Sirna Therapeutics™

Sirna Therapeutics

# SETTING THE PLAN IN *MOTION*

2002 Annual Report

In 2002, we set a plan in motion to rebuild the company and ensure the creation of future shareholder value. We began 2003 by raising $48 million to fund the development of ribonucleic acid interference (RNAi) therapeutics.

We believe that RNAi has the potential to silence disease-causing genes and has wide therapeutic application in humans. With a new plan, a new name was needed to reflect our mission. We have renamed the company Sirna Therapeutics – meaning “silencing RNA”.

# dear shareholder,

2002 was a defining year for our company – we were determined to restructure our research and development efforts and identify the best path forward for our company. Our goal was to develop a business plan that leveraged our outstanding scientific expertise and strong intellectual property position in nucleic acid technology. After reviewing our technology and program portfolio, I am pleased to report that we have developed, and are now implementing, a plan that focuses our research and development efforts on RNAi-based therapeutics – a program that we began over 18 months ago.

We own or have rights to over 180 issued or allowed patents relating to nucleic acid technology. We believe this intellectual property portfolio combined with our expertise in nucleic acid technology gives us a strategic advantage in the development of RNAi-based therapeutics. We have redirected our research to RNAi because we believe it is one of the most powerful therapeutic applications for nucleic acid-based medicine and it represents the best prospects for commercial success. To fund our RNAi development programs, we recently raised $48 million from leading venture capital groups: The Sprout Group, Venrock Associates, Oxford Bioscience Partners, Techno Venture Management and Granite Global Ventures. Our ability to attract this size of investment and caliber of investors to finance our development is a validation of:

- Our position as a leader in the field of RNAi therapeutics;
- The strength and experience of our management and scientific teams, and;
- The breadth of our intellectual property related to RNA and RNAi.

In 2003, we have made significant progress towards redefining our company. With our funding in place, we now have a new name, a new focus and a renewed passion for the future in this exciting new field.

## A NEW COMPANY, A NEW NAME

As a company developing therapeutics that silence RNA, we changed our name to Sirna Therapeutics – a name that better reflects our focus on targeted gene silencing. Sirna Therapeutics is a new company heading in a new direction that leverages our experience in RNA.

## A NEW STRATEGIC FOCUS

Our plan is based on applying our knowledge and strong intellectual property position in nucleic acid technology to develop RNAi-based therapeutics. Over the last decade, we have developed a strong scientific foundation – one built on talented scientists and robust intellectual property. We have a broad intellectual property position in nucleic acid technology, with rights to over 180 issued or allowed patents and an additional 50 patents filed to date for RNAi.

# shareholder letter continued.

This foundation of accomplishments and expertise is a critical component in the development of RNAi-based therapeutics and, we believe, gives us a leading position in the field.

We are using our expertise to design, stabilize, deliver, scale-up, and manufacture small interfering nucleic acids (siNAs) that facilitate the process of RNAi, a mechanism used by cells in the body to regulate the expression of genes and replication of viruses. The RNAi mechanism induces the destruction of target RNA using a naturally occurring cellular protein machinery. Harnessing the natural process of RNAi holds potential for the development of a brand new class of drugs with unrivaled specificity toward a wide range of diseases.

Our researchers are currently developing RNAi therapeutics against hepatitis C virus and macular degeneration. Both programs are in the lead identification stage of development. Our experience working in the field of hepatitis C, and the validity of the target and liver uptake of our siRNAs, make this a logical first systemic target. Our knowledge of angiogenesis as it relates to macular degeneration provides us with an attractive target for local delivery of siRNAs against another validated target, the VEGF pathway.

We are partnered with Chiron in the development of ANGIOZYME®, a ribozyme-based product, and believe that it has significant potential for the treatment of cancer. The Phase II metastatic colorectal cancer trial has been completed and the results from the preliminary analysis of the 24-week data will be presented at the upcoming American Society of Clinical Oncology meeting in June 2003. The future development plan for ANGIOZYME is under discussion with Chiron.

In 2002, Elan, our joint venture partner for HERZYME™, a ribozyme-based product, announced that they would no longer pursue an oncology strategy and would not provide funding for HERZYME beyond the recently completed Phase I trial. As a result, Sirna Therapeutics and Elan concluded the joint venture, and we will retain full rights to HERZYME. We do not intend to pursue independent development, and are seeking a development partner.

We terminated our ribozyme-based HEPTAZYME™ Phase II program due to the low therapeutic index of the compound. We have decided not to pursue the next generation ribozyme development program, as we believe RNAi has greater potential as a therapeutic targeting the hepatitis C virus.

# FOCUSED ON RNAi-BASED THERAPEUTICS.

Process development and manufacturing continue to be key assets for our company. We hope to capitalize on these assets by entering into licensing, process development and pilot manufacturing arrangements with collaborators, such as Geron Corporation, to generate revenues while maintaining this capability for our own RNAi therapeutic programs.

Our diagnostic program has demonstrated proof-of-principle for the use of allosteric ribozymes for both diagnostic protein and nucleic acid detection. We have decided not to develop our diagnostic technology internally and intend to spin off or sell this technology to focus our resources on RNAi therapeutic development.

## RENEWED PASSION FOR THE FUTURE

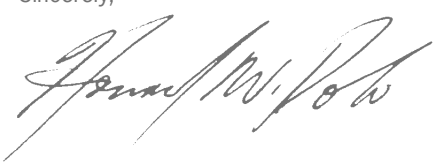
With the recent closing of our $48 million private financing, we have been given an opportunity to execute our new strategy. These funds will allow us to support RNAi program discovery and development through 2005. We plan to advance these programs through preclinical development and expect to begin a Phase I clinical trial in 2005.

In 2003, we will begin delivering on the promise of RNAi technology. Specifically, we have set the following RNAi-related milestones in 2003:

- Publish/present RNAi *in vitro* and *in vivo* data
- Select a lead HCV clinical candidate
- Select a lead macular degeneration clinical candidate

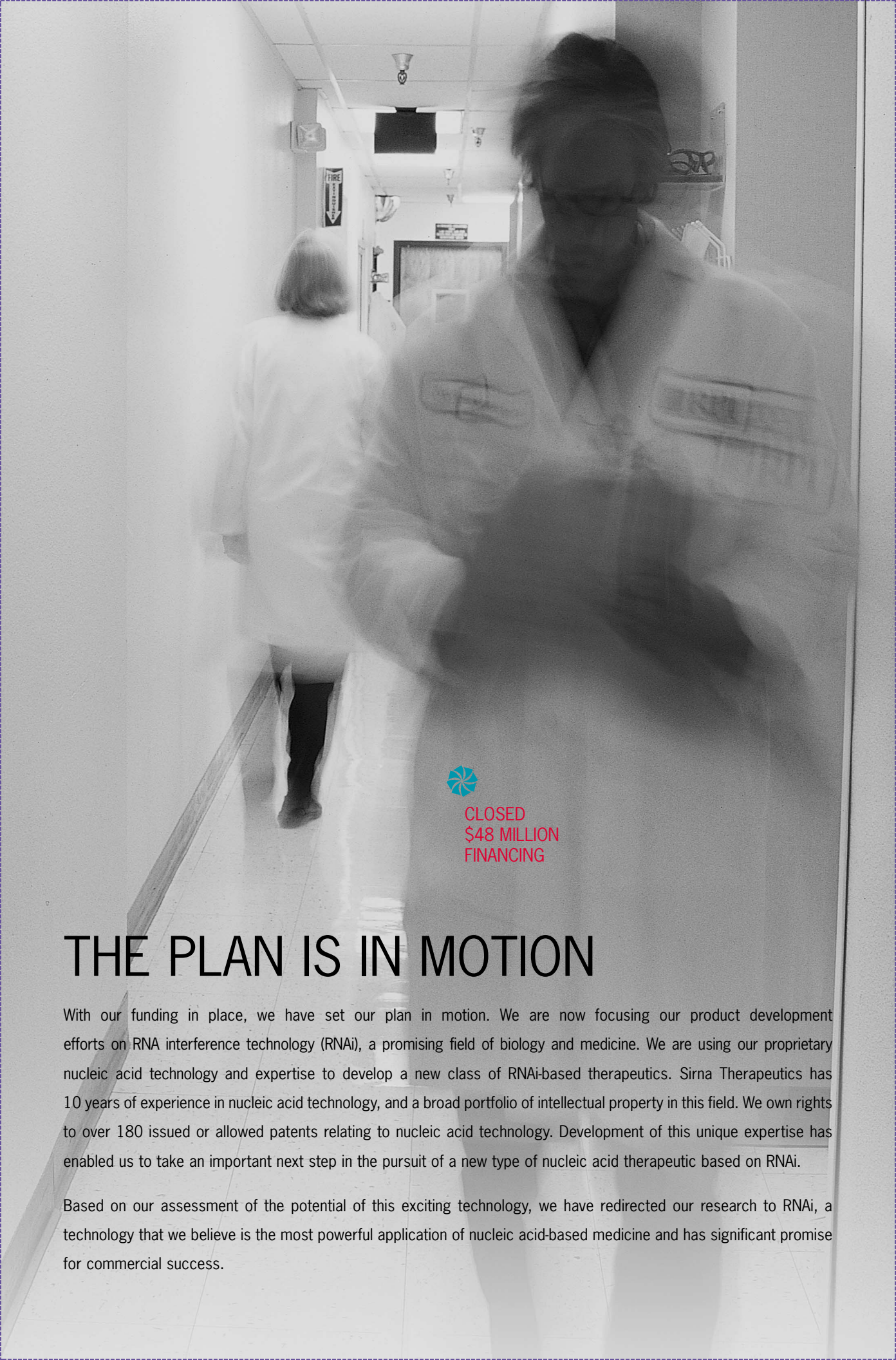
At Sirna Therapeutics, we have set a plan in motion. We are confident that we have the scientific expertise, intellectual property, management skills, manufacturing prowess and financial backing to achieve our goals. We are committed to success and would like to thank you for your continued support.

Sincerely,



Howard W. Robin
President and Chief Executive Officer

April 21, 2003



CLOSED
$48 MILLION
FINANCING

# THE PLAN IS IN MOTION

With our funding in place, we have set our plan in motion. We are now focusing our product development efforts on RNA interference technology (RNAi), a promising field of biology and medicine. We are using our proprietary nucleic acid technology and expertise to develop a new class of RNAi-based therapeutics. Sirna Therapeutics has 10 years of experience in nucleic acid technology, and a broad portfolio of intellectual property in this field. We own rights to over 180 issued or allowed patents relating to nucleic acid technology. Development of this unique expertise has enabled us to take an important next step in the pursuit of a new type of nucleic acid therapeutic based on RNAi.

Based on our assessment of the potential of this exciting technology, we have redirected our research to RNAi, a technology that we believe is the most powerful application of nucleic acid-based medicine and has significant promise for commercial success.

leveraging our outstanding scientific experience and intellectual property portfolio.

# LEVERAGE.

## MOVING RNAi FORWARD

As its name suggests, RNAi is a cellular mechanism to regulate the expression of genes and the replication of viruses that is mediated by small interfering RNA (siRNA) molecules. Sirna Therapeutics has shown that it can use its stabilized small interfering nucleic acid molecules (siNAs) to reduce the expression of many genes without affecting other genes. Altering the function of the messenger RNA (mRNA) therefore can be used to modulate the cell's machinery. As its name suggests, mRNA provides the means of implementing a set of instructions encoded by DNA to program the cell's machinery.

RNAi technology is a comparatively recent discovery believed by scientists to constitute an important aspect of a cell's natural defense mechanism against foreign RNA. Importantly, the cell responds to a double stranded form of RNA introduced into the cell by targeting for destruction of mRNA with the same sequence as the double stranded RNA. Therefore, by introducing an engineered siRNA we can cause the specific destruction of a target mRNA that has the same sequence as the siRNA.

By destroying mRNA species with one siRNA sequence, the cell effectively blocks the production of a specific protein encoded by the destroyed mRNA. This biological process has already been used with great success in the laboratory to identify the function of genes and their respective proteins by observing how plant or animal cells respond to the gene's silencing. RNAi provides a faster and more effective way to turn off genes than other known methods because it takes advantage of a natural cellular process.

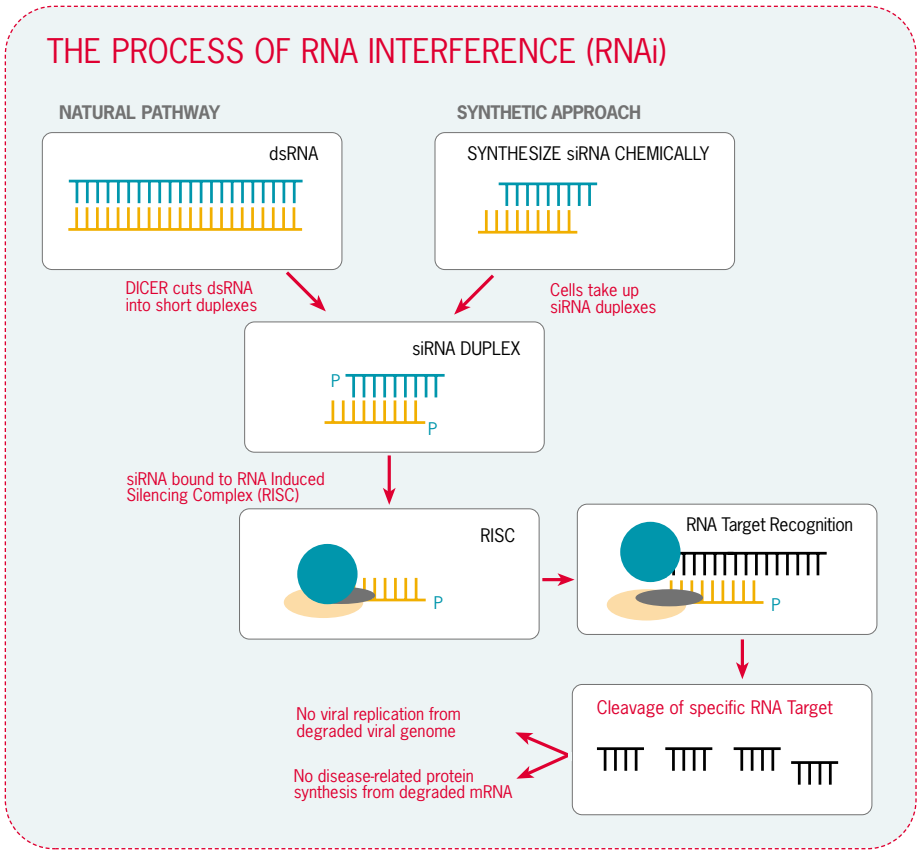
## RNAi-BASED THERAPEUTICS

Harnessing the natural process of RNAi holds immense promise for the development of a brand new class of drugs that are capable of turning off disease-causing genes. Although development is in its early stages, these drugs are expected to have potentially broad therapeutic applications.


dedicated to the
development of
RNAi-based therapeutics.
DEDICATION.
PUBLISH/PRESENT
RNAi IN VITRO DATA


# COMMITMENT.

committed to applying the company's established expertise in nucleic acid technology to the exciting new field of RNAi technology.




# RESEARCH PROGRAMS

Currently our researchers are focusing on the development of RNAi-based therapeutics that target hepatitis C virus (HCV) and macular degeneration. We will be constantly evaluating both these programs and additional areas in which we may want to initiate programs.

## HEPATITIS C

There are approximately 3.9 million HCV-infected individuals in the United States and over 170 million worldwide. Of the 3.9 million infected individuals in the United States, approximately 70% have chronic hepatitis C and are potential candidates for treatment. Each year in the United States, hepatitis C infects between 250,000 and 500,000 new individuals and leads to between 8,000 and 10,000 deaths. It is one of the most common blood-borne infections in the United States and has been identified as a "silent epidemic" and "a daunting challenge to public health" by the United States Congress. Current therapies for hepatitis C are effective in approximately 50% of patients and often have serious side effects.

We are developing an RNAi-based therapeutic targeting the hepatitis C virus. This program is in the lead identification phase of development. We have identified several stabilized siNAs that we are currently screening in cell culture and appropriate animal model systems of HCV infection.

RNAi holds the potential for the development of a brand new class of drugs.

# DEVELOPMENT.

SELECT A LEAD HEPATITIS C CLINICAL CANDIDATE

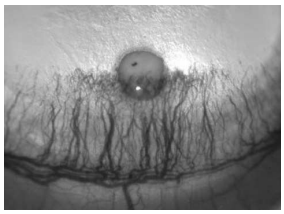
## MACULAR DEGENERATION

Age-related macular degeneration, or AMD, is caused by the deterioration of the central portion of the retina. This disease is the leading cause of irreversible vision loss among those over the age of 55 in the western world. There are two different forms of AMD: dry AMD and wet AMD. The wet form accounts for 10% to 15% of all AMD cases but is associated with severe vision loss. Over one million people in the United States have wet AMD, with 200,000 new cases per year. Wet AMD results from a proliferation of abnormal blood vessels beneath the retina. Wet AMD can lead to rapid vision loss for most patients.

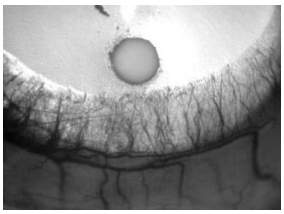
It has recently been demonstrated that blocking of the Vascular Endothelial Growth Factor (VEGF) signaling pathway results in benefit for patients with this disease.

We are in the lead identification phase of development for an RNAi-based therapeutic that targets the VEGF pathway to treat macular degeneration. The animal data that we have already seen in this program is promising. To date, we have demonstrated that we can inhibit the formation of new blood vessels in a rat animal model system of corneal neovascularization using our stabilized siNAs targeting the VEGF pathway.

STABILIZED siRNA TARGETING VEGFR-1 mRNA
(INHIBITS CORNEAL ANGIOGENESIS IN A RAT MODEL)



VEGF Alone



VEGF + Active siRNA
Single 20 μg dose

our researchers are beginning to deliver on the promise of RNAi.

# DELIVER.


applied research focused on advancing candidate drugs from the laboratory to the clinic.
RESEARCH.
SELECT A LEAD MACULAR DEGENERATION CLINICAL CANDIDATE

## RNAi ADVANTAGES

RNAi-based therapeutics are expected to have significant advantages over traditional approaches to treating diseases, including the following:

- Broad Therapeutic Application – All diseases for which an abnormal gene function can be identified as a cause or as an essential contributing factor are potentially treatable with RNAi-based drugs.
- Therapeutic Precision – Side effects associated with traditional drugs may be reduced or avoided by using RNAi-based drugs designed to destroy only disease associated and targeted RNA.
- Target RNA Destruction – Compared to most drugs that only temporarily prevent targeted gene function, RNAi-based drugs should destroy the target RNA and stop the associated undesirable protein production required for disease progression.

Sirna Therapeutics has 10 years of chemical and pharmacological nucleic acid expertise, and a strong portfolio of patents in this area of research. We expect that these capabilities and expertise will allow us to strategically design and rapidly synthesize RNAi therapeutics, which would retain all the properties required for molecular recognition but have resistance to degrading enzymes. We believe that our expertise and infrastructure provide us with a dramatic head start in the development of effective RNAi-based therapeutics.

experienced management and scientific teams with the passion and commitment to reap the benefits of existing resources.

# MANAGEMENT.

turning RNAi theory into
reality. Sirna Therapeutics.

# PROMISE.

We are extremely excited about the opportunities before us. Our scientific expertise, intellectual property position, skilled management and vast knowledge of RNA put us in an ideal position to advance RNAi-based therapeutics into the clinic. A group of leading investors in the biotechnology field have put their trust in our ability to achieve our goals and we are pleased that you have joined us in this mission.

Sirna Therapeutics is a new company heading in a new direction that leverages all our experience and expertise. We expect to play a leading role in the development of RNAi therapeutics.

Sirna Therapeutics, Inc. (formerly Ribozyme Pharmaceuticals, Inc.)

# Statement of Operations

| (unaudited) | December 31 2002 | 2001 |
|---|---|---|
| Total revenues | $ 5,147,706 | $ 8,307,883 |
| Expenses | | |
| Research and development | 28,659,341 | 56,688,960 |
| General and administrative | 5,505,035 | 4,512,197 |
| Total expenses | 34,164,376 | 61,201,157 |
| Operating loss | (29,016,670) | (52,893,274) |
| Other (expense) income | | |
| Interest income | 389,155 | 2,164,638 |
| Interest expense | (802,631) | (819,576) |
| Other income | 69 | 50,950 |
| Equity in loss of unconsolidated affiliate | (5,276,211) | (8,340,899) |
| Total other (expense) income | (5,689,618) | (6,944,887) |
| Net loss | (34,706,288) | (59,838,161) |
| Accretion of dividends on preferred stock | 1,570,407 | 775,346 |
| Net loss applicable to common stock | $ (36,276,695) | $ (60,613,507) |
| Net loss per share | $ (1.80) | $ (3.59) |
| Shares used in computing net loss per share | 20,134,359 | 16,883,324 |

Sirna Therapeutics, Inc. (formerly Ribozyme Pharmaceuticals, Inc.)

# Condensed Balance Sheet

| (unaudited) | December 31 2002 | 2001 |
|---|---|---|
| **ASSETS** | | |
| Cash, cash equivalents and securities available-for-sale | $ 8,820,978 | $ 34,995,070 |
| Accounts receivable | 483,645 | 1,543,197 |
| Equipment & leasehold improvements, net | 4,523,809 | 4,588,313 |
| Deferred patent costs, net | 5,886,733 | 5,544,614 |
| Investment in joint venture | 0 | 3,577,340 |
| Other assets, net | 2,182,960 | 1,774,674 |
| Total assets | $ 21,898,125 | $ 52,023,208 |
| **LIABILITIES AND STOCKHOLDERS' (DEFICIT) EQUITY** | | |
| Current liabilities | $ 5,033,196 | $ 5,127,436 |
| Other long-term liabilities, and convertible debt and redeemable preferred stock | 20,818,078 | 26,497,488 |
| Stockholders' (deficit) equity | (3,953,149) | 20,398,284 |
| Total liabilities & stockholders' (deficit) equity | $ 21,898,125 | $ 52,023,208 |

The financial statements should be read together with the Notes to Consolidated Financial Statements, and the information contained in Management's Discussion and Analysis of Financial Condition and Results of Operations in the Company's Form 10-K filed with the Securities and Exchange Commission on March 28, 2003.

# Shareholder Information

## 2002 CORPORATE MANAGEMENT

Howard W. Robin
President & CEO

Nassim Usman, PhD
Vice President, Research and Development & CSO

Marvin Tancer
Vice President, Operations & CFO

Barry Polisky, PhD
Vice President, Research

Bharat Chowrira, PhD, JD
Vice President, Legal Affairs, Licensing & Patent Counsel

## 2002 BOARD OF DIRECTORS

Jeremy Cook, Chairman
Bioscience Managers Limited

John Groom
ELAN Corporation

Howard W. Robin
President & CEO,
Sirna Therapeutics

Sam Saks, MD
JAZZ Pharmaceuticals

Anders Wiklund
Wiklund International

## TRANSFER AGENT

American Stock Transfer & Trust Co.

## STOCK INFORMATION

Sirna Therapeutics, Inc. common stock is traded over-the-counter on the Nasdaq National Market System under the symbol RNAI.

## INDEPENDENT AUDITORS

Ernst & Young LLP
Denver, Colorado

## CORPORATE COUNSEL

James R. Tanenbaum
Morrison & Foerster LLP
New York, New York

## PATENT COUNSEL

David A. Bochnem
McDonnell Bochnem, Hubert & Berghoff
Chicago, Illinois

## CONTACT INFORMATION

Sirna Therapeutics, Inc.
2950 Wilderness Place
Boulder, Colorado 80301
T 303.449.6500
F 303.449.6995

## ANNUAL MEETING

May 29, 2003 at 10:00 a.m. at Sirna Therapeutics corporate headquarters.

## FORWARD-LOOKING STATEMENT

Our discussion contains forward-looking statements based upon current expectations that involve risks and uncertainties, such as our plans, objectives, expectations and intentions. Our actual results and the timing of certain events could differ materially from those anticipated in these forward-looking statements as a result of factors we identify in the section titled “Risk Factors” in our Form 10-K filed with the U.S. Securities and Exchange Commission on March 28, 2003.

Sirna Therapeutics is a new company heading in a new direction. We expect to play a leading role in the development of RNAi therapeutics.

Sirna Therapeutics

Sirna Therapeutics, Inc. | 2950 Wilderness Place | Boulder, Colorado 80301 | T 303.449.6500 | F 303.449.6995