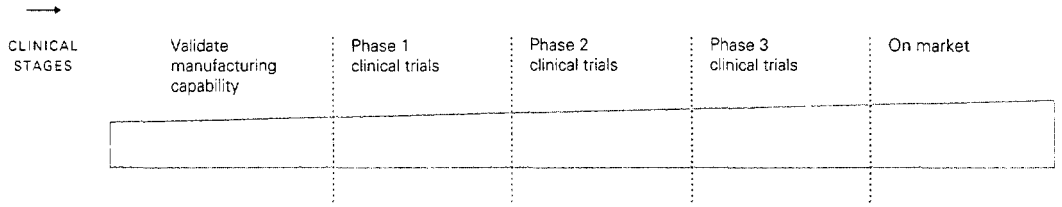
AMD

Market information

Age-related macular degeneration (AMD) is the most common form of irreversible and severe vision loss in Americans age 65 and older. Approximately 1.7 million Americans suffer from wet AMD and that number is expected to double by 2030.



Discovery



Isis has pioneered the design of antisense drugs that can selectively direct alternative splicing to make one protein versus another. Today, Isis continues its research with Ercole Biotech, Inc., a company specifically focused on this mechanism. In the future, many diseases may be amenable to this approach.

Micro-RNA

Researchers recently have discovered new families of natural antisense molecules made inside the cell called micro-RNAs. These molecules appear to serve as master regulatory molecules for many biological processes. Isis researchers have been able to use micro-RNA in two ways. The first involves turning off, or inhibiting, genes in order to stop the production of a protein; an equivalent process to traditional antisense. The second involves turning on, or up-regulating, genes so that specific proteins are made. Isis is broadening its micro-RNA research by establishing a program in Singapore with funding from the government's Economic Development Board.

Applying core research to drug discovery

Isis' drug discovery programs have produced 11 antisense drugs and constitute an efficient engine that is turning out exciting new product opportunities.

- The company continues its internal and partnered cancer research programs. Isis has reported significant progress in its Lilly collaboration with the selection of LY2181308 for clinical development. The Phase 1 program is expected to begin in 2004.

- The anti-inflammatory program that produced alicaforsen and ISIS 104838 is discovering new drugs that can be administered by inhalation for pulmonary diseases.

- Isis' metabolic disease program that produced ISIS 113715 has screened more than 70 gene targets that may be involved in diabetes or obesity. The company's researchers have identified multiple drug candidates that are progressing toward the clinic.

- The cardiovascular program, which discovered ISIS 301012, is moving beyond lipid management to targets involved in atherogenesis, cardiovascular inflammation processes and other heart disease areas.

In addition to these highlighted programs, Isis is conducting research in other areas including ophthalmology and dermatology.

SARS drug discovery: an example of the efficiency of antisense

Through funding from ITRI of Taiwan and the Singapore EDB, Isis is identifying new antisense drugs against SARS. Isis recently achieved two milestones in its ITRI partnership with the identification of potent, second-generation antisense drugs that inhibit SARS, and the successful completion of preclinical studies evaluating aerosol and parenteral delivery of antisense drugs. Within months, Isis' scientists were able to identify a target sequence and develop therapeutic drug leads. These accomplishments demonstrate the efficiency of antisense technology.

Ibis/Biosensor technology

Ibis has used Isis' expertise in RNA-based drug discovery to create an entirely new technology platform that has the potential to revolutionize the identification of infectious disease. This platform consists of a biosensor and proprietary analytical processes and tools to interpret data to identify known and unknown biologic agents.

The universe of pathogens and infectious organisms is large, complicated and constantly changing. The task of accurately identifying these organisms is extremely difficult. The complexity of this challenge increases with the emergence of new organisms, especially those that have multiple strain variants or have been bioengineered.

Current technologies are not able to identify pathogens rapidly and effectively. Commonly-used methods largely rely on either culture or single-agent nucleic acid tests. Culture techniques are generally slow and labor intensive, taking days or weeks to identify an organism. Standard nucleic acid tests can only identify one pathogen per test because they require prior knowledge of the agent to be identified.

These limitations of existing approaches are the strengths of the company's biosensor. Scientists have created a system that can rapidly and simultaneously identify a broad range of infectious organisms contained in a sample, including organisms that are newly emerging, genetically altered and unculturable. No currently-marketed product is capable of performing this type of broad-based analysis in a single pass. The technology, called Triangulation Identification Genetic Evaluation of Risks (TIGER), has largely been developed in collaboration with San Diego-based Science Applications International Corporation (SAIC), and funded by the Defense Advance Research Projects Agency (DARPA).

In 2003, company scientists successfully demonstrated proof-of-principle of the TIGER biosensor with the identification of a variety of bacteria and viruses in both environmental and human samples. A military agency collaborated with Ibis scientists to validate TIGER technology by using it to track an epidemic strain of streptococci in armed forces recruits.

Using the TIGER method, Ibis scientists were able to identify within hours the specific strain of streptococci that caused the outbreak. These test results were confirmed by classical strain-typing methods, which took more time to complete. This example demonstrated the biosensor's ability to provide specific, timely and accurate data to identify and monitor the spread of infectious disease.

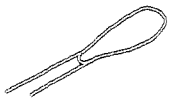
There are thousands of infectious organisms, and the company's biosensor platform can accurately identify a broad range of them in a single rapid test.

TIGER technology employs key insights

The genetic code of organisms is composed of variable regions surrounded by regions that are constant across species. Certain variable areas can be used to determine the identity of organisms. Ibis' scientists have invented proprietary methods to find these areas. Armed with this knowledge, the TIGER system can recognize organisms through a four step process:

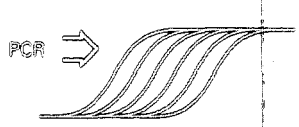
STEP 1

Collect a sample from any source such as a throat swab, blood, dirt, air or water.



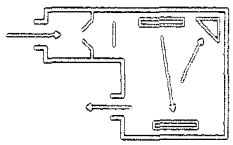
STEP 2

Extract genetic code from the sample and use proprietary broad-spectrum, unbiased nucleic acid primers to produce enough copies of the variable region in order to make a precise measurement.



STEP 3

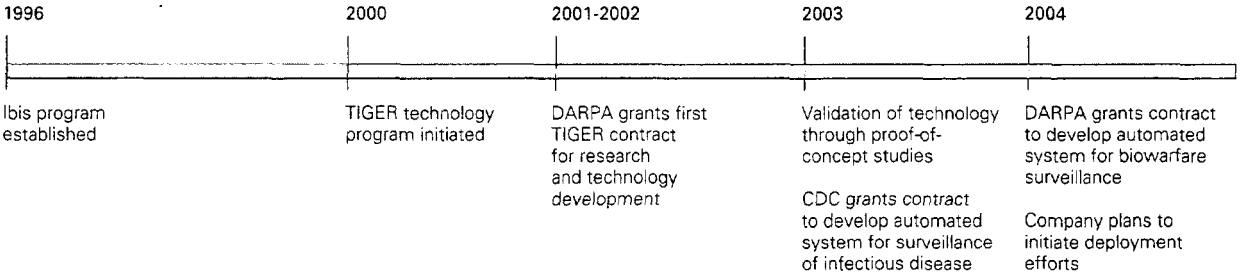
Weigh the variable region by mass spectrometry methods to determine the genetic base-count fingerprint for an organism.



STEP 4

Interpret results through a proprietary process and database to identify an organism based on its base count fingerprint.

Biosensor development timeline



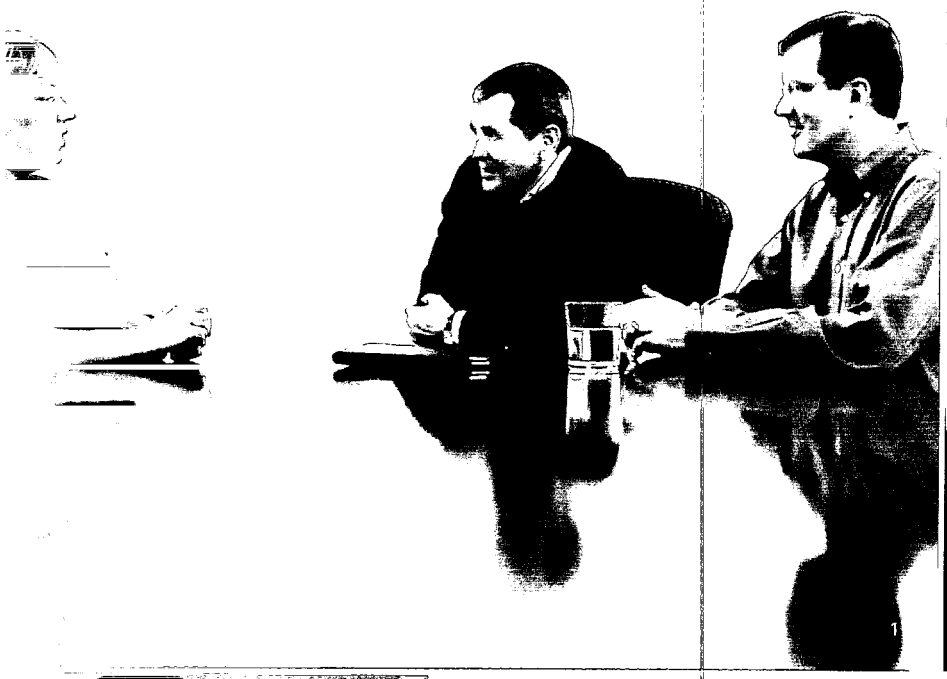
In early 2004, DARPA granted Ibis a new contract valued at up to $19.5 million to build a fully integrated, self-contained system, called TIGER 2.0. The company is producing this automated system to perform the analysis of samples with minimal technician intervention.

Building on Ibis' work with DARPA, The Centers for Disease Control and Prevention (CDC) provided a $6 million grant in October 2003 to develop a variation of the TIGER 2.0 biosensor for the identification, monitoring and tracking of newly emerging infectious diseases. The automation of the system and its planned deployment for disease surveillance and biowarfare defense are the first steps toward the commercialization of TIGER technology. Isis believes this technology represents a worldwide opportunity. In the future, the technology has the potential for broader applications in mainstream markets such as blood supply monitoring and clinical diagnostics.

The company has been awarded up to $55 million in government grants for the development of its therapeutic and biosensor technology. This funding is significant, as it has provided the resources to develop an asset Isis may not have afforded on its own.

Ibis Therapeutics®

The company's Ibis program utilizes Isis' expertise in RNA-based technology to create additional product opportunities for both the identification and treatment of infectious disease. Since 1997, Ibis' technology has been supported by DARPA and other government agencies because of its value in bioweapons defense, public health and homeland security. In addition to funding the TIGER biosensor technology, the government has awarded grants to Ibis for the discovery of small molecule RNA-binding drugs that could be used to treat patients following a biological attack. The company also continues to advance its internal drug discovery efforts, with promising progress in the area of hepatitis C and broad-spectrum antibacterial agents.



Together, Isis' core management team has nearly a century of experience in advancing and exploiting RNA-based technologies.

Leadership

Management team photos:
(from L to R)

(1) Lynne Parshall, Dr. Stanley Crooke, Dr. Frank Bennett, (2) Dr. Richard Brown, (3) Lynne Parshall, (4) Dr. David Ecker, (5) Patricia Lowenstam, (6) Dr. Aron Stein, Dr. Arthur Levin, John McNeil

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Patricia Lowenstam
Vice President,
Human Resources and Operations

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Vice President, Informatics

Aron F. Stein, Ph.D.
Vice President, Regulatory Affairs and Quality Assurance

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Forward-Looking Statement

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 the company's goals, expectations, intentions or beliefs is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those risks or uncertainties inherent in the process of developing technology and systems used to identify infectious agents, discovering, developing and commercializing drugs that can be proven to be 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 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, 2003, 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.

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