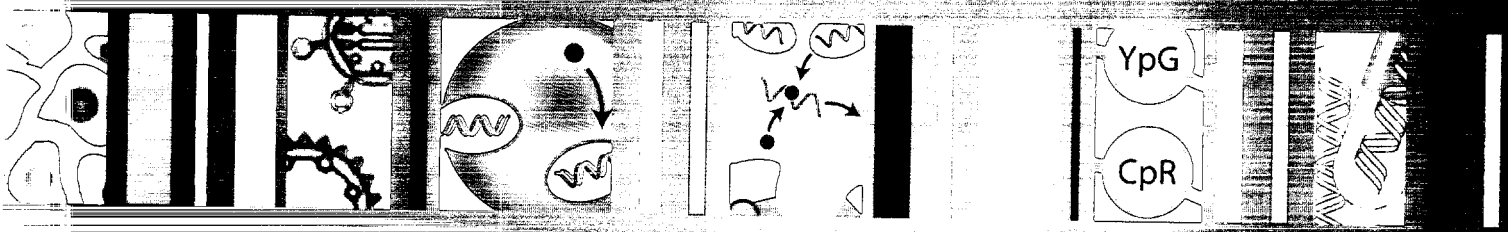
Ars
* Hybridon INC

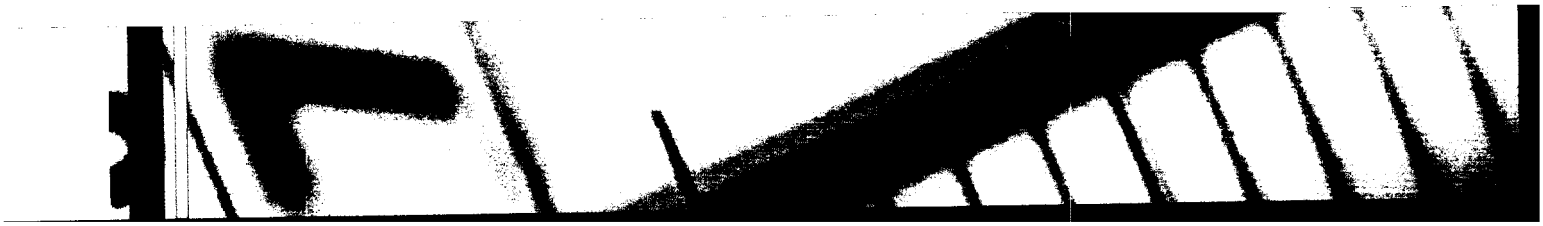
CREATING MEDICINES BASED ON TOLL-LIKE RECEPTORS



2004 ANNUAL REPORT

Hybridon

Our mission is to advance novel drugs that modulate the body's immune system to treat cancer, asthma, allergies and infectious diseases.



ACCOMPLISHMENTS IN 2004

We can report on a series of accomplishments taking place over the last year, including:

- Initiation of our first Phase 2 trial for IMOxine®, our lead drug candidate;
- Presentations of preclinical data at several major medical and scientific meetings on all of our IMO programs;
- Signing of two new antisense license agreements with Alnylam Pharmaceuticals, Inc. and VasGene Therapeutics, Inc., bringing the total number of antisense licensees to nine;
- Strengthening of our Board of Directors with the addition of Alison Taunton-Rigby, Ph.D., O.B.E. and bringing the number of independent directors on the board to five;
- Closing of two equity financings, resulting in an additional $17 million in funding for the Company; and
- Converting of virtually all of our Series A preferred stock to common stock and paying off the remainder of our debt.

Dear Hybridon Stockholders,

We are very pleased to report that Hybridon's transition from a technology platform company to a product development company is now complete. Our IMO™ discovery program has now matured into a series of promising drug candidates. Our mission is now to advance novel drugs that modulate the body's immune system to treat cancer, asthma, allergies and infectious diseases.

During this past year, we focused our development efforts on our immune modulatory oligonucleotide (IMO) programs and on establishing collaborations to realize the potential for our antisense programs. Hybridon has once again demonstrated its leadership in DNA chemistry by pioneering a novel approach to creating new chemical entities, which mimic bacterial DNA and trigger the immune system. There is currently much enthusiasm for development of novel drugs that direct our immune system to fight disease, and we believe our IMO programs represent an excellent opportunity to potentially deliver high-value new drugs to patients.

Following the Pathway to Opportunity – Toll-like Receptor 9

Toll-like receptors (TLRs) are part of the body's first line of defense against invading pathogens. Over 2000 publications within the last seven years have described this key component of the immune system and have established TLRs as potential drug targets, able to modulate immune response for therapeutic benefit in a number of diseases. Significant interest has been demonstrated by large pharmaceutical companies in drug candidates targeted to the TLR9 pathway. For instance, in March 2005, a private biotechnology company licensed its TLR9 cancer program to a large pharmaceutical company under an agreement with a potential value in excess of $500 million. We believe Hybridon's synthetic DNA TLR9 program is currently the only 2nd-generation technology in this exciting new area providing greater flexibility than 1st-generation technology.

Building a Pipeline of IMO Drug Candidates

2004 marks the first year that Hybridon has advanced its own drug compound into a multi-center Phase 2 proof-of-concept human clinical trial. Our lead candidate is IMOxine,® a TLR9 agonist that is presently in a Phase 2 monotherapy trial in patients with Renal Cell Carcinoma. IMOxine has been administered to over 50 healthy subjects and oncology patients in Phase 1 trials and continues to generate positive preclinical data in a broad range of cancers. In 2005, we plan to initiate a second clinical trial with IMOxine in combination with either a chemotherapy agent or monoclonal antibody to validate the promising preclinical efficacy data we observed in humans. We also are developing additional IMO candidates that have shown promising activity in preclinical models for applications including asthma and allergies, infectious diseases, and vaccine adjuvants. Our pipeline strategy is to focus our resources on advancing the current IMOxine cancer programs, seek partnerships to leverage IMOxine into additional combination trials, and to initiate further development of IMO lead candidates in other diseases. We expect to continue to derive value from our antisense technology through collaborations and partnerships.

Expanding Our Intellectual Property Estate

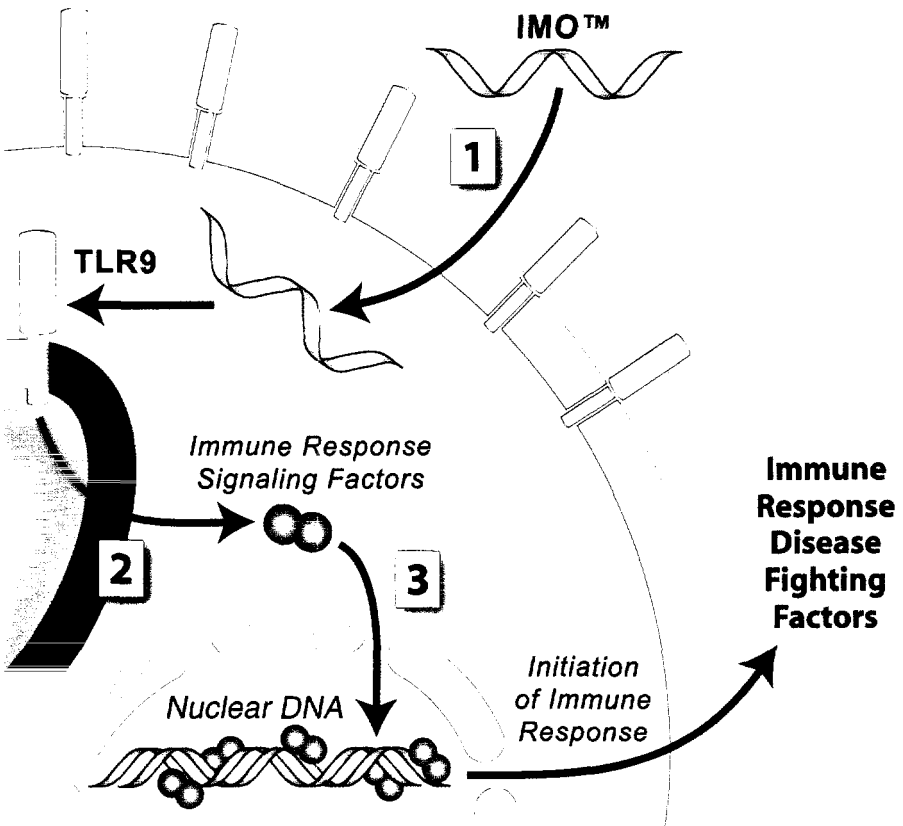
We continue to make significant progress in advancing the basic science of immune modulation. These discoveries are being applied to the development of novel therapeutics aimed at treating diseases such as cancer, asthma, allergies and infectious diseases.

Our success depends in part on our ability to secure proprietary protection for product candidates. As of the end of 2004, we owned or exclusively licensed over 612 patents and patent applications, worldwide. Of these patents, we owned 29 U.S. patents and U.S. patent applications and over 80 corresponding worldwide patent applications in a growing portfolio of patents relating to our IMO technology. We also owned or exclusively licensed over 532 worldwide patents and patent applications relating to our antisense technology. As we continue to build this extensive portfolio of intellectual property assets, we plan to continue to explore licensing and partnership opportunities to leverage these assets into products.

Financial Update

We have made significant progress in managing our costs and funneling our resources into projects that will provide the best return for our stockholders. For 2004, we reported total revenues of $0.9 million and a net loss applicable to common stockholders of $0.16 per share compared with total revenues of $0.9 million and a net loss applicable to common stockholders of $0.45 per share in 2003. Research and development expenses were substantially unchanged at $10.8 million in 2003 and $10.3 million in 2004. General and administrative expenses decreased from $6.9 million in 2003 to $4.3 million in 2004. At the end of 2004, Hybridon reported $14.4 million in cash, cash equivalents and investments compared to $13.7 million at the end of 2003.

HOW TOLL-LIKE RECEPTORS WORK



1. Toll-like receptors, or TLRs, act as the immune system's first line of defense by identifying the DNA of pathogens (carriers of disease including bacteria).

2. Hybridon's Immunomodulatory Oligonucleotides, or IMOs, fight disease by mimicking bacterial DNA so that the IMOs are specifically identified by Toll-like receptor 9 (TLR9), which signals the body to begin the immune response against disease.

3. When TLR9 is activated, it stimulates a response that involves multiple immune response components acting to fight disease in two ways: through an innate immune response and an adaptive immune response.

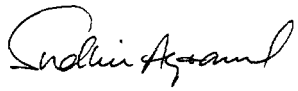
Hybridon's IMO drug candidates take advantage of both types of immune response, enabling them to activate the immune system against widely different types of disease such as cancer and infectious diseases as well as asthma and allergies.

Looking Ahead

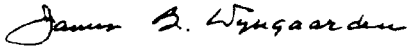
We are excited about our prospects in 2005 as we advance our pipeline of programs through clinical development and work to expand our partnering efforts. Our partners, including The Immune Response Corporation, Aegera Therapeutics, Inc. and VasGene, Inc. are also making progress in their clinical and preclinical programs. As we look forward throughout 2005 we expect to:

- Advance our lead IMOxine monotherapy clinical program in Renal Cell Carcinoma through the first cohort of our Phase 2 trial;
- Report preclinical results on IMOxine and our other IMO programs at several major medical meetings throughout the year;
- Initiate a second IMOxine Phase 1/2 cancer clinical trial in combination with chemotherapy or a monoclonal antibody;
- Secure at least one validating partnership with a leading pharmaceutical or biotechnology company for one or more of our IMO programs; and
- Expand our drug development team to manage the multiple clinical programs we expect in our pipeline in 2005 and 2006.

We wish to thank our Board of Directors, employees and stockholders for their continuing support and dedication to the science and promising programs that now make up the Hybridon product portfolio. We look forward to reporting on our progress toward our ambitious goals throughout the year.



Sudhir Agrawal, D.Phil.
Chief Executive Officer



James B. Wyngaarden, M.D.
Chairman

PRODUCT PIPELINE

CANDIDATE	INDICATION	RESEARCH	PRECLINICAL	PHASE 1	PHASE 2
IMOxine®	Cancer				*
IMOxine & Chemo	Cancer				(Expected Q2 '05)
IMOxine & Mabs	Cancer				
IMOxine & Radiation	Cancer				
HYB2093	Asthma/Allergy				
HYB2125	Hepatitis C				
HYB676	VEGF (Ocular)				

*Renal Cell Carcinoma Q4 '04

HYBRIDON, INC.

CONSOLIDATED CONDENSED STATEMENTS OF OPERATIONS

(in thousands, except per share data)

	YEARS ENDED DECEMBER 31	
	2004	2003
Revenues	$ 942	$ 897
Operating Expenses		
Research & Development	10,305	10,817
General & Administrative	4,273	6,924
Stock-based Compensation	(713)	543
Total Operating Expenses	13,865	18,284
(Loss) from Operations	(12,923)	(17,387)
Investment Income	217	294
Interest Expense	(29)	(118)
Net (Loss)	(12,735)	(17,211)
Accretion of Preferred Stock Dividends	(2,676)	(5,529)
Net (Loss) Applicable to Common Stockholders	$ (15,411)	$ (22,740)
Basic and Diluted Net (Loss) Per Common Share Applicable to Common Stockholders	$ (0.16)	$ (0.45)
Shares Used In Computing Basic and Diluted Net (Loss) Per Common Share	98,914	51,053

CONSOLIDATED CONDENSED BALANCE SHEET DATA

(in thousands)

	AT DECEMBER 31	
	2004	2003
Cash, Cash Equivalents and Investments	$ 14,413	$ 13,668
Other Assets	978	742
Total Assets	$ 15,391	$ 14,410
9% Notes Payable	$ —	$ 1,306
Other Current Liabilities	1,858	1,927
Non-current Liabilities and Deferred Revenue	764	651
Total Stockholders' Equity	12,769	10,526
Total Liabilities & Stockholders' Equity	$ 15,391	$ 14,410

UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
Washington, D.C. 20549

FORM 10-K

For Annual and Transition Reports Pursuant to Sections 13
or 15(d) of the Securities Exchange Act of 1934

☑ ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

For the Fiscal Year Ended December 31, 2004

OR

☐ TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934

Commission File Number: 001-31918

HYBRIDON, INC.

(Exact name of Registrant as specified in its certificate of incorporation)

Delaware	04-3072298
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
345 Vassar Street Cambridge, Massachusetts (Address of principal executive offices)	02139 (Zip Code)

(617) 679-5500
(Registrant's telephone number, including area code)

Securities registered pursuant to Section 12(b) of the Act: None

Securities registered pursuant to Section 12(g) of the Act:

Common Stock, $.001 par value
(Including Associated Preferred Stock Purchase Rights)
(Title of Class)

Indicate by check mark whether the registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the registrant was required to file such reports), and (2) has been subject to the filing requirements for the past 90 days. Yes ☑ No ☐

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K. ☐

Indicate by check mark whether the registrant is an accelerated filer (as defined in Exchange Act Rule 12b-2). Yes ☐ No ☑

The approximate aggregate market value of the voting stock held by non-affiliates of the registrant was $60,166,000 based on the last sale price of the registrant's common stock on the American Stock Exchange on June 30, 2004. As of March 1, 2005, the registrant had 110,989,836 shares of common stock outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the Registrant's Proxy Statement with respect to the
Annual Meeting of Stockholders to be held on June 15, 2005 .... Items 10, 11, 12, 13 and 14 of Part III.

HYBRIDON, INC.

FORM 10-K

INDEX

PART I.

Item 1. *Business*

Overview

We are engaged in the discovery, development and commercialization of novel therapeutics based on synthetic DNA for the treatment of cancer, asthma/allergies and infectious diseases. Our activities are primarily focused on the development of our immunomodulatory oligonucleotide, or IMO, technology. Our IMO compounds are synthetic DNA-based sequences that are designed to mimic bacterial DNA and be recognized by a specific protein receptor called Toll-like Receptor 9, or TLR9, which triggers the activation and modulation of the immune system. We also have been a pioneer in the development of antisense technology, which uses synthetic DNA to block the production of disease causing proteins at the cellular level. In 2003 and 2004, we devoted substantially all of our research and development efforts to our IMO technology and products and expect to continue to focus our research and development efforts in 2005 and in future years on our IMO technology and products. We plan to continue to seek to enter into collaborations with third parties for the development and commercialization of products based on our antisense technology.

Drug Development Strategy

In the near term, we are focusing our internal drug development efforts on the lead IMO drug candidate in our pipeline, HYB2055. We are developing HYB2055 for oncology applications under the name IMOxine. In October 2004, we commenced patient recruitment for an open label, multi-center phase 2 clinical trial of IMOxine as a monotherapy in patients with metastatic or recurrent clear cell renal carcinoma. We plan to recruit a minimum of 46 patients into the first stage of the trial.

In addition to the phase 2 clinical trial of IMOxine, we are conducting a phase 1 clinical trial of IMOxine in patients with refractory solid tumor cancers, which was closed to enrollment in November 2004. In November 2004, we announced interim results of this phase 1 clinical trial of IMOxine, which is being conducted at the Lombardi Comprehensive Cancer Center at Georgetown University Medical Center in Washington, D.C. We anticipate announcing further results in the second quarter of 2005. In the interim results of the phase 1 trial, IMOxine was found to be well tolerated with no dose-limiting toxicity observed. Adverse effects recognized through March 1, 2005 have been consistent with the expected immune stimulation activity of IMOxine, consisting primarily of mild to moderate injection site reactions, pain, and "flu-like" symptoms. The interim results provided evidence of dose response effects on immunology parameters in patients with a variety of cancer types including patients with renal cell carcinoma, melanoma, colorectal cancer, sarcoma, breast cancer, non-small cell lung cancer and other cancers.

In addition to these trials, we may in the future conduct trials in which we evaluate IMOxine for the treatment of other specific types of cancer, as a monotherapy and/or in combination with other anticancer agents, including chemotherapeutics, antibodies, and vaccines/antigens.

Collaboration Strategy

In addition to developing drug candidates on our own, we are seeking to establish alliances with other parties for the development and commercialization of products based on our IMO and antisense technologies.

We believe that pharmaceutical and biotechnology companies may seek to use our IMO compounds as a monotherapy for the treatment of specific diseases or in combination with, or as an adjuvant to, their own chemotherapeutics, vaccines and monoclonal antibodies. In particular, we are developing HYB2055 in a lower dosage form, under the name Amplivax, for use as a vaccine adjuvant. We licensed Amplivax to The Immune Response Corporation for use in its development of a potential therapeutic and prophylactic vaccine for HIV infection, and we plan to seek additional licensees for Amplivax in the future. In June 2004, The Immune Response Corporation initiated a phase 1/2 clinical trial involving the use of Amplivax as an adjuvant to REMUNE, an immune-based HIV therapeutic vaccine being developed by The Immune Response Corporation.

We also believe that our antisense technology may prove useful to pharmaceutical and biotechnology companies that are seeking to develop drug candidates that down-regulate gene targets discovered by, or proprietary to, such companies. In addition to collaborations based on gene targets whose proprietary rights are controlled by third parties, we are seeking collaborators to continue development of our most advanced antisense drug candidate GEM231 and our other antisense drug candidates. GEM231 is a 2nd generation antisense compound for treating solid tumor cancers that we developed to inhibit Protein Kinase A, or PKA, a protein that has been shown to be present at increased levels in the cells of many human cancers. We completed enrollment of a phase 1/2 clinical trial of GEM231 as a combination therapy with irinotecan, an anticancer drug marketed in the United States under the name Camptosar®. We presented interim data from this trial at the 2004 Annual Meeting of the American Society of Clinical Oncology, or ASCO.

We have already entered into nine collaboration and licensing agreements for our antisense technology including agreements with Alnylam Pharmaceuticals, Inc. and VasGene Therapeutics Inc. which were entered into during 2004. We are seeking to enter into additional collaboration agreements for our antisense technologies.

Our Product Pipeline

The table below summarizes the principal products that we or our collaborators are developing and the therapeutic use and development status of these products.

Product Description	Therapeutic Use	Development Status
IMO		
IMOxine[1]	Cancer	phase 2
Amplivax[2]	HIV	phase 1/2
IMOxine[3] (used in combination)	Cancer	preclinical candidate
HYB2093	Asthma/allergy	preclinical candidate
HYB2125	Hepatitis C	preclinical candidate
Antisense		
GEM231[4]	Cancer	phase 1/2
GEM640 (AEG35156)[5]	Cancer	phase 1
MBI1121[6]	Human papillomavirus	phase 1
Veglin[7]	Cancer	phase 1
HYB676	Ophthalmology	preclinical candidate

1. Being used as a monotherapy in patients with metastatic or recurrent clear cell renal carcinoma.
2. Being used as an adjuvant in combination with REMUNE®, an immune-based HIV therapeutic vaccine developed by The Immune Response Corporation under a collaboration agreement with us.
3. Being used in combination with chemotherapy, selected monoclonal antibodies and radiation.
4. We are seeking to enter into a collaboration for further development of this product.
5. Being developed by Aegera Therapeutics, Inc. under a collaboration agreement with us.
6. Migenix Inc. has the rights to develop MBI1121 under a collaboration agreement with us.
7. Being developed by VasGene Therapeutics Inc. under a collaboration agreement with us.

In addition, we have developed several antisense drug candidates for specific applications that are not currently in active development programs but could be suitable candidates for collaborations. These include:

Product Description	Therapeutic Use	Development Status
GEM92	HIV	phase 1
GEM240	Cancer	preclinical candidate

Immunomodulatory Oligonucleotide (IMO) Technology

Overview

Our IMO technology has evolved from our research and clinical experience with antisense oligonucleotides. We learned from this research and clinical experience that some types of oligonucleotides can act as potent stimulators of the immune system. Our early insights and those of others showed that oligonucleotides containing specific nucleotide segments, or motifs, mimic in the human body the immune stimulating effects of bacterial DNA. Nucleotides are the molecules that are linked together to form DNA. Using our DNA chemistry, we have designed and are developing a new, proprietary class of IMO compounds. We believe these compounds, which we refer to as IMO compounds, may offer a number of potential advantages over earlier immune stimulatory oligonucleotides.

We are designing our IMO compounds to be used in the treatment of conditions such as cancer, allergic asthma and other allergies, and infectious diseases, either alone as a monotherapy or in combination therapies with chemotherapeutics, radiation, vaccines and antibodies.

Background

The human immune system protects the body against viruses, bacteria and other infectious agents, referred to as pathogens. It also acts to identify and eliminate abnormal cells, such as cancer cells. The immune system works through various mechanisms which recognize pathogens and abnormal cells. These mechanisms initiate a series of interactions resulting in stimulation of specific genes in response to the pathogens or abnormal cells. The activities of the immune system are undertaken by its two components: the innate immune system and the adaptive immune system.

The role of the innate immune system is to provide a rapid, non-specific response to a pathogenic invasion or to the presence of a foreign substance in the body and to activate the adaptive immune system. The innate immune system consists of cells such as macrophages, dendritic cells and monocytes. When the body is presented with a foreign pathogen, cells of the innate immune system are activated, resulting in a cascade of signaling events that cause the production of proteins to fight the infection. Unlike the antibodies and proteins produced by the adaptive immune system described below, the proteins produced by the innate immune system are not pathogen-specific, but rather are active against a broad spectrum of pathogens. Moreover, once the infection is resolved, the innate immune system will not remember the pathogen.

In contrast to the innate immune system, the adaptive immune system provides a pathogen-specific response to a pathogenic invasion. The adaptive immune system does this by recognition of specific cell surface proteins, called antigens, which signal the presence of a pathogen. This process is initiated through signals produced by the innate immune system. Upon recognition of a foreign antigen, the adaptive immune system produces antibodies and antigen-specific toxic immune cells that specifically detect and destroy infected cells. This response is referred to as an antigen-specific immune response. An antigen-specific immune response normally takes several weeks to develop the first time. However, once activated by a specific pathogen, the adaptive immune system "remembers" the antigens of the pathogen. In this manner, if the pathogen again invades the body, the presence of the "remembered" antigens will allow the adaptive immune system to respond once more, this time in a matter of days. Scientists generally believe that the adaptive immune system also may be able to eliminate abnormal cells, such as cancer cells.

The human immune reaction is initially commenced by activation of the innate immune system. One way this occurs is through recognition by the immune system of a pathogen-associated molecular pattern, referred to as a PAMP. These patterns include components of DNA that are present with great frequency in pathogens and with low frequency, or not at all, in humans. The presence of a PAMP acts as a signal to the immune system of the presence of a foreign pathogen and starts an immune response.

In the case of bacteria, one common PAMP is a combination of DNA known as a CpG dinucleotide or CpG DNA. A CpG dinucleotide, or motif, consists of a cytosine (C) molecule and guanine (G) molecule linked by a phosphate bond (p). Most bacteria contain this CpG motif at the expected frequency of one in sixteen base pairs in their genome. Vertebrates, including humans, display many fewer CpG dinucleotides, and

usually the cytosine (C) molecule of the CpG motif is methylated, unlike bacterial CpG dinucleotides where the cytosine (C) molecule is unmethylated. Methylation is the substitution of a methyl group, a molecule containing one carbon atom and three hydrogen atoms, for a hydrogen atom. In this way, self DNA, which is methylated, is not mistaken for pathogen DNA.

CpG DNA has been shown to be recognized by a specific protein receptor called Toll-like Receptor 9, or TLR9. TLR9 is located inside some types of immune cells. Scientists generally believe that once TLR9 recognizes bacterial DNA, such as CpG DNA, it triggers an immune response through a cascade of cell signals that ultimately leads to the release of immune system molecules both from the innate and eventually the adaptive immune systems. These molecules attack the infection. Additional receptors other than TLR9 may also contribute to or modify the recognition of certain CpG DNA, emphasizing the structural importance of CpG DNA in TLR-specific signaling.

Our IMO compounds are intended to mimic bacterial DNA. We believe the sequences of these compounds are recognized as bacterial DNA by TLR9 and possibly other receptors. As a result, we believe that our IMO compounds can trigger an innate immune response similar to the innate immune response triggered by bacterial DNA. Results from our preclinical studies and our initial clinical trials of our IMO compounds suggest this response leads to signaling events that include production of cytokines. Cytokines are a specific type of immune system molecule that are known to have broad spectrum therapeutic properties against infectious disease as well as against cancer. These signals from the innate immune system also may trigger responses of the adaptive immune system.

Because recognition of IMO compounds by TLR9 or other receptors may lead to both innate and adaptive immune responses, we believe IMO compounds may have the potential to be useful in treatment of a wide variety of diseases either as a monotherapy or in combination with other agents such as chemotherapeutics, radiation, vaccines, antigens and monoclonal antibodies. We and independent third parties who are investigating CpG DNA drug candidates that work in a manner similar to our IMO compounds are currently exploring the use of these drug candidates in clinical trials for cancer, asthma, allergies and infectious diseases.

Therapeutic Potential of IMO Compounds

Because IMO compounds can generate a broad range of immune responses, we believe they may provide therapeutic benefits in a number of areas:

- *Cancer.* Cancer cells are recognized by the body as abnormal cells and trigger an immune response. However, the body's immune response to cancer cells is notoriously weak. The benefits of immune stimulation by bacterial DNA in cancer patients have been long recognized. IMO compounds have been shown to activate dendritic cells and B cells and induce Th1 cytokine secretion in human cell-based assays. The secreted cytokines are known to stimulate natural killer cells to destroy cells within a tumor mass. In pre-clinical studies in mouse models, our IMO compounds have also been shown to enhance the activity of selected chemotherapeutic agents, selected anticancer antibodies and radiation.

- *Allergic Asthma and Other Allergies.* Based on preclinical studies of our IMO compounds in mouse models, we believe that IMO compounds have potential for use in the treatment of allergic asthma, other allergies and other diseases that result from an overreaction of the immune system by suppressing specific allergen induced allergic responses. In these studies the type of cytokines produced as a result of the activation of immune cells by IMO compounds suppressed asthmatic and allergic immune conditions while simultaneously promoting an immune response that further alleviated asthmatic and allergic conditions.

- *Infectious Diseases.* According to published reports, various CpG DNA sequences have been shown in studies in mice and other animals to activate an immune defense against pathogens that is of a general nature and not directed at any specific microorganism. As a result, we believe that our IMO compounds have the potential to be used prophylactically to ward off the danger of infection or to boost the immune response to an early-stage or ongoing infection. Some of our IMO compounds have been shown in ongoing preclinical studies to induce Th1-type cytokines, IFN-α in non-human primate

studies for example. These cytokines are useful as anti-infectious agents against bacteria, viruses, and parasites. We have a portfolio of various IMO structures, including compounds that induce high levels of IFN-α, which may be suitable for treating Hepatitis C and other viral infections.

- *Combinations with Vaccines.* In preclinical studies in mice, the immune response triggered by IMO compounds has been shown to increase the effectiveness of vaccines and peptides. As a result, we believe that IMO compounds have the potential to be used in combination with, or as an adjuvant to, vaccines. The Immune Response Corporation is evaluating our Amplivax IMO compound for use as an adjuvant in combination with REMUNE in a phase 1/2 clinical trial.

IMO Chemistry

Based on our expertise in synthetic oligonucleotide chemistry compiled over the past fifteen years, we have developed a portfolio of IMO compounds containing different proprietary synthetic motifs and different site-specific sequences. In our preclinical studies of several IMO compounds and initial clinical trials of our lead IMO compound, our IMO compounds have triggered an immune response that has resulted in the expression of many cytokines. This immune response and the resulting expression of cytokines have varied depending on the sequence and structure of the IMO compound. We believe that by varying the synthetic motifs, site-specific sequences and secondary structures in the IMO compounds, we can design IMO compounds that optimize immunostimulatory activity and induce different profiles of immune response. As a result, we believe we may create IMO compounds that are optimized for the treatment of different diseases.

HYB2055 Drug Discovery and Development

IMOxine

We are focusing our internal drug development efforts on the lead drug candidate in our pipeline, HYB2055, for oncology applications under the name IMOxine. We selected HYB2055 for clinical development because of the potency it demonstrated as an immune modulator in preclinical models, both *in vitro* and *in vivo*. We filed an Investigational New Drug Application, or IND, for HYB2055 with the FDA that became effective March 6, 2003.

In March 2004, we completed a phase 1 clinical trial of HYB2055 in 28 healthy volunteers over a broad range of dosing levels. In this trial, HYB2055 was well tolerated by the volunteers, who did not experience any significant treatment-related adverse effects. In addition, HYB2055 demonstrated biological activity in the volunteers, according to the several parameters monitored in the study.

In May 2003, we commenced a phase 1 clinical trial of IMOxine in patients with refractory solid tumor cancers at the Lombardi Comprehensive Cancer Center at Georgetown University Medical Center in Washington, D.C. We announced enrollment completion and interim results from the phase 1 oncology trial in November 2004. We enrolled 23 patients in this trial and one patient continues to receive IMOxine treatment as of March 1, 2005 (for over one year). Interim results from the trial included that IMOxine was found to be well tolerated with no significant dose-limiting toxicity observed. The adverse effects patients experienced as of the November 2004 announcement were consistent with the expected immune stimulation activity of IMOxine, and primarily have been mild to moderate injection site reactions, pain and "flu-like" symptoms including rigors/chills, fever, nausea, myalgia, headache, malaise and fatigue. Observations that were considered serious adverse events and possibly related to IMOxine treatment have been transient dyspnea with hypoxia (1 patient), rigors/chills 1 hour post dose (1 patient), abdominal pain with nausea/vomiting (1 patient) and anemia requiring transfusion (2 patients). The one patient continuing to receive IMOxine therapy has had no additional adverse effects since the November 2004 announcement. The interim results of this phase 1 trial provided evidence of dose response effects on immunology parameters in patients with a variety of cancer types, including renal cell carcinoma, melanoma, colorectal cancer, sarcoma, breast cancer, non-small cell lung cancer and other cancers.

In February 2005, Hybridon agreed to support a single-patient investigator-sponsored IND involving the weekly administration of IMOxine at a dosage of 0.64 mg/kg per week. The investigator is Michael

Seiden, M.D., Ph.D., of Massachusetts General Hospital. The single patient has chemotherapy resistant epithelial ovarian carcinoma.

We are currently conducting a phase 2 clinical trial of IMOxine in patients with metastatic or recurrent clear cell renal carcinoma. The trial, for which we began patient recruitment in October 2004, is a two-stage, multi-center, open label study of IMOxine as a monotherapy. The primary objective of the study is to determine tumor response by Response Evaluation Criteria in Solid Tumors, or RECIST. Secondary study objectives are safety, duration of response, time to progression, survival one year after the last dose and the treatment effect on quality of life. In the trial, one of two dose levels of 0.16 or 0.64 mg/kg is administered by weekly subcutaneous injection. Treatment duration is defined as 24 weeks based on safety and the absence of disease progression. We expect that patients can continue to receive IMOxine treatment beyond 24 weeks based on investigator recommendations and independent medical monitor concurrence. We plan to recruit a minimum of 46 patients in the first stage of the trial and anticipate preliminary results related to the primary objective within the first half of 2006. We expect the second stage of the trial to be a continuation of the same trial design if warranted by the first stage interim results.

Amplivax

In addition to cancer applications, we are also developing HYB2055 for use as a vaccine adjuvant. We are developing HYB2055 in a lower dosage form under the name Amplivax for these applications. We licensed Amplivax to The Immune Response Corporation for use in its development of a potential therapeutic and prophylactic vaccine for HIV infection, and we plan to seek additional licensees for Amplivax in the future. In June 2004, The Immune Response Corporation initiated a phase 1/2 clinical trial involving the use of Amplivax as an adjuvant to REMUNE, an immune-based HIV therapeutic vaccine being developed by The Immune Response Corporation.

Additional Applications

We believe that HYB2055, or similar compounds based on our IMO technology, may also be used as a monotherapy for treatment of infectious diseases, allergic asthma and other allergies. We may explore the potential of these uses either on our own, or with collaborators through submission of additional INDs.

Antisense Technology

Overview

Most drugs are chemicals that stimulate or suppress the function of a particular molecule, usually a protein, which causes a disease. The drug acts by binding to the target molecule and interrupting the disease-causing activity of the target molecule. Frequently, however, sites on other non-target molecules present in the body resemble the target-binding site of a disease-causing molecule and, as a result, the conventional drug binds to some degree to those non-target molecules. Most drug side effects arise due to this off-target activity.

In contrast, antisense drug candidates interact with the target molecule with extremely high specificity. Antisense drug candidates are designed to bind to a unique messenger RNA (mRNA) target and thereby block production of the specific protein encoded by the target mRNA. We believe that drugs based on antisense technology may be more effective and cause fewer side effects than conventional drugs because antisense drugs are designed to intervene in a highly specific fashion in the production of proteins, rather than after the proteins are made.

Background

A normal cell produces a particular set of normal proteins in the right amount for the body to function properly. A diseased cell produces inappropriate proteins or the wrong amount of normal proteins. A cell produces inappropriate types or amounts of proteins when its DNA expression changes, either through mutation as in many types of cancer cells or through an imbalance of normal bodily function. In some

instances, inappropriate proteins act directly to cause or support a disease. In other instances, inappropriate proteins interfere with proteins that prevent or combat disease.

Cells make proteins in a two-stage process. All proteins are based on the DNA which comprises the cellular genome. DNA is a string of individual building blocks chemically known as nucleotides. The specific sequence in which the nucleotides are arranged is the code that embodies genetic information into the DNA. First, the cell uses its genetic DNA code as a pattern to create a molecule of messenger RNA or mRNA consisting of a string of nucleotides in a sequence that is the exact mirror image of, or complementary to, the sequence of the coding strand of nucleotides in the DNA. This mRNA strand is called the "sense" sequence. In the next step, the cell translates the information contained in the "sense" sequence into a specific protein.

Therapeutic Potential of Antisense Compounds

A synthetic DNA molecule with a sequence exactly complementary to a portion of a specific mRNA can bind to and inhibit the function of that mRNA. This exact complement of the sense mRNA is referred to as an antisense oligonucleotide. By inhibiting binding to a specific mRNA target, the antisense oligonucleotide blocks synthesis of the protein.

We believe that the pharmaceutical industry is increasingly rich in potential gene-based drug targets. We further believe that the increase in the number of potential targets provides us with increasing opportunities to employ our antisense technology. Once a gene coding for a disease-associated protein is identified, it should be possible to design a synthetic DNA with an antisense mechanism designed to stop production of that protein. Moreover, in contrast with small molecule drug discovery which may take many years, we can design an antisense drug candidate for a gene target in about 90 days after that gene target has been identified.

Hybridon Antisense Technology

We and other companies recognized early in the exploration of antisense technology that natural DNA-based oligonucleotides are not suitable as drug candidates because they are rapidly degraded in the blood and other tissues before they can reach their intended target within cells. Early modifications made by us and other companies to increase the biological stability of oligonucleotides lead to a chemical class of oligonucleotides which we refer to as 1st generation antisense compounds. To date, the FDA has approved only one 1st generation antisense compound, which one of our competitors developed and which is currently marketed by Novartis Ophthalmics to treat a viral infection through local delivery. Several 1st generation antisense drug candidates of third parties have failed to show activity in late stage clinical trials.

We have focused our efforts on the design and creation of more advanced synthetic DNA chemistries which we refer to as 2nd generation antisense compounds. We believe that 2nd generation antisense compounds may show more favorable pharmaceutical characteristics and significantly improved therapeutic utility as compared to 1st generation antisense compounds. We believe that these 2nd generation antisense compounds may exhibit the following desirable characteristics in comparison with 1st generation compounds: (1) fewer side effects; (2) greater stability in the body, enabling patients to take doses less frequently; (3) greater potency, permitting patients to take lower doses; and (4) greater potential for multiple routes of administration, including by injection, orally or topically.

The following companies have licensed Hybridon's antisense technology: Aegera Therapeutics, Inc., Alnylam Pharmaceuticals, Inc., Avecia Biotechnology, Epigenesis Pharmaceuticals, Inc., Integrated DNA Technologies, Inc., Isis Pharmaceuticals, Inc., Methylgene Inc., Migenix Inc. and VasGene Therapeutics Inc.

Antisense Drug Development and Discovery

Clinical Development

GEM231 for the Treatment of Cancer. GEM231 is designed to inhibit protein kinase A, or PKA. PKA is a protein that plays a key role in the control of the growth and differentiation of mammalian cells. Levels of PKA have been shown to be increased in the cells of many human cancers. GEM231 has been shown to have preclinical anti-tumor activity in models of various types of cancer, alone and in combination with various

agents. In August 2004, we completed enrollment of a phase 1/2 clinical trial of GEM231 at Vanderbilt University Medical Center as a combination therapy with irinotecan, an anticancer drug marketed in the United States under the name Camptosar®. In March 2004, we presented interim data from this trial showing that the combination of irinotecan at 125 mg/m^2 with GEM231 at 40 mg/m^2 per day was well tolerated in patients in the trial. Higher dosages of irinotecan and/or GEM231 were associated with dose-limiting toxicities such as fatigue, nausea, diarrhea, anorexia, weight loss and death attributable to pulmonary embolism. Preliminary evidence was seen of GEM231 effects on PKA activity in the blood and on irinotecan pharmacokinetics. We expect to collect and analyze the final data from the trial by the end of 2005. Even if the final pharmacokinetic data and other findings from this phase 1/2 trial are favorable, we do not plan to continue further development of GEM231 without a collaborator.

One patient who was withdrawn from the Hybridon sponsored trial due to prolonged treatment interruption was enrolled onto a single-patient physician-sponsored IND held by Mace Rothenberg, M.D., of Vanderbilt Medical Center. The single patient had breast cancer and received 125 mg/m^2 of irinotecan plus 40 mg/m^2 per day of GEM231.

GEM640/AEG35156 is an antisense compound being developed by Aegera Therapeutics, Inc. under a collaboration with us. GEM640 is targeted to the XIAP protein and is intended for the treatment of cancer. XIAP is an inhibitor of apoptosis, which is the process by which disrupted cells are dismantled without causing inflammation or other response. Cancer cells often fail to undergo apoptosis despite damage caused by chemotherapy or radiotherapy. Aegera began a phase 1 trial of GEM640/AEG35156 in 2004.

Veglin™ is an antisense drug candidate being developed by VasGene Therapeutics, Inc. and targeted against Vascular Endothelial Growth Factor (VEGF). VEGF contributes to the growth of new blood vessels, which is critical to disease processes including cancer and macular degeneration. In June 2004, VasGene announced the presentation of phase 1 data. The primary objective of this study was to determine the Maximum Tolerated Dose (MTD) and toxicity profile of Veglin among relapsed and refractory patients with a variety of tumor types. Patients in the trial received Veglin intravenously by two-hour infusion for five days followed by a seven-day rest period, for a maximum treatment duration of four months. Results demonstrated that Veglin was well tolerated by patients with a wide variety of cancers. VasGene anticipates initiating multi-center phase 2 clinical trials during 2005 for patients with renal cell carcinoma and/or other specific malignancies.

GEM92 is an antisense compound that is targeted to a specific region of the genome of the human immunodeficiency virus HIV-1 known as the *gag* region. In 1997, we conducted a phase 1 study that showed GEM92 was well tolerated by the participating subjects. We are not currently pursuing development of GEM92.

Preclinical Development

We have two principal antisense compounds that we are developing in the preclinical testing phase:

- HYB676 is a 2nd generation antisense agent targeted to VEGF as a potential drug candidate for age-related macular degeneration.

- GEM240 is targeted to inhibit the protein mdm2 which is increased in many human cancers.

Research and Development

For the years ended December 31, 2004, 2003 and 2002, we spent approximately $10.3 million, $10.8 million and $7.9 million, respectively, on research and development activities. Our collaborators sponsored only a nominal portion of these research and development activities in 2004, 2003 and 2002.

Patents, Proprietary Rights and Licenses

Patents and Proprietary Rights

Our success depends in part on our ability to obtain and maintain proprietary protection for our product candidates, technology and know-how, to operate without infringing the proprietary rights of others and to prevent others from infringing our proprietary rights. Our policy is to seek to protect our proprietary position by, among other methods, filing U.S. and foreign patent applications related to our proprietary technology, inventions and improvements that are important to the development of our business. We also rely on trade secrets, know-how, continuing technological innovation and in-licensing opportunities to develop and maintain our proprietary position.

As of December 31, 2004, we owned 29 U.S. patents and U.S. patent applications and over 80 corresponding world wide patents and patent applications relating to our IMO technology. As of December 31, 2004, we owned or exclusively licensed over 532 world wide patents and patent applications relating to our antisense technology of which 137 are U.S. patents and U.S. patent applications. The issued patents held or exclusively licensed by us include composition of matter patents on our own advanced DNA chemistries covering the use of these chemistries with various genes or sequences, patents covering therapeutic targets, patents covering immune modulation and patents covering oral and other routes of administering our synthetic DNA. These issued patents expire at various dates ranging from 2006 to 2022.

The composition of matter patents covering GEM231 expire at various dates ranging from 2010 to 2022. We have applied for composition of matter patents covering HYB2055.

The patent positions of companies like ours are generally uncertain and involve complex legal and factual questions. Our ability to maintain and solidify our proprietary position for our technology will depend on our success in obtaining effective claims and enforcing those claims once granted. We do not know whether any of our patent applications or those patent applications which we license will result in the issuance of any patents. Our issued patents and those that may issue in the future, or those licensed to us, may be challenged, invalidated or circumvented, and the rights granted thereunder may not provide us proprietary protection or competitive advantages against competitors with similar technology. Furthermore, our competitors may independently develop similar technologies or duplicate any technology developed by us. Because of the extensive time required for development, testing and regulatory review of a potential product, it is possible that, before any of our products can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thus reducing any advantage of the patent, which could adversely affect our ability to protect future drug development and, consequently, our operating results and financial position.

Because patent applications in the United States and many foreign jurisdictions are typically not published until eighteen months after filing, or in some cases not at all, and because publications of discoveries in the scientific literature often lag behind actual discoveries, we cannot be certain that we were the first to make the inventions claimed in each of our issued patents or pending patent applications, or that we were the first to file for protection of the inventions set forth in these patent applications.

Litigation may be necessary to defend against or assert claims of infringement, to enforce patents issued to us, to protect trade secrets or know-how owned by us, or to determine the scope and validity of the proprietary rights of others. In addition, the U.S. Patent and Trademark Office may declare interference proceedings to determine the priority of inventions with respect to our patent applications or reexamination or reissue proceedings to determine if the scope of a patent should be narrowed. Litigation or any of these other proceedings could result in substantial costs to and diversion of effort by us, and could have a material adverse effect on our business, financial condition and results of operations. These efforts by us may not be successful.

Trade Secrets

We may rely, in some circumstances, on trade secrets to protect our technology. However, trade secrets are difficult to protect. We seek to protect our proprietary technology and processes, in part, by confidentiality agreements with our employees, consultants, scientific advisors and other contractors. There can be no

assurance that these agreements will not be breached, that we will have adequate remedies for any breach, or that our trade secrets will not otherwise become known or be independently discovered by competitors. To the extent that our employees, consultants or contractors use intellectual property owned by others in their work for us, disputes may also arise as to the rights in related or resulting know-how and inventions.

Licenses

We are a party to a number of royalty-bearing license agreements under which we have acquired rights to patents, patent applications and technology of third parties. Our principal license agreement is with University of Massachusetts Medical Center. Under the terms of our license agreement with the University of Massachusetts Medical Center, we are the worldwide, exclusive licensee under a number of U.S. issued patents and various patent applications owned by UMass Medical Center relating to antisense oligonucleotides and their production and use. Many of these patents and patent applications have corresponding applications on file or corresponding patents in other major industrial countries. The patents licensed to us by the University of Massachusetts Medical Center expire at dates ranging from 2006 to 2019. This license expires upon the expiration of the last to expire of the patents covered by the license.

Other license agreements under which we are the licensee include:

- an exclusive license agreement with Louisiana State University covering patents and patent applications jointly owned by us and Louisiana State University relating to mdm2,
- a non-exclusive license agreement with Genzyme Corporation covering patents and patent applications relating to mdm2,
- a non-exclusive license agreement with Integrated DNA Technologies, Inc., covering patents and patent applications that broadly claim chemical modifications to synthetic DNA,
- an exclusive license agreement with Dr. Yoon S. Cho-Chung covering patents and patent applications relating to Protein Kinase A,
- an exclusive license agreement with Children's Hospital Medical Center covering patents and patent applications relating to VEGF and
- a non-exclusive license agreement with VasGene Therapeutics, Inc. covering patents and patent applications relating to the use of VEGF for ophthalmic applications.

Under these licenses we are obligated to pay royalties on net sales by us of products or processes covered by a valid claim of a patent or patent application licensed to us. We also are required in some cases to pay a specified percentage of any sublicense income that we may receive. These licenses impose various commercialization, sublicensing, insurance and other obligations on us. Our failure to comply with these requirements could result in termination of the licenses. Each of these licenses terminates upon the expiration of the last to expire of the patents covered by the license.

Corporate Alliances

An important part of our business strategy is to enter into research and development collaborations, licensing agreements and other strategic alliances, primarily with biotechnology and pharmaceutical corporations, to develop and commercialize drugs based on our technologies.

Isis Pharmaceuticals, Inc.

We are a party to a collaboration and license agreement with Isis Pharmaceuticals, Inc. Under the agreement, we granted Isis a license, with the right to sublicense, to our antisense chemistry and delivery patents and patent applications. We retained the right to use these patents and patent applications in our own drug discovery and development efforts and in collaborations with third parties. In consideration of the license, in 2001 Isis paid us $15.0 million in cash and issued to us 857,143 shares of its common stock having an aggregate fair market value on the date of issuance of $17.3 million. Under the agreement, Isis is also required

to pay us a portion of specified sublicense income it receives from some types of sublicenses of our patents and patent applications. In 2003 and 2004, Isis made such payments to us in connection with sublicenses of our patents and patent applications.

In addition under the agreement, we licensed from Isis specified antisense patents and patent applications, principally Isis' suite of RNase H patents and patent applications. We have the right under the agreement to use these patents and patent applications in our drug discovery and development efforts and in some types of collaborations with third parties. In consideration of this license, in 2002 we paid Isis approximately $716,000 in cash and issued to Isis 1,005,499 shares of our common stock having an aggregate fair market value on the date of issuance of approximately $1.2 million. We also agreed to pay Isis a nominal annual maintenance fee and a modest royalty on sales of products covered by specified patents and patent applications sublicensed to us by Isis. The licenses granted under the Isis agreement terminate upon the last to expire of the patents and patent applications licensed under the agreement. We may terminate at any time the sublicense by Isis to us of the patents and patent applications for which we have maintenance fee and royalty obligations to Isis.

Other Collaborations

We are a party to nine other collaboration and license arrangements involving the use of our IMO or antisense technologies and specified indications. Some of these include:

- *VasGene Therapeutics, Inc.* On October 29, 2004, we entered into reciprocal Collaboration and License Agreements with VasGene Therapeutics, Inc. pursuant to which both parties agreed to collaborate on the research and development of VEGF antisense products. We intend to pursue the treatment of opthalmologic and other non-cancer diseases that are susceptible to treatment based on localized administration under one agreement, and VasGene intends to pursue the treatment of cancer and other non-ophthalmologic diseases that are susceptible to treatment through systemic administration under the other agreement.

  We are entitled to receive milestone payments, royalties, and sublicensing payments. Additionally, we would be entitled to reimbursement of research services we perform in accordance with the terms of the agreement at the request of VasGene. We may have to pay VasGene royalties and sublicensing payments. Likewise, VasGene would be entitled to reimbursement of research services that it performed under the agreement at our request. The milestones, if fully achieved, would result in payments to us totalling $8.0 million for each non-cancer VEGF antisense product developed by VasGene. Milestone payments would be triggered by the achievement of specific events in the development and commercial launch process.

- *Alnylam Pharmaceuticals, Inc.* On August 2, 2004, we entered into a Collaboration and License Agreement with Alnylam Pharmaceuticals, Inc. pursuant to which we granted to Alnylam an exclusive license to a series of patents and patent applications relating to the therapeutic use of oligonucleotides that inhibit the production of the protein VEGF. Under the license, Alnylam's rights are limited to targeting VEGF for ocular indications with RNAi molecules. We are entitled to receive an up-front payment, annual license fees, milestone payments, royalties and sublicensing payments from Alnylam under the terms of the agreement. The upfront payment, license fees and milestone payments payable to us under the agreement could total approximately $4.4 million, if all the milestones are achieved. Milestone payments are triggered by the achievement of specific events in the development process.

- *Aegera Therapeutics Inc.* We are a party to an agreement with Aegera Therapeutics, Inc. that relates to the development of an antisense drug targeted to the XIAP gene, a gene which has been implicated in the resistance of cancer cells to chemotherapy. In July 2003, Aegera and we announced that we had selected AEG35156/GEM640, an antisense oligonucleotide, targeted to the XIAP gene, as the development candidate. Aegera has advised us in 2003 that it has completed preclinical toxicology studies of AEG35156/GEM640 and in 2004, that it initiated a phase 1 clinical trial in the first quarter of 2004. Under the terms of the license we may receive up to approximately $7.7 million in up-front

and milestone payments upon the achievement of specified development milestones. We are also entitled to receive a royalty on net sales of any drugs that are approved for sale.

- *The Immune Response Corporation.* We are a party to an agreement with Immune Response that relates to the development of Amplivax as an adjuvant for use in combination with Immune Response's REMUNE® vaccine candidate for the prevention and treatment of HIV-1. Under the terms of the agreement, we granted Immune Response, during an exclusivity period, a worldwide license to Amplivax as an HIV vaccine adjuvant for the prevention and treatment of HIV. In order to maintain the exclusivity of the license, Immune Response must make payments to us at specified times under the agreement. We are also entitled to receive a royalty on net sales of the REMUNE vaccine combined with Amplivax if it is approved for sale.
- *Migenix Inc. (formerly Micrologix Biotechnology, Inc.)* We are a party to an agreement with Migenix that relates to the development of an antisense drug for the treatment of human papillomavirus. Origenix, a former subsidiary of ours, and the entity from which Migenix acquired the rights to the development, previously conducted a phase 1 clinical trial of this drug candidate. Under the terms of the agreement we may receive, in cash or equity, up to approximately $5.8 million in up-front and milestone payments upon the achievement of specified development milestones. We are also entitled to receive a royalty on net sales of the drug if it is approved for sale.
- *Epigenesis Pharmaceuticals, Inc.* We are a party to an agreement with Epigenesis that relates to the development of up to five antisense drugs for the treatment of respiratory disease. Under the agreement, we received an upfront payment and are entitled to receive a royalty on net sales of the drug if it is approved for sale.

Under these arrangements, we typically license to our collaborators our chemistries and delivery patents and patent applications on a non-exclusive basis, and any patents and patent applications that we have that are directed at the genes that are the subject of the arrangement on an exclusive basis. In addition, although our collaborators are responsible for the development and commercialization of the product, we typically provide specified research, development and compound optimization services to our collaborators. In consideration for the license and these services, we typically are entitled to receive license fees and are entitled to receive research payments, payments upon achievement of development milestones and royalties on product sales and sublicensing, if earned. The licenses granted under these agreements typically terminate upon the later of the last to expire of the patents licensed under the agreements or a specified number of years after the first commercial sale of products covered by the agreements. These agreements may be terminated by either party upon a material breach. Our collaborators may terminate these agreements at any time upon written notice.

Academic and Research Collaborations

We have entered into a number of collaborative research relationships with independent researchers, leading academic and research institutions and U.S. government agencies. These research relationships allow us to augment our internal research capabilities and obtain access to specialized knowledge and expertise.

In general, our collaborative research agreements require us to pay various amounts to support the research. We usually provide the synthetic DNA for the collaboration, which the collaborator then tests. If in the course of conducting research under its agreement with us a collaborator, solely or jointly with us, creates any invention, we generally have an option to negotiate an exclusive, worldwide, royalty-bearing license to the invention. Inventions developed solely by our scientists in connection with a collaborative relationship generally are owned exclusively by us. Most of these collaborative agreements are nonexclusive and can be cancelled with limited notice.

Government Regulation

The testing, manufacturing, labeling, advertising, promotion, distribution, import, export, and marketing, among other things, of drugs are extensively regulated by governmental authorities in the U.S. and other countries. In the U.S., the FDA regulates pharmaceutical products under the Federal Food, Drug, and

Cosmetic Act, or FDCA, and other laws. Both before and after approval for marketing is obtained, violations of regulatory requirements may result in various adverse consequences, including the FDA's delay in approving or refusal to approve a drug, withdrawal of approval, suspension or withdrawal of an approved product from the market, operating restrictions, warning letters, product recalls, product seizures, injunctions, fines, and the imposition of civil or criminal penalties.

The steps required before a product may be approved for marketing in the U.S. generally include:

- preclinical laboratory tests and animal tests under the FDA's good laboratory practices regulations;
- the submission to the FDA of an investigational new drug application, or IND, for human clinical testing, which must become effective before human clinical trials may begin;
- adequate and well-controlled human clinical trials to establish the safety and efficacy of the product for each indication;
- satisfactory completion of an FDA inspection of the manufacturing facility or facilities at which the product is made to assess compliance with the FDA's current good manufacturing practices regulations, or cGMP; and
- the submission to the FDA of a new drug application, or NDA.

Preclinical tests include laboratory evaluation of the product, as well as animal studies to assess the potential safety and efficacy of a drug. The results of the preclinical tests, together with manufacturing information and analytical data, are submitted to the FDA as part of an IND, which must become effective before human clinical trials may be commenced. The IND will automatically become effective 30 days after its receipt by the FDA, unlessthe FDA before that time raises concerns or questions about the conduct of the trials as outlined in the IND. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before clinical trials can proceed. If these issues are unresolved, the FDA may not allow the clinical trials to commence. There is no guarantee that submission of an IND will result in the FDA allowing clinical trials to begin.

Clinical trials typically are conducted in three sequential phases, but the phases may overlap or be combined. Clinical trials are conducted under protocols detailing the objectives of the trials, the parameters to be used in monitory safety and the effectiveness criteria to be evaluated. Each protocol must be submitted to the FDA as part of the IND prior to beginning the trial. Each trial must be reviewed and approved by an independent Institutional Research Board before it can begin. Subjects must provide informed consent for all trials.

- In phase 1, the initial introduction of the drug into human subjects, the drug is usually tested for safety or adverse effects, dosage tolerance, and pharmacologic action;
- Phase 2 usually involves controlled trials in a limited patient population to:
  - evaluate preliminarily the efficacy of the drug for specific, targeted conditions,
  - determine dosage tolerance and appropriate dosage, and
  - identify possible adverse effects and safety risks; and
- Phase 3 trials generally further evaluate clinical efficacy and test further for safety within an expanded patient population.

Phase 1, 2, and 3 testing may not be completed successfully within any specified period, or at all. We, an Institutional Review Board, or the FDA, may suspend or terminate clinical trials at any time on various grounds, including a finding that the patients are being exposed to an unacceptable health risk.

The results of the preclinical and clinical studies, together with other detailed information, including information on the manufacture and composition of the product, are submitted to the FDA as part of an NDA for approval prior to the marketing and commercial shipment of the product. In most cases, the NDA must be accompanied by a substantial user fee. The FDA also will inspect the manufacturing facility used to produce

the product for compliance with cGMPs. The FDA may deny a new drug application if all applicable regulatory criteria are not satisfied or may require additional clinical, toxicology or manufacturing data. Even after an NDA results in approval to market a product, the FDA may limit the indications or place other limitations that restrict the commercial application of the product. After approval, some types of changes to the approved product, such as adding new indications, manufacturing changes and additional labeling claims, are subject to further FDA review and approval. The FDA may withdraw product approval if compliance with regulatory standards is not maintained or if safety problems occur after the product reaches the market. In addition, the FDA requires surveillance programs to monitor the consistency of manufacturing and the safety of approved products that have been commercialized. Holders of an approved NDA are required to report certain adverse reactions and production problems to the FDA to provide updated safety and efficacy information and to comply with requirements concerning advertising and promotional labeling. The agency has the power to require changes in labeling or to prevent further marketing of a product based on new data that may arise after commercialization. Also, new federal, state, or local government requirements may be established that could delay or prevent regulatory approval of our products under development.

We will also be subject to a variety of foreign regulations governing clinical trials and sales of our products. Whether or not FDA approval has been obtained, approval of a product by the comparable regulatory authorities of foreign countries must be obtained prior to the commencement of marketing of the product in those countries. The approval process varies from country to country and the time may be longer or shorter than that required for FDA approval. For marketing outside the U.S., we are also subject to foreign regulatory requirements governing human clinical trials. The requirements governing the conduct of clinical trials, product licensing, approval, pricing, and reimbursement vary greatly from country to country.

In addition to regulations enforced by the FDA, we are also subject to regulation under the Occupational Safety and Health Act, the Toxic Substances Control Act, the Resource Conservation and Recovery Act, and other present and potential future federal, state, or local regulations. Our research and development activities involve the controlled use of hazardous materials, chemicals and various radioactive compounds. Although we believe that our safety procedures for handling and disposing of such materials comply with the standards prescribed by state and federal regulations, the risk of accidental contamination or injury from these materials cannot be completely eliminated. In the event of such an accident, we could be held liable for any damages that result and any such liability could exceed our resources.

Manufacturing

We were a party to a supply agreement with Avecia Biotechnology, which was formally known as Boston Biosystems Inc., under which we purchased our requirements for oligonucleotide compounds from Avecia at a preferential price, which expired in March 2004. We have continued to purchase all of the oligonucleotides we are using in our ongoing clinical trials and pre-clinical testing from Avecia. The terms of the agreement have been extended until such time as a new agreement is negotiated. We expect that we will enter into a longer term arrangement with Avecia or new arrangements with other third-party manufacturers to supply us with the oligonucleotide compounds that we need for our research, preclinical, clinical and if we receive approval of a product, commercial supply purposes.

Competition

We expect that our product candidates will address several different markets defined by the potential indications for which these product candidates are developed and ultimately approved by regulatory authorities. For several of these indications, these product candidates will be competing with products and therapies either currently existing or expected to be developed, including IMO-like compounds and antisense oligonucleotides developed by third parties. Many of these existing products and therapies are marketed by large pharmaceutical companies, have recognized brand names and are widely accepted by physicians and patients.

Competition among these products and therapies will be based, among other things, on product efficacy, safety, reliability, availability, price, and patent position.

The timing of market introduction of our products and competitive products will also affect competition among products. We also expect the relative speed with which we can develop products, complete the clinical trials and approval processes and supply commercial quantities of the products to the market to be an important competitive factor. Our competitive position will also depend upon our ability to attract and retain qualified personnel, to obtain patent protection or otherwise develop proprietary products or processes and to secure sufficient capital resources for the often substantial period between technological conception and commercial sales.

There are a number of companies, both privately and publicly held, that are conducting research and development, preclinical and clinical and commercial activities relating to technologies and products that are similar to our technologies and products, including large pharmaceutical companies with programs in CpG DNA compounds that have a similar mechanism of action to our IMO compounds or in antisense technology and biotechnology companies with similar programs. Our principal competitors include Isis Pharmaceuticals, Inc., Genta Inc., Coley Pharmaceutical Group and Dynavax Technologies Corp.

The primary indications for which we are developing our antisense and IMO products are cancer and infectious diseases. None of our competitors is currently marketing any antisense or IMO-like product for cancer or infectious diseases, except for Isis which is currently marketing an antisense product for the treatment of cytomegalovirus retinitis in patients with AIDS. However, our competitors are developing a number of product candidates for cancer and infectious diseases that are currently in clinical trials.

- Isis has seven antisense compounds presently in clinical trials.
- Genta is in late-stage clinical trials for an oligonucleotide compound for the treatment of various cancers.
- Dynavax has a CpG DNA compound in clinical trials for four indications. These indications include the treatment of cancer, asthma/allergy and infectious disease.
- Coley has two CpG DNA compounds in clinical trials for three indications. These indications include treatment of cancer, asthma/allergy and infectious disease.

Many of our competitors, particularly the pharmaceutical and biotechnology companies with which we compete, have substantially greater financial, technical and human resources than we have. In addition, many of our competitors have significantly greater experience than we have in undertaking preclinical studies and human clinical trials of new pharmaceutical products, obtaining FDA and other regulatory approvals of products for use in health care and manufacturing, marketing and selling approved products.

Employees

As of March 1, 2005, we employed 24 individuals full-time, including 17 employees in research and development. Ten of our employees hold a doctoral degree. None of our employees are covered by a collective bargaining agreement, and we consider relations with our employees to be good.

Information Available on the Internet

Our internet address is www.hybridon.com. We make available free of charge through our web site our Annual Reports on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to these reports filed or furnished pursuant to Section 12(a) or 15(d) of the Securities Exchange Act of 1934, as amended, as soon as reasonably practicable after we electronically file or furnish such materials to the Securities and Exchange Commission.

Item 2. ***Properties***

We lease approximately 26,000 square feet of laboratory and office space, including 6,000 square feet of specialized preclinical lab space, in Cambridge, Massachusetts under a lease that expires April 30, 2007. We believe these facilities are adequate to accommodate our needs for the near term.

Item 3. ***Legal Proceedings***

None.

Item 4. ***Submission of Matters to a Vote of Security Holders***

None.

Executive Officers and Key Employees of Hybridon

The following table sets forth the names, ages and positions of our executive officers and other key employees as of March 1, 2005:

Name	Age	Position
Sudhir Agrawal, D. Phil	51	President, Chief Executive Officer, Chief Scientific Officer and Director
Robert G. Andersen	54	Chief Financial Officer, Vice President of Operations, Treasurer and Secretary
Naveen N. Anand, Ph.D., MBA.....	44	Vice President of Corporate and Business Development
Timothy M. Sullivan, Ph.D.	50	Vice President of Development Programs
Jinyan Tang, Ph.D.	61	Vice President of Chemistry

Dr. Sudhir Agrawal joined us in 1990 and has served as our Chief Scientific Officer since January 1993, our Senior Vice President of Discovery since March 1994, our President since February 2000, a director since March 1993 and our Chief Executive Officer since August 2004. Prior to his appointment as Chief Scientific Officer, he served as our Principal Research Scientist from February 1990 to January 1993 and as our Vice President of Discovery from December 1991 to January 1993. He served as Acting Chief Executive Officer from February 2000 until September 2001. Prior to joining us, Dr. Agrawal served as a Foundation Scholar at the Worcester Foundation from 1987 through 1991. Dr. Agrawal served as a Research Associate at the Medical Research Council's Laboratory of Molecular Biology in Cambridge, England from 1985 to 1986, studying DNA chemistry and synthetic oligonucleotides. Dr. Agrawal received a D. Phil. in chemistry in 1980, an M.Sc. in organic chemistry in 1975 and a B.Sc. in chemistry, botany and zoology in 1973 from Allahaban University in India. Dr. Agrawal is one of the most published researchers in the field of antisense technology. He has authored more than 260 research papers and reviews and has edited three books. He is a member of the editorial board of Antisense Research & Development Journal, Trends in Molecular Medicine, Investigational Drug Journal, and Current Cancer Drug Targets, and is associate editor of Molecular Biotechnology. Dr. Agrawal is the co-author of more than 230 patents worldwide.

Robert G. Andersen joined us in November 1996 as Vice President of Systems Engineering and Management Information Systems and has served as our Vice President of Operations and Planning since 1997, our Treasurer since March 1998 and our Chief Financial Officer since February 2000. Prior to joining us, Mr. Andersen held a variety of management positions at Digital Equipment Corporation from 1986 to 1996, most recently as Group Manager of the Applied Objects Business Unit. From 1978 to 1986, Mr. Andersen held technical management positions at United Technologies Corporation, most recently as Director of Quality for Otis Elevator Company's European Operations based in Paris, France and Worldwide Director of Controls for Otis Group. Mr. Andersen received an M.S. in Management from Northeastern University in 1978 and his B.E.E. magna cum laude in Electrical Engineering from The City College of New York in 1972. He is also a graduate of the United Technologies Advanced Studies Program.

Dr. Naveen Anand joined us in December 2004 as Vice President of Corporate and Business Development after serving as a consultant to us from September 2004 to December 2004. From 2002 to 2004, Dr. Anand served as Vice President, Business Development at Shire Biologics in Montréal, Canada, and from 1999 to 2002 he held the position of Vice President, Business Development and Licensing, at Procyon Biopharma, a Canadian biotechnology company. Dr. Anand served as Manager, New Products and New Markets Development at Aventis Pasteur in Toronto, Canada (now part of Sanofi Aventis) from 1991 to

1999. Dr. Anand received his B.S and Masters in Pharmaceutical Sciences from Panjab University in Chandigarh, India; his Ph.D. from the University of Cambridge in the U.K.; and his MBA from the University of Toronto.

Dr. Timothy Sullivan joined us in 2002 as Senior Director, Preclinical Drug Development. His prior professional experience includes positions as Executive Director of Non-clinical Drug Safety Evaluation for Purdue Pharma L.P. from 1999 to 2002 and Vice President of Eastern Operations for Oread, Inc., a contract drug development organization, from 1997 to 1999. Prior to 1997, Mr. Sullivan held a variety of technical management roles with other pharmaceutical companies and contract research organizations (Adria, Battelle, Roma Toxicology Centre), and in veterinary medicine (International Minerals & Chemical). Dr. Sullivan brings broad expertise in the design, execution, and application of drug development programs. Dr. Sullivan earned his B.S. in Microbiology from Michigan State University in 1975. His graduate studies were at Purdue University, where he earned a M.S. degree in Health Physics in 1978 and a Ph.D. in Toxicology in 1981.

Dr. Jinyan Tang joined us in 1991 and has served as our Vice President of Chemistry since 2000. Dr. Tang was our Vice President of Process Research and Development from 1995 to 1997 and Vice President of Production from 1997 to 2000. Prior to joining us, Dr. Tang served as Visiting Fellow at the Worcester Foundation from 1988 to 1991. Dr. Tang served as Visiting Research Professor at the University of Colorado in 1988 and Associate Professor at the Shanghai Institute of Biochemistry, Chinese Academy of Sciences from 1985 to 1988 where he specialized in oligonucleotide chemistry. Dr. Tang received a B.Sc. in Biochemistry in 1965 and a Ph.D. of Biochemistry in 1978 from the Shanghai Institute of Biochemistry, Chinese Academy of Sciences.

PART II.

Item 5. ***Market For Registrant's Common Equity, Related Stockholder Matters and Issuer Purchases of Equity Securities***

Market Information

Our common stock has been listed on the American Stock Exchange under the symbol "HBY" since December 5, 2003. Prior to December 5, 2003, our common stock was quoted on the OTC Bulletin Board under the symbol "HYBN". Quotes on the OTC Bulletin Board may have reflected inter-dealer prices without retail markups, markdowns or commissions and may not necessarily have represented actual transactions.

The following table sets forth, for the periods indicated, the high and low sales prices per share of our common stock during each of the quarters set forth below as reported on the OTC Bulletin Board for the periods from January 1, 2003 through December 4, 2003 and on the American Stock Exchange from December 5, 2003 through December 31, 2004:

	High	Low
2004		
First Quarter	$1.51	$0.92
Second Quarter	1.10	0.51
Third Quarter	0.69	0.36
Fourth Quarter	0.68	0.40
2003		
First Quarter	$1.01	$0.65
Second Quarter	1.11	0.70
Third Quarter	1.81	0.78
Fourth Quarter	1.65	0.95

The number of common stockholders of record on March 1, 2005 was 460.

We have never declared or paid cash dividends on our common stock, and we do not expect to pay any cash dividends on our common stock in the foreseeable future.

Since December 4, 2003, our series A convertible preferred stock has paid dividends at 1.0% per year, payable semi-annually in arrears. Prior to December 4, 2003, our series A convertible preferred stock paid dividends at 6.5% per year payable semi-annually in arrears. We may pay these dividends either in cash or in additional shares of series A convertible preferred stock, at our discretion, subject to the restriction under the indenture described above.

Sales of Unregistered Securities

There were no sales of unregistered securities during the fourth quarter of 2004.

Item 6. *Selected Financial Data*

The following selected financial data are derived from the consolidated financial statements of Hybridon, Inc. The data should be read in conjunction with the consolidated financial statements, related notes, and other financial information included herein.

	Year Ended December 31,				
	2004	2003	2002	2001	2000
	(In thousands, except per share data)				
Statement of Operations Data:					
Alliance revenue(1)	$ 942	$ 897	$ 29,606	$ 1,122	$ 344
Operating expenses:					
Research and development	10,305	10,817	7,877	4,868	3,620
General and administrative	4,273	6,924	7,054	5,051	3,184
Stock-based compensation from repriced options	(713)	543	(1,297)	1,762	—
Total operating expenses	13,865	18,284	13,634	11,681	6,804
(Loss) income from operations	(12,923)	(17,387)	15,972	(10,559)	(6,460)
Other income (expense):					
Investment income, net	217	190	650	577	229
Interest expense	(29)	(118)	(150)	(1,319)	(2,154)
Loss on conversion of 8% convertible subordinated notes payable	—	—	—	(1,412)	—
Gain on sale of securities, net	—	104	—	5,217	—
(Loss) income from continuing operations	(12,735)	(17,211)	16,472	(7,496)	(8,385)
Income from discontinued operations(2)	—	—	—	2,663	5,462
(Loss) income before income taxes	(12,735)	(17,211)	16,472	(4,833)	(2,923)
Income tax benefit (provision)	—	—	500	(500)	—
Net (loss) income	(12,735)	(17,211)	16,972	(5,333)	(2,923)
Accretion of preferred stock dividend	(2,676)	(5,529)	(4,246)	(8,342)	(4,087)
Net (loss) income applicable to common stockholders	$ (15,411)	$ (22,740)	$ 12,726	$ (13,675)	$ (7,010)
Basic net (loss) income per common share from:					
Continuing operations	$ (0.13)	$ (0.34)	$ 0.36	$ (0.26)	$ (0.48)
Discontinued operations	—	—	—	0.09	0.31
Net (loss) income per share	(0.13)	(0.34)	0.36	(0.17)	(0.17)
Accretion of preferred stock dividends	(0.03)	(0.11)	(0.09)	(0.27)	(0.23)
Net (loss) income per share applicable to common stockholders	$ (0.16)	$ (0.45)	$ 0.27	$ (0.44)	$ (0.40)
Diluted net (loss) income per common share from:					
Continuing operations	$ (0.13)	$ (0.34)	$ 0.32	$ (0.26)	$ (0.48)
Discontinued operations	—	—	—	0.09	0.31
Net (loss) income per share	(0.13)	(0.34)	0.32	(0.17)	(0.17)
Accretion of preferred stock dividends	(0.03)	(0.11)	(0.08)	(0.27)	(0.23)
Net (loss) income per share applicable to common stockholders	$ (0.16)	$ (0.45)	$ 0.24	$ (0.44)	$ (0.40)
Shares used in computing basic net (loss) income per common share(3)	98,914	51,053	46,879	30,820	17,418
Shares used in computing diluted net (loss) income per common share(3)	98,914	51,053	52,984	30,820	17,418
Balance Sheet Data:					
Cash, cash equivalents and short-term investments	$ 14,413	$ 13,668	$ 19,175	$ 31,834	$ 3,532
Working capital (deficit)	13,181	10,740	17,638	27,259	(4,238)
Total assets	15,391	14,410	21,249	32,309	10,001
Restricted cash	—	—	—	—	5,000
Capital lease obligations, current portion	—	—	34	—	—
9% convertible subordinated notes payable	—	1,306	1,306	1,306	1,306
8% convertible subordinated notes payable	—	—	—	288	8,046
Series A convertible preferred stock	—	5	7	6	6
Accumulated deficit	(299,294)	(283,883)	(261,143)	(273,868)	(260,193)
Total stockholders' equity (deficit)	12,769	10,526	17,444	(33)	(7,530)

(1) See Note 6(f) of notes to consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K for information on the alliance revenue recognized during 2002.

(2) Consolidated financial statements reflect the financial results of our Hybridon Specialty Products Division as a discontinued operation for the years ended December 31, 2001 and 2000. Reported revenues, expenses and cash flows exclude the operating results of discontinued operations.

(3) Computed on the basis described in Note 11 of notes to consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K.

Quarterly Operating Results (Unaudited)

The following table presents the unaudited statement of operations data for each of the eight quarters in the period ended December 31, 2004. The information for each of these quarters is unaudited, but has been prepared on the same basis as the audited financial statements appearing elsewhere in this Annual Report on Form 10-K. In our opinion, all necessary adjustments, consisting only of normal recurring adjustments, have been made to present fairly the unaudited quarterly results when read in conjunction with the audited financial statements and the notes thereto appearing elsewhere in this document. These operating results are not necessarily indicative of the results of operations that may be expected for any future period.

	Three Months Ended							
	Dec. 31 2004	Sep. 30 2004	Jun. 30 2004	Mar. 31 2004	Dec. 31 2003	Sep. 30 2003	Jun. 30 2003	Mar. 31 2003
	(In thousands, except per share data)							
Statement of Operations Data:								
Alliance revenues	$ 131	$ 78	$ 88	$ 645	$ 108	$ 334	$ 120	$ 335
Operating expenses:								
Research and development	2,349	2,610	2,541	2,805	2,986	2,567	2,858	2,406
General and administrative	801	1,550	1,025	897	1,475	943	1,282	3,224
Stock-based compensation from repriced options	(121)	(18)	(257)	(317)	(98)	506	129	6
Total operating expenses	3,029	4,142	3,309	3,385	4,363	4,016	4,269	5,636
Loss from operations	(2,898)	(4,064)	(3,221)	(2,740)	(4,255)	(3,682)	(4,149)	(5,301)
Investment income	74	57	50	36	43	28	36	82
Interest expense	—	—	—	(29)	(29)	(29)	(29)	(29)
Gain on sale of securities, net	—	—	—	—	—	—	104	—
Net loss	(2,824)	(4,007)	(3,171)	(2,733)	(4,241)	(3,683)	(4,038)	(5,248)
Accretion of preferred stock dividend	—	—	—	(2,676)	(2,127)	(1,138)	(1,194)	(1,071)
Net loss applicable to common stockholders	$ (2,824)	$ (4,007)	$(3,171)	$(5,409)	$(6,368)	$(4,821)	$(5,232)	$(6,319)
Basic and diluted net loss per share applicable to common stockholders	$ (0.03)	$ (0.04)	$ (0.03)	$ (0.07)	$ (0.10)	$ (0.10)	$ (0.12)	$ (0.14)
Shares used in computing basic and diluted loss per common share(1)	110,911	105,301	98,269	80,972	64,119	50,704	43,485	45,700

(1) Computed on the basis described in Note 11 of notes to consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K.

Item 7. ***Management's Discussion and Analysis of Financial Condition and Results of Operations***

We are engaged in the discovery, development and commercialization of novel therapeutics based on synthetic DNA for the treatment of cancer, asthma/allergies and infectious diseases. Our activities are primarily focused on the development of our immunomodulatory oligonucleotide, or IMO, technology. Our IMO compounds are synthetic DNA-based sequences that are designed to mimic bacterial DNA and be recognized by a specific protein receptor called Toll-like Receptor 9, or TLR9, which triggers the activation and modulation of the immune system. We also have been a pioneer in the development of antisense technology, which uses synthetic DNA to block the production of disease causing proteins at the cellular level. In 2003 and 2004, we devoted substantially all of our research and development efforts to our IMO technology and products and expect to continue to focus our research and development efforts in 2005 and in future years on our IMO technology and products. We plan to continue to seek to enter into collaborations with third parties for the development and commercialization of products based on our antisense technology.

Since we began operations in February 1990, we have been involved primarily in research and development and manufacturing. To date, almost all of our revenues have been from collaborative and license agreements. In addition, we generated revenues from the sale of synthetic DNA and reagent products manufactured by our Hybridon Specialty Products Division, or HSP, prior to our selling HSP in September 2000. The sale of HSP together with the sale of our interest in Methylgene, our first spin-off company, and net proceeds from our Collaboration and License Agreement with Isis Pharmaceuticals, Inc. generated approximately $52.5 million.

We have incurred total losses of $299.3 million through December 31, 2004 and expect to incur substantial operating losses in the future. In order to commercialize our therapeutic products, we need to address a number of technological challenges and to comply with comprehensive regulatory requirements. In 2005, we expect that our research and development expenses will be similar to those in 2004 as we continue to advance IMOxine through clinical development.

Critical Accounting Policies

This management's discussion and analysis of financial condition and results of operations is based on our consolidated financial statements, which have been prepared in accordance with accounting principles generally accepted in the United States. The preparation of these financial statements requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and the disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period. On an ongoing basis, management evaluates its estimates and judgments, including those related to revenue recognition. Management bases its estimates and judgments on historical experience and on various other factors that are believed to be reasonable under the circumstances, the results of which form the basis for making judgments about the carrying values of assets and liabilities that are not readily apparent from other sources. Actual results may differ from these estimates under different assumptions or conditions.

While our significant accounting policies are more fully described in Note 2 of the notes to our consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K, we believe the most critical accounting policy affecting the portrayal of our financial condition is revenue recognition.

Revenue Recognition

We recognize revenue in accordance with SEC Staff Accounting Bulletin No. 104, or SAB 104. SAB 104 requires that four basic criteria be met before revenue can be recognized:

- persuasive evidence of an arrangement exists;
- delivery has occurred, services have been rendered or obligations have been satisfied;

- the fee is fixed or determinable; and
- collectibility is reasonably assured.

Determination of the last three criteria are based on management's judgments regarding the fixed nature of the fee charged for services rendered or products delivered and the collectibility of these fees. Should changes in conditions cause management to determine these criteria are not met for any future transactions, revenues recognized for any reporting period could be adversely affected.

During 2001, we received a total of $32.3 million in cash and stock under our collaboration and license agreement with Isis. This amount and future amounts due under this license agreement are non-refundable. Prior to amending the agreement in August 2002, we recognized the revenue from Isis on a straight-line basis over the 10-year term of the agreement. Our decision to recognize Isis revenue over the term of the Isis agreement was based primarily on a continuing obligation contained in the license agreement which we had interpreted as neither inconsequential nor perfunctory according to SAB 101, *"Revenue Recognition in Financial Statements"*. In 2002, the agreement was amended. The amendment limited each party's obligation to participate in collaboration committee meetings and terminated the obligations of each party to pay the remaining installment payments due from each party under the agreement. Based on this amendment, we determined that our obligations under the agreement were inconsequential and perfunctory according to SAB 101 and as such did not preclude recognition of revenue. For this reason, in the third quarter of 2002, we recognized the revenue and directly related and incremental expenses that we had previously deferred.

Results of Operations

Years ended December 31, 2004, 2003 and 2002

Revenues

Total revenues remained fairly constant at $0.9 million for both 2003 and 2004. Total revenues decreased by $28.7 million from $29.6 million in 2002 to $0.9 million in 2003. Our revenues for 2003 and 2004 were comprised of payments under various collaboration and licensing agreements for research and development, including reimbursement of third party expenses, and as milestone payments, license fees, sublicense fees, and royalty payments. The significant difference in revenues between 2003 and 2002 was primarily due to our recognition in the third quarter of 2002 of $27.9 million of deferred revenue as a result of the August 2002 amendment to the license agreement with Isis.

Research and Development Expenses

Research and development expenses decreased by approximately $0.5 million, or 5%, from $10.8 million in 2003 to $10.3 million in 2004 and increased by approximately $2.9 million, or 37%, from $7.9 million in 2002 to $10.8 million in 2003. The decrease in 2004 was primarily attributable to a decrease in spending on antisense technology as we completed enrollment in our GEM231 phase 1/2 clinical trial and lower salary expenses due to a decrease in bonuses and other compensation savings resulting from the retirement of one of our officers. These decreases were partially offset by an increase in our HYB2055 costs in 2004 reflecting additional manufacturing costs we incurred to acquire additional supply of HYB2055. The increase in 2003 was primarily attributable to the ramp up of our immune modulatory development efforts, including the initiation in 2003 of clinical trials of IMOxine, increased costs associated with the clinical trials of GEM231 and increased costs relating to the filing of patents related to new discoveries, offset by a reduction in manufacturing costs associated with our antisense program.

Our current research and development efforts relate primarily to HYB2055. We have reduced our focus on antisense technology significantly, including the development of GEM231. We plan to continue to seek to enter into collaborations with third parties for the development and commercialization of products based on our antisense technology.

- In 2004, 2003 and 2002, we incurred approximately $2.5, $2.3 and $1.8 million, respectively, in direct expenses in connection with developing HYB2055. These expenses included payments to independent

contractors and vendors for preclinical studies, drug manufacturing and related costs and an allocation for patent preparation costs and related filing fees but exclude internal costs such as payroll and overhead. In October 2004, we commenced patient recruitment for an open label, multi-center phase 2 clinical trial of IMOxine as a monotherapy in patients with metastatic or recurrent clear cell renal carcinoma. We plan to recruit a minimum of 46 patients into the first stage of the trial. We are also conducting a phase 1 clinical trial of IMOxine in patients with refractory solid tumor cancers, which is being conducted at the Lombardi Comprehensive Cancer Center at Georgetown University Medical Center in Washington, D.C. Patient enrollment for this phase 1 oncology trial is complete. In May 2004, we also completed a phase 1 study of HYB2055 in healthy volunteers in the UK. Because the development of HYB2055 is in the early stage and given the technological and regulatory hurdles likely to be encountered in the development and commercialization of HYB2055, the future timing and costs of this research and development program is uncertain.

- In 2004, 2003 and 2002, we incurred approximately $0.3, $0.6 and $1.2 million, respectively, in direct expenses in connection with developing GEM231. These direct expenses included payments to independent contractors and vendors for clinical studies, patent preparation costs and related filing fees and drug manufacturing and related costs but exclude internal costs such as payroll and overhead. The decrease from 2003 to 2004 reflected a decreasing patient enrollment rate as the trial moved toward completion. The decrease from 2002 to 2003 reflects the manufacturing costs we incurred in 2002 to acquire a supply of GEM231 for use in our clinical trials in 2002, 2003 and 2004. We completed enrollment of a phase 1/2 clinical trial of GEM231 as a combination therapy with irinotecan, an anticancer drug marketed in the Untied States under the name Camptosar. The decrease from 2003 to 2004 reflects the reduction in clinical trial expenses as the phase 1/2 trial of GEM231 moved to completion. We do not expect to incur significant expenses in 2005 in connection with the development of GEM231, because we do not intend to continue further development of GEM231 without having a collaboration agreement in place.

General and Administrative Expenses

General and administrative expenses decreased by approximately $2.6 million, or 38%, from $6.9 million in 2003 to $4.3 million in 2004 and decreased by approximately $0.1 million, or 2%, from $7.0 million in 2002 to $6.9 million in 2003. General and administrative expenses consisted primarily of salary expense, consulting fees and professional legal fees associated with our regulatory filing requirements and business development. These costs were generally consistent from period to period. The $2.6 million decrease in 2004 primarily reflects the one-time expense for the $1.9 million premium paid in repurchasing shares of our common stock in 2003 and other consulting and professional fees related to the repurchase of our common stock in 2003. The 2004 decrease also reflects a decrease in legal expenses due mainly to decreased expenses incurred in connection with the patent interference proceeding conducted in 2003. These decreases were partially offset by a $0.7 million charge relating to the resignation of our former Chief Executive Officer in 2004.

The difference between 2003 and 2002 expenses primarily reflects our recognition in 2002 of $2.1 million of deferred expenses as a result of the August 2002 amendment to the license agreement with Isis. No direct expenses associated with our agreement with Isis were included in general and administrative expense in 2004 or 2003. The impact of recognizing deferred expenses from Isis in 2002 was offset by a one-time expense in 2003 of $1.9 million representing the premium over fair market value that we paid in repurchasing shares of our common stock in the first quarter of 2003 and by other consulting and professional fees related to the repurchase of our common stock.

Stock-Based Compensation

As a result of our repricing of stock options in September 1999, some of our outstanding stock options are subject to variable plan accounting which requires us to measure the intrinsic value of the repriced options through the earlier of the date of exercise, cancellation or expiration at each reporting date. We recorded a

credit to operating results of approximately $0.7 million in 2004 as a result of a decrease in the intrinsic value of these options. In 2003, we incurred stock-based compensation expense of $0.5 million in operating results, which resulted from an increase in the intrinsic value of these options. We recorded a credit to operating results of approximately $1.3 million in 2002 as a result of a decrease in the intrinsic value of these options. We expect that compensation charges and credits may occur in the future based upon changes in the intrinsic value of our repriced stock options and upon pending adoption of SFAS No. 123 (revised 2004), *"Share-Based Payment"*, which is a revision of SFAS No. 123, *"Accounting for Stock-Based Compensation"*. SFAS No. 123(R) supersedes APB Opinion No. 25, *"Accounting for Stock Issued to Employees"*, and amends SFAS No. 95, *"Statement of Cash Flows"*.

Investment Income, net

Investment income remained relatively constant at approximately $190,000 in 2003 and $217,000 in 2004 and decreased by approximately $460,000 from $650,000 in 2002 to $190,000 in 2003. The decrease from 2002 to 2003 is primarily attributable to lower interest income as a result of lower cash and investment balances in 2003.

Interest Expense

Interest expense decreased by approximately $89,000 from $118,000 in 2003 to $29,000 in 2004 and decreased by $32,000 from $150,000 in 2002 to $118,000 in 2003. The decrease from 2003 to 2004 was due to the maturity of our 9% notes on April 1, 2004. Upon the maturity of these notes, we paid $1.3 million, representing the outstanding principal amount of our 9% notes, plus accrued interest. The decrease from 2002 to 2003 was attributable to the maturity of our 8% notes in November 2002.

Gain on Sale of Securities, net

The $104,000 gain on sale of the securities in 2003 represents the gain on the sale of shares of Migenix common stock that we received as payment under our agreement with Migenix. There were no gains on sales of securities during 2004 and 2002.

Income Tax Credit (Expense)

In 2002, we recognized a $0.5 million tax credit to operations that represented a reversal of the income tax expense recorded in 2001 as a result of income subject to the Alternative Minimum Tax or AMT. In March 2002, the National Economic Stabilization and Recovery Act temporarily rescinded the AMT as it applies to us. As a result, we received a $450,000 refund and recognized a $0.5 million credit to operations during 2002.

Preferred Stock Dividends

On December 4, 2003, shareholders approved amendments to our Certificate of Incorporation that:

- reduced the liquidation preference of our series A convertible preferred stock from $100 per share to $1 per share;
- reduced the annual dividend on our series A convertible preferred stock from 6.5% to 1%; and
- increased the number of shares of our common stock issuable upon conversion of our series A convertible preferred stock by 25% over the number of shares that would otherwise be issuable. This special conversion extended for a 60-day period between December 4, 2003 and February 2, 2004 inclusive.

During the 60-day conversion period, the conversion ratio was increased such that the series A convertible preferred shareholders received approximately 29.41 shares of common stock for each preferred share converted instead of the 23.53 shares that they would normally have received. During the conversion period holders of 99.9% of the series A convertible preferred stock converted their preferred stock to common stock.

The preferred stock dividends for each of the three years ended December 31, 2004 were as follows:

	Preferred Stock Dividends		
	2004	2003	2002
Accretion of dividends expected to be paid on Series A Preferred Stock	$ 503	$3,402,856	$4,246,282
Accretion of dividend that would have been paid on April 1, 2004 and reversal since preferred shares were converted in January and February 2004	(570,000)	570,000	—
Market value of 25% additional shares issued upon conversion	3,245,492	1,556,000	—
Total preferred stock dividend	$2,675,995	$5,528,856	$4,246,282

As shown above, the value of the 25% additional shares issued during the special preferred stock conversion periods is recorded as an addition to dividends in the statement of operations during 2004 of $3.2 million and during 2003 of $1.6 million. As a result of the amendment to our Certificate of Incorporation and the series A convertible preferred stock conversions, the preferred stock liquidation preference was reduced from $73.1 million at December 3, 2003 to $0.5 million at December 31, 2003 and $655 at December 31, 2004.

All preferred stock dividends are payable, at our election, either in cash or shares of series A convertible preferred stock.

Net Operating Loss Carryforwards

As of December 31, 2004, we had cumulative net operating losses of approximately $254.9 million and tax credit carryforwards of approximately $4.6 million. The Tax Reform Act of 1986 contains provisions that may limit our ability to utilize net operating loss and tax credit carryforwards in any given year if certain events occur, including cumulative changes in ownership interests in excess of 50% over a three-year period. We have completed several financings since the effective date of the Tax Act, which, as of December 31, 2004, have resulted in ownership changes, as defined under the Tax Act, which will limit our ability to utilize all of our available net operating loss and tax credit carryforwards in the future. The Company has not prepared an analysis to determine the effect of the ownership change limitation on its ability to utilize its net operating losses and tax credit carryforwards.

Liquidity and Capital Resources

Sources of Liquidity

We require cash to fund our operating expenses, to make capital expenditures and to pay debt service. Historically, we have funded our cash requirements primarily through the following:

- equity and debt financing;
- license fees and research funding under collaborative and license agreements;
- interest income; and
- lease financings.

We have also funded our cash requirements through the following:

- manufacturing of synthetic DNA and reagent products within HSP prior to its sale in 2000;
- the sale of HSP for which we received a total of $15.0 million in 2000 and 2001; and
- the sale of our shareholding in MethylGene Inc. for which we received net proceeds of $6.9 million in 2001.

In August 2004, we raised approximately $5.1 million in gross proceeds from a private placement to institutional and overseas investors. In the private placement, we sold 8,823,400 shares of common stock and warrants to purchase 1,764,680 shares of common stock. The warrants to purchase common stock have an exercise price of $0.67 per share and will expire if not exercised on or prior to August 27, 2009. The warrants may be exercised by cash payment only. On or after February 27, 2005, we may redeem the warrants if the closing sales price of the common stock for each day of any 20 consecutive trading day period is greater than or equal to $1.34 per share. The redemption price will be $0.01 per share of common stock underlying the warrants. We may exercise our right to redeem the warrants by providing 30 days prior written notice to the holders of the warrants. The net proceeds to us from the offering, excluding the proceeds of any future exercise of the warrants, totaled approximately $4.7 million.

In April 2004, we raised approximately $11.8 million in gross proceeds through a registered direct offering. In the offering, we sold 16,899,800 shares of common stock and warrants to purchase 3,041,964 shares of common stock to institutional and other investors. The warrants to purchase common stock have an exercise price of $1.14 per share and are exercisable at any time on or after October 21, 2004 and on or prior to April 20, 2009. The warrants may be exercised by cash payment only. On or after October 21, 2005, we may redeem the warrants if the closing sales price of the common stock for each day of any 20 consecutive trading day period ending within 30 days prior to providing notice of redemption is greater than or equal to $2.60 per share. The redemption price will be $0.01 per share of common stock underlying the warrants. We may exercise our right to redeem the warrants by providing 30 days prior written notice to the holders of the warrants. The net proceeds to us from the offering, excluding the proceeds of any future exercise of the warrants, totaled approximately $10.7 million.

In August 2003, we raised approximately $14.6 million in gross proceeds from a private placement to institutional and accredited investors. In the private placement, we sold 20,053,022 shares of our common stock and warrants to purchase 6,015,934 shares of our common stock. The warrants to purchase common stock have an exercise price of $1.00 per share and will expire if not exercised by August 28, 2008. The warrants may be exercised by paying cash or by invoking a cashless exercise feature. We may redeem the warrants at a price of $0.05 per share of common stock issuable upon exercise of the warrants if the average closing price of our common stock for a ten consecutive trading day period is greater than or equal to $2.00 per share. The net proceeds to us from the placement, excluding the proceeds of any future exercise of the warrants, totaled approximately $13.1 million. As part of this transaction, we issued to selected dealers and placement agents warrants to purchase 2,458,405 shares of common stock at an exercise price of $0.73 per share and warrants to purchase 1,325,342 shares of common stock at an exercise price of $1.00 per share.

Cash Flows

As of December 31, 2004, we had approximately $14.4 million in cash and cash equivalents and investments, a net increase of approximately $0.7 million from December 31, 2003. We used $13.3 million of cash in operating activities during 2004, principally to fund our research and development expenses and our general and administrative expenses. The $13.3 million primarily consists of our $12.7 million net loss for the period, as adjusted for non-cash expenses including depreciation and amortization and a non-cash benefit for stock-based compensation.

The net cash used in investing activities during 2004 of $3.5 million reflects our purchase of approximately $18.6 million in "available-for-sale" securities offset by our sale of $12.3 million of "available-for-sale" securities and the proceeds of approximately $2.9 million from securities that matured in 2004.

The net cash provided by financing activities during 2004, reflects the $4.7 million in net proceeds that we raised in our August 2004 private placement and the $10.7 million in net proceeds that we raised through our April 2004 registered direct offering offset by the use of $1.3 million of our cash to repay our 9% notes upon their maturity. Cash from other financing activities included proceeds from the exercise of stock options and warrants.

Funding Requirements

We have incurred operating losses in most fiscal years and had an accumulated deficit of $299.3 million at December 31, 2004. We had cash, cash equivalents and short-term investments of $14.4 million at December 31, 2004. Based on our current operating plan, we believe that these funds will be sufficient to fund operations into January 2006. However, we could reduce planned activities if we need to conserve such funds. We plan to continue operating as a going concern.

We do not expect to generate significant additional funds internally until we successfully complete development and obtain marketing approval for products, either alone or in collaboration with third parties, which we expect will take a number of years. In addition, we have no committed external sources of funds. As a result, in order for us to continue to pursue our clinical and preclinical development programs and continue operations beyond January 2006, we must raise additional funds in 2005 from debt, equity financings or from collaborative arrangements with biotechnology or pharmaceutical companies. There can be no assurance that the requisite funds will be available in the necessary time frame or on terms acceptable to us. Should we be unable to raise sufficient funds, we may be required to significantly curtail our operating plans and possibly relinquish rights to portions of our technology or products. In addition, increases in expenses or delays in clinical development may adversely impact our cash position and require further cost reductions. No assurance can be given that we will be able to operate profitably on a consistent basis, or at all, in the future.

We believe that the key factors that will affect our internal and external sources of cash are:

- the success of our clinical and preclinical development programs;
- the receptivity of the capital markets to financings by biotechnology companies; and
- our ability to enter into strategic collaborations with biotechnology and pharmaceutical companies and the success of such collaborations.

Contractual Obligations

As of December 31, 2004, our contractual obligations were as follows:

	Payments Due by Period		
Contractual Obligations	**Total**	**Less than 1 year**	**1-3 years**
Lease Commitments	$1,426,000	$ 611,000	$ 815,000
Employment Agreements	1,892,000	1,082,000	810,000
Consulting & Collaboration Agreements	79,000	79,000	—
Total	$3,397,000	$1,772,000	$1,625,000

Our only material lease commitment relates to our facility in Cambridge, Massachusetts. Under our license agreements, we are obligated to make milestone payments upon achieving specified milestones and to pay royalties to our licensors. These contingent milestone and royalty payment obligations are not included in the above table. We do not expect to make any material capital expenditures in 2005.

FORWARD-LOOKING STATEMENTS

This annual report contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. All statements, other than statements of historical facts, included or incorporated in this report regarding our strategy, future operations, financial position, future revenues, projected costs, prospects, plans and objectives of management are forward-looking statements. The words "believes," "anticipates," "estimates," "plans," "expects," "intends," "may," "projects," "will," and "would" and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We cannot guarantee that we actually will achieve the plans, intentions or expectations disclosed in our forward-looking statements and you should not place undue reliance on our forward-looking statements. There are a number of important

factors that could cause our actual results to differ materially from those indicated or implied by forward-looking statements. These important factors include those set forth below under "Risk Factors." These factors and the other cautionary statements made in this annual report should be read as being applicable to all related forward-looking statements whenever they appear in this annual report. In addition, any forward-looking statements represent our estimates only as of the date that this annual report is filed with the SEC and should not be relied upon as representing our estimates as of any subsequent date. We do not assume any obligation to update any forward-looking statements. We disclaim any intention or obligation to update or revise any forward-looking statement, whether as a result of new information, future events or otherwise.

RISK FACTORS

The following important factors could cause actual results to differ from those indicated by forward-looking statements made by us in this annual report on Form 10-K and elsewhere from time to time.

Risks Relating to Our Financial Results and Need for Financing

We have incurred substantial losses and expect to continue to incur losses. We will not be successful unless we reverse this trend.

We have incurred losses in every year since our inception, except for 2002 when our recognition of revenues under a license and collaboration agreement resulted in us reporting net income for that year. As of December 31, 2004, we had incurred operating losses of approximately $299.3 million. We expect to continue to incur substantial operating losses in future periods. These losses, among other things, have had and will continue to have an adverse effect on our stockholders' equity, total assets and working capital.

We have received no revenues from the sale of drugs. To date, almost all of our revenues have been from collaborative and license agreements and the sale of manufactured synthetic DNA and reagent products by our Hybridon Specialty Products Division prior to our selling that division in September 2000. We have devoted substantially all of our efforts to research and development, including clinical trials, and we have not completed development of any drugs. Because of the numerous risks and uncertainties associated with developing drugs, we are unable to predict the extent of any future losses, whether or when any of our products will become commercially available, or when we will become profitable, if at all.

We will need additional financing, which may be difficult to obtain. Our failure to obtain necessary financing or doing so on unattractive terms could adversely affect our discovery and development programs and other operations.

We will require substantial funds to conduct research and development, including preclinical testing and clinical trials of our drugs. We will also require substantial funds to conduct regulatory activities and to establish commercial manufacturing, marketing and sales capabilities. We believe that, based on our current operating plan, our existing cash and cash equivalents and short-term investments, will be sufficient to fund our cash requirements into January 2006. However, we could reduce planned activities if we need to conserve such funds. We will need to raise additional funds to operate our business beyond such time. We believe that the key factors that will affect our ability to raise cash are:

- the success of our clinical and preclinical development programs;
- the receptivity of the capital markets to financings by biotechnology companies; and
- our ability to enter into strategic collaborations with biotechnology and pharmaceutical companies and the success of such collaborations.

Additional financing may not be available to us when we need it or may not be available to us on favorable terms. We could be required to seek funds through arrangements with collaborators or others that may require us to relinquish rights to some of our technologies, drug candidates or drugs which we would otherwise pursue on our own. In addition, if we raise additional funds by issuing equity securities, our then existing stockholders will experience dilution. The terms of any financing may adversely affect the holdings or

the rights of existing stockholders. If we are unable to obtain adequate funding on a timely basis or at all, we may be required to significantly curtail one or more of our discovery or development programs. For example, we significantly curtailed expenditures on our research and development programs during 1999 and 2000 because we did not have sufficient funds available to advance these programs at planned levels.

Risks Relating to Our Business, Strategy and Industry

We are depending heavily on the success of our lead drug candidate, IMOxine, which is in clinical development. If we are unable to commercialize this product, or experience significant delays in doing so, our business will be materially harmed.

We are investing a significant portion of our time and financial resources in the development of our lead drug candidate, IMOxine. We anticipate that our ability to generate product revenues will depend heavily on the successful development and commercialization of this product. The commercial success of this product will depend on several factors, including the following:

- successful completion of clinical trials;
- receipt of marketing approvals from the FDA and equivalent foreign regulatory authorities;
- establishing commercial manufacturing arrangements with third party manufacturers;
- launching commercial sales of the product, whether alone or in collaboration with others; and
- acceptance of the product in the medical community and with third party payors.

Our efforts to commercialize this product are at an early stage, as we are currently conducting a phase 1 clinical trial of this product candidate in patients with refractory solid tumor cancers and a phase 2 clinical trial in patients with metastatic or recurrent clear cell renal carcinoma. If we are not successful in commercializing this product, or are significantly delayed in doing so, our business will be materially harmed.

If our clinical trials are unsuccessful, or if they are significantly delayed, we may not be able to develop and commercialize our products.

We may not be able to successfully complete any clinical trial of a potential product within any specified time period. In some cases, we may not be able to complete the trial at all. Moreover, clinical trials may not show our potential products to be both safe and efficacious. Thus, the FDA and other regulatory authorities may not approve any of our potential products for any indication.

In order to obtain regulatory approvals for the commercial sale of our products, we will be required to complete extensive clinical trials in humans to demonstrate the safety and efficacy of our drug candidates. We may not be able to obtain authority from the FDA or other equivalent foreign regulatory agencies to complete these trials or commence and complete any other clinical trials.

The results from preclinical testing of a drug candidate that is under development may not be predictive of results that will be obtained in human clinical trials. In addition, the results of early human clinical trials may not be predictive of results that will be obtained in larger scale, advanced stage clinical trials. A failure of one or more of our clinical trials can occur at any stage of testing. Further, there is to date little data on the long-term clinical safety of our lead compounds under conditions of prolonged use in humans, nor on any long-term consequences subsequent to human use. We may experience numerous unforeseen events during, or as a result of, preclinical testing and the clinical trial process that could delay or prevent our ability to receive regulatory approval or commercialize our products, including:

- regulators or institutional review boards may not authorize us to commence a clinical trial or conduct a clinical trial at a prospective trial site;
- our preclinical tests or clinical trials may produce negative or inconclusive results, and we may decide, or regulators may require us, to conduct additional preclinical testing or clinical trials or we may abandon projects that we expect may not be promising;

- we might have to suspend or terminate our clinical trials if the participating patients are being exposed to unacceptable health risks;
- regulators or institutional review boards may require that we hold, suspend or terminate clinical research for various reasons, including noncompliance with regulatory requirements;
- the cost of our clinical trials may be greater than we currently anticipate; and
- the effects of our products may not be the desired effects or may include undesirable side effects or the products may have other unexpected characteristics.

As an example, in 1997, after reviewing the results from the clinical trial of GEM91, a 1st generation antisense compound and our lead drug candidate at the time, we determined not to continue the development of GEM91 and suspended clinical trials of this product candidate.

The rate of completion of clinical trials is dependent in part upon the rate of enrollment of patients. The rate of enrollment in our ongoing phase 2 clinical trial of IMOxine has thus far been slower than anticipated and may delay the completion of trial beyond the time we expected. Patient accrual is a function of many factors, including:

- the size of the patient population,
- the proximity of patients to clinical sites,
- the eligibility criteria for the study,
- the nature of the study,
- the existence of competitive clinical trials and
- the availability of alternative treatments.

Our product development costs will increase if we experience delays in our clinical trials. We do not know whether planned clinical trials will begin as planned, will need to be restructured or will be completed on schedule, if at all. Significant clinical trial delays also could allow our competitors to bring products to market before we do and impair our ability to commercialize our products.

We face substantial competition which may result in others discovering, developing or commercializing drugs before or more successfully than us.

The biotechnology industry is highly competitive and characterized by rapid and significant technological change. We face, and will continue to face, intense competition from organizations such as pharmaceutical and biotechnology companies, as well as academic and research institutions and government agencies. Some of these organizations are pursuing products based on technologies similar to our technologies. Other of these organizations have developed and are marketing products, or are pursuing other technological approaches designed to produce products, that are competitive with our product candidates in the therapeutic effect these competitive products have on diseases targeted by our product candidates. Our competitors may discover, develop or commercialize products or other novel technologies that are more effective, safer or less costly than any that we are developing. Our competitors may also obtain FDA or other regulatory approval for their products more rapidly than we may obtain approval for ours.

Many of our competitors are substantially larger than we are and have greater capital resources, research and development staffs and facilities than we have. In addition, many of our competitors are more experienced than we are in drug discovery, development and commercialization, obtaining regulatory approvals and drug manufacturing and marketing.

We anticipate that the competition with our products and technologies will be based on a number of factors including product efficacy, safety, availability and price. The timing of market introduction of our products and competitive products will also affect competition among products. We expect the relative speed with which we can develop products, complete the clinical trials and approval processes and supply commercial quantities of the products to the market to be important competitive factors. Our competitive

position will also depend upon our ability to attract and retain qualified personnel, to obtain patent protection or otherwise develop proprietary products or processes and to secure sufficient capital resources for the period between technological conception and commercial sales.

Because the products that we may develop will be based on new technologies and therapeutic approaches, the market may not be receptive to these products upon their introduction.

The commercial success of any of our products for which we may obtain marketing approval from the FDA or other regulatory authorities will depend upon their acceptance by the medical community and third party payors as clinically useful, cost-effective and safe. Many of the products that we are developing are based upon technologies or therapeutic approaches that are relatively new and unproven. The FDA has only granted marketing approval for one product based on antisense technology which is currently being marketed by another company for the treatment of cytomegalovirus retinitis, an infectious disease, in patients with AIDs. The FDA has not granted marketing approval to any products based on IMO technology and no such products are currently being marketed. As a result, it may be more difficult for us to achieve regulatory approval or market acceptance of our products. Our efforts to educate the medical community on these potentially unique approaches may require greater resources than would be typically required for products based on conventional technologies or therapeutic approaches. The safety, efficacy, convenience and cost-effectiveness of our products as compared to competitive products will also affect market acceptance.

Competition for technical and management personnel is intense in our industry, and we may not be able to sustain our operations or grow if we are unable to attract and retain key personnel.

Our success is highly dependent on the retention of principal members of our technical and management staff, including Sudhir Agrawal. Dr. Agrawal serves as our President, Chief Scientific Officer and Chief Executive Officer. Dr. Agrawal has extensive experience in the pharmaceutical industry, has made significant contributions to the field of nucleic acid chemistry and is named as an inventor on over 200 patents and patent applications worldwide. Dr. Agrawal provides the scientific leadership for our research and development activities and directly supervises our research staff. The loss of Dr. Agrawal's services would be detrimental to our ongoing scientific progress and the execution of our business plan.

We are a party to an employment agreement with Dr. Agrawal, but this agreement may be terminated by us or Dr. Agrawal for any reason or no reason at any time upon notice to the other party. We do not carry key man life insurance for Dr. Agrawal.

Furthermore, our future growth will require hiring a significant number of qualified technical and management personnel. Accordingly, recruiting and retaining such personnel in the future will be critical to our success. There is intense competition from other companies and research and academic institutions for qualified personnel in the areas of our activities. If we are not able to continue to attract and retain, on acceptable terms, the qualified personnel necessary for the continued development of our business, we may not be able to sustain our operations or grow.

Regulatory Risks

We may not be able to obtain marketing approval for products resulting from our development efforts.

All of the products that we are developing or may develop in the future will require additional research and development, extensive preclinical studies and clinical trials and regulatory approval prior to any commercial sales. This process is lengthy, often taking a number of years, is uncertain and is expensive. Since our inception, we have conducted clinical trials of a number of compounds. In 1997, we determined not to continue clinical development of GEM91, our lead product candidate at the time. Currently, we are conducting clinical trials of IMOxine, our lead IMO drug candidate.

We may need to address a number of technological challenges in order to complete development of our products. Moreover, these products may not be effective in treating any disease or may prove to have

undesirable or unintended side effects, unintended alteration of the immune system over time, toxicities or other characteristics that may preclude our obtaining regulatory approval or prevent or limit commercial use.

We are subject to comprehensive regulatory requirements, which are costly and time consuming to comply with; if we fail to comply with these requirements, we could be subject to adverse consequences and penalties.

The testing, manufacturing, labeling, advertising, promotion, export and marketing of our products are subject to extensive regulation by governmental authorities in Europe, the United States and elsewhere throughout the world.

In general, submission of materials requesting permission to conduct clinical trials may not result in authorization by the FDA or any equivalent foreign regulatory agency to commence clinical trials. In addition, submission of an application for marketing approval to the relevant regulatory agency following completion of clinical trials may not result in the regulatory agency approving the application if applicable regulatory criteria are not satisfied, and may result in the regulatory agency requiring additional testing or information.

Any regulatory approval of a product may contain limitations on the indicated uses for which the product may be marketed or requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the product. Any product for which we obtain marketing approval, along with the facilities at which the product is manufactured, any post-approval clinical data and any advertising and promotional activities for the product will be subject to continual review and periodic inspections by the FDA and other regulatory agencies.

Both before and after approval is obtained, violations of regulatory requirements may result in:

- the regulatory agency's delay in approving, or refusal to approve, an application for approval of a product;
- restrictions on such products or the manufacturing of such products;
- withdrawal of the products from the market;
- warning letters;
- voluntary or mandatory recall;
- fines;
- suspension or withdrawal of regulatory approvals;
- product seizure;
- refusal to permit the import or export of our products;
- injunctions or the imposition of civil penalties; and
- criminal penalties.

We have only limited experience in regulatory affairs and our products are based on new technologies; these factors may affect our ability or the time we require to obtain necessary regulatory approvals.

We have only limited experience in filing the applications necessary to gain regulatory approvals. Moreover, the products that result from our research and development programs will likely be based on new technologies and new therapeutic approaches that have not been extensively tested in humans. The regulatory requirements governing these types of products may be more rigorous than for conventional drugs. As a result, we may experience a longer regulatory process in connection with obtaining regulatory approvals of any product that we develop.

Risks Relating to Collaborators

We need to establish collaborative relationships in order to succeed.

An important element of our business strategy includes entering into collaborative relationships for the development and commercialization of products based on our discoveries. We face significant competition in seeking appropriate collaborators. Moreover, these arrangements are complex to negotiate and time-consuming to document. We may not be successful in our efforts to establish collaborative relationships or other alternative arrangements.

The success of collaboration arrangements will depend heavily on the efforts and activities of our collaborators. Our collaborators will have significant discretion in determining the efforts and resources that they will apply to these collaborations. The risks that we face in connection with these collaborations include the following:

- disputes may arise in the future with respect to the ownership of rights to technology developed with collaborators;
- disagreements with collaborators could delay or terminate the research, development or commercialization of products, or result in litigation or arbitration;
- we may have difficulty enforcing the contracts if one of our collaborators fails to perform;
- our collaborators may terminate their collaborations with us, which could make it difficult for us to attract new collaborators or adversely affect the perception of us in the business or financial communities;
- collaborators have considerable discretion in electing whether to pursue the development of any additional drugs and may pursue technologies or products either on their own or in collaboration with our competitors that are similar to or competitive with our technologies or products that are the subject of the collaboration with us; and
- our collaborators may change the focus of their development and commercialization efforts. Pharmaceutical and biotechnology companies historically have re-evaluated their priorities following mergers and consolidations, which have been common in recent years in these industries. The ability of our products to reach their potential could be limited if our collaborators decrease or fail to increase spending relating to such products.

Given these risks, it is possible that any collaborative arrangements into which we enter may not be successful. Previous collaborative arrangements to which we were a party with F. Hoffmann-La Roche and G.D. Searle & Co. both were terminated prior to the development of any product. The failure of any of our collaborative relationships could delay our drug development or impair commercialization of our products.

Risks Relating to Intellectual Property

If we are unable to obtain patent protection for our discoveries, the value of our technology and products will be adversely affected.

Our patent positions, and those of other drug discovery companies, are generally uncertain and involve complex legal, scientific and factual questions.

Our ability to develop and commercialize drugs depends in significant part on our ability to:

- obtain patents;
- obtain licenses to the proprietary rights of others on commercially reasonable terms;
- operate without infringing upon the proprietary rights of others;

- prevent others from infringing on our proprietary rights; and
- protect trade secrets.

We do not know whether any of our patent applications or those patent applications which we license will result in the issuance of any patents. Our issued patents and those that may issue in the future, or those licensed to us, may be challenged, invalidated or circumvented, and the rights granted thereunder may not provide us proprietary protection or competitive advantages against competitors with similar technology. Furthermore, our competitors may independently develop similar technologies or duplicate any technology developed by us. Because of the extensive time required for development, testing and regulatory review of a potential product, it is possible that, before any of our products can be commercialized, any related patent may expire or remain in force for only a short period following commercialization, thus reducing any advantage of the patent.

Because patent applications in the United States and many foreign jurisdictions are typically not published until 18 months after filing, or in some cases not at all, and because publications of discoveries in the scientific literature often lag behind actual discoveries, neither we nor our licensors can be certain that we or they were the first to make the inventions claimed in issued patents or pending patent applications, or that we or they were the first to file for protection of the inventions set forth in these patent applications.

Third parties may own or control patents or patent applications and require us to seek licenses, which could increase our development and commercialization costs, or prevent us from developing or marketing products.

We may not have rights under some patents or patent applications related to our products. Third parties may own or control these patents and patent applications in the United States and abroad. Therefore, in some cases, to develop, manufacture, sell or import some of our products, we or our collaborators may choose to seek, or be required to seek, licenses under third party patents issued in the United States and abroad or under patents that might issue from United States and foreign patent applications. In such an event, we would be required to pay license fees or royalties or both to the licensor. If licenses are not available to us on acceptable terms, we or our collaborators may not be able to develop, manufacture, sell or import these products.

We may lose our rights to patents, patent applications or technologies of third parties if our licenses from these third parties are terminated. In such an event, we might not be able to develop or commercialize products covered by the licenses.

We are party to ten royalty-bearing license agreements under which we have acquired rights to patents, patent applications and technology of third parties. Under these licenses we are obligated to pay royalties on net sales by us of products or processes covered by a valid claim of a patent or patent application licensed to us. We also are required in some cases to pay a specified percentage of any sublicense income that we may receive. These licenses impose various commercialization, sublicensing, insurance and other obligations on us. Our failure to comply with these requirements could result in termination of the licenses. These licenses generally will otherwise remain in effect until the expiration of all valid claims of the patents covered by such licenses or upon earlier termination by the parties. The issued patents covered by these licenses expire at various dates ranging from 2006 to 2022. If one or more of these licenses is terminated, we may be delayed in our efforts, or be unable, to develop and market the products that are covered by the applicable license or licenses.

We may become involved in expensive patent litigation or other proceedings, which could result in our incurring substantial costs and expenses or substantial liability for damages or require us to stop our development and commercialization efforts.

There has been substantial litigation and other proceedings regarding patent and other intellectual property rights in the biotechnology industry. We may become a party to various types of patent litigation or other proceedings regarding intellectual property rights from time to time even under circumstances where we are not practicing and do not intend to practice any of the intellectual property involved in the proceedings.

For instance, in 2002, we became involved in an interference declared by the United States Patent and Trademark Office, or USPTO, involving a patent application exclusively licensed by us from University of Massachusetts Medical Center, or UMMC, and three patents issued to the National Institutes of Health, or NIH. In January, 2005, we and UMMC entered into an Interference Settlement Agreement with the NIH. The agreement is subject to approval of the Board of Patent Appeals and Interferences. In addition, in 2003, we became involved in an interference declared by the USPTO involving another patent exclusively licensed to us from UMMC and a patent application assigned jointly to the University of Montreal and The Massachusetts Institute of Technology. On August 6, 2004, the USPTO entered judgment in favor of the patent application jointly assigned to the University of Montreal and The Massachusetts Institute of Technology and against certain claims of the patent exclusively licensed to us from UMMC. We are neither practicing nor intending to practice the intellectual property involved in either of the interference proceedings in which we are involved.

The cost to us of any patent litigation or other proceeding, including the interferences referred to above, even if resolved in our favor, could be substantial. Some of our competitors may be able to sustain the cost of such litigation or proceedings more effectively than we can because of their substantially greater financial resources. If any patent litigation or other proceeding is resolved against us, we or our collaborators may be enjoined from developing, manufacturing, selling or importing our drugs without a license from the other party and we may be held liable for significant damages. We may not be able to obtain any required license on commercially acceptable terms or at all.

Uncertainties resulting from the initiation and continuation of patent litigation or other proceedings could have a material adverse effect on our ability to compete in the marketplace. Patent litigation and other proceedings may also absorb significant management time.

Risks Relating to Product Manufacturing, Marketing and Sales and Reliance on Third Parties

Because we have limited manufacturing experience, we are dependent on third-party manufacturers to manufacture products for us. If we cannot rely on third-party manufacturers, we will be required to incur significant costs and devote significant efforts to establish our own manufacturing facilities and capabilities.

We have limited manufacturing experience and no commercial scale manufacturing capabilities. In order to continue to develop our products, apply for regulatory approvals and ultimately commercialize products, we need to develop, contract for or otherwise arrange for the necessary manufacturing capabilities.

We currently rely upon third parties to produce material for preclinical and clinical testing purposes and expect to continue to do so in the future. We also expect to rely upon third parties to produce materials that may be required for the commercial production of our products.

There are a limited number of manufacturers that operate under the FDA's current good manufacturing practices regulations capable of manufacturing our products. As a result, we may have difficulty finding manufacturers for our products with adequate capacity for our needs. If we are unable to arrange for third party manufacturing of our products on a timely basis, or to do so on commercially reasonable terms, we may not be able to complete development of our products or market them.

Reliance on third party manufacturers entails risks to which we would not be subject if we manufactured products ourselves, including:

- reliance on the third party for regulatory compliance and quality assurance,
- the possibility of breach of the manufacturing agreement by the third party because of factors beyond our control,
- the possibility of termination or nonrenewal of the agreement by the third party, based on its own business priorities, at a time that is costly or inconvenient for us,

- the potential that third party manufacturers will develop know-how owned by such third party in connection with the production of our products that is necessary for the manufacture of our products, and
- reliance upon third party manufacturers to assist us in preventing inadvertent disclosure or theft of our proprietary knowledge.

We purchased oligonucleotides for preclinical and clinical testing from Avecia at a preferential price under a supply agreement, which expired in March 2004. We have continued to purchase all of the oligonucleotides we are using in our ongoing clinical trials and pre-clinical testing from Avecia. The terms of the agreement have been extended until such time as a new agreement is negotiated. If Avecia determines not to accept any purchase order for oligonucleotides or we are unable to enter into a new manufacturing arrangement with Avecia or a new contract manufacturer on a timely basis or at all, our ability to supply the product needed for our clinical trials could be materially impaired.

We have no experience selling, marketing or distributing products and no internal capability to do so.

If we receive regulatory approval to commence commercial sales of any of our products, we will face competition with respect to commercial sales, marketing and distribution. These are areas in which we have no experience. To market any of our products directly, we would need to develop a marketing and sales force with technical expertise and with supporting distribution capability. In particular, we would need to recruit a large number of experienced marketing and sales personnel. Alternatively, we could engage a pharmaceutical or other healthcare company with an existing distribution system and direct sales force to assist us. However, to the extent we entered into such arrangements, we would be dependent on the efforts of third parties. If we are unable to establish sales and distribution capabilities, whether internally or in reliance on third parties, our business would suffer materially.

If third parties on whom we rely for clinical trials do not perform as contractually required or as we expect, we may not be able to obtain regulatory approval for or commercialize our products and our business may suffer.

We do not have the ability to independently conduct the clinical trials required to obtain regulatory approval for our products. We depend on independent clinical investigators, contract research organizations and other third party service providers in the conduct of the clinical trials of our products and expect to continue to do so. For example, we have contracted with PAREXEL International to manage our Phase 2 trials clinical trials of IMOxine. We rely heavily on these parties for successful execution of our clinical trials, but do not control many aspects of their activities. We are responsible for ensuring that each of our clinical trials is conducted in accordance with the general investigational plan and protocols for the trial. Moreover, the FDA requires us to comply with standards, commonly referred to as good clinical practices, for conducting, recording and reporting clinical trials to assure that data and reported results are credible and accurate and that the rights, integrity and confidentiality of trial participants are protected. Our reliance on third parties that we do not control does not relieve us of these responsibilities and requirements. Third parties may not complete activities on schedule or may not conduct our clinical trials in accordance with regulatory requirements or our stated protocols. The failure of these third parties to carry out their obligations could delay or prevent the development, approval and commercialization of our products. If we seek to conduct any of these activities ourselves in the future, we will need to recruit appropriately trained personnel and add to our infrastructure.

If we are unable to obtain adequate reimbursement from third party payors for any products that we may develop or acceptable prices for those products, our revenues and prospects for profitability will suffer.

Most patients will rely on Medicare and Medicaid, private health insurers and other third party payors to pay for their medical needs, including any drugs we may market. If third party payors do not provide adequate coverage or reimbursement for any products that we may develop, our revenues and prospects for profitability will suffer. Congress recently enacted a limited prescription drug benefit for Medicare recipients in the

Medicare Prescription Drug and Modernization Act of 2003. While the program established by this statute may increase demand for our products, if we participate in this program, our prices will be negotiated with drug procurement organizations for Medicare beneficiaries and are likely to be lower than we might otherwise obtain. Non-Medicare third party drug procurement organizations may also base the price they are willing to pay on the rate paid by drug procurement organizations for Medicare beneficiaries.

A primary trend in the United States healthcare industry is toward cost containment. In addition, in some foreign countries, particularly the countries of the European Union, the pricing of prescription pharmaceuticals is subject to governmental control. In these countries, pricing negotiations with governmental authorities can take six to 12 months or longer after the receipt of regulatory marketing approval for a product. To obtain reimbursement or pricing approval in some countries, we may be required to conduct a clinical trial that compares the cost effectiveness of our product candidates or products to other available therapies. The conduct of such a clinical trial could be expensive and result in delays in commercialization of our products.

Third party payors are challenging the prices charged for medical products and services, and many third party payors limit reimbursement for newly-approved healthcare products. In particular, third party payors may limit the indications for which they will reimburse patients who use any products that we may develop. Cost control initiatives could decrease the price we might establish for products that we may develop, which would result in lower product revenues to us.

We face a risk of product liability claims and may not be able to obtain insurance.

Our business exposes us to the risk of product liability claims that is inherent in the manufacturing, testing and marketing of human therapeutic drugs. Although we have product liability and clinical trial liability insurance that we believe is adequate, this insurance is subject to deductibles and coverage limitations. We may not be able to obtain or maintain adequate protection against potential liabilities. If we are unable to obtain insurance at acceptable cost or otherwise protect against potential product liability claims, we will be exposed to significant liabilities, which may materially and adversely affect our business and financial position. These liabilities could prevent or interfere with our commercialization efforts.

Risks Relating to an Investment in Our Common Stock

Our corporate governance structure, including provisions in our certificate of incorporation and by-laws, our stockholder rights plan and Delaware law, may prevent a change in control or management that stockholders may consider desirable.

Section 203 of the Delaware General Corporation Law and our certificate of incorporation, by-laws and stockholder rights plan contain provisions that might enable our management to resist a takeover of our company or discourage a third party from attempting to take over our company. These provisions include:

- a classified board of directors,
- limitations on the removal of directors,
- limitations on stockholder proposals at meetings of stockholders,
- the inability of stockholders to act by written consent or to call special meetings, and
- the ability of our board of directors to designate the terms of and issue new series of preferred stock without stockholder approval.

These provisions could have the effect of delaying, deferring, or preventing a change in control of us or a change in our management that stockholders may consider favorable or beneficial. These provisions could also discourage proxy contests and make it more difficult for you and other stockholders to elect directors and take other corporate actions. These provisions could also limit the price that investors might be willing to pay in the future for shares of our common stock.

Our stock price has been and may in the future be extremely volatile. In addition, because an active trading market for our common stock has not developed, our investors' ability to trade our common stock may be limited. As a result, investors may lose all or a significant portion of their investment.

Our stock price has been volatile. During the period from January 1, 2003 to December 31, 2004, the closing sales price of our common stock ranged from a high of $1.69 per share to a low of $0.41 per share. The stock market has also experienced significant price and volume fluctuations, and the market prices of biotechnology companies in particular have been highly volatile, often for reasons that have been unrelated to the operating performance of particular companies. The market price for our common stock may be influenced by many factors, including:

- results of clinical trials of our product candidates or those of our competitors;
- the regulatory status of our product candidates;
- failure of any of our product candidates, if approved, to achieve commercial success;
- the success of competitive products or technologies;
- regulatory developments in the United States and foreign countries;
- developments or disputes concerning patents or other proprietary rights;
- the departure of key personnel;
- variations in our financial results or those of companies that are perceived to be similar to us;
- our cash resources;
- the terms of any financing conducted by us;
- changes in the structure of healthcare payment systems;
- market conditions in the pharmaceutical and biotechnology sectors and issuance of new or changed securities analysts' reports or recommendations; and
- general economic, industry and market conditions.

In addition, our common stock has historically been traded at low volume levels and may continue to trade at low volume levels. As a result, any large purchase or sale of our common stock could have a significant impact on the price of our common stock and it may be difficult for investors to sell our common stock in the market without depressing the market price for the common stock or at all.

As a result of the foregoing, investors may not be able to resell their shares at or above the price they paid for such shares. Investors in our common stock must be willing to bear the risk of fluctuations in the price of our common stock and the risk that the value of their investment in our stock could decline.

Item 7A. ***Quantitative and Qualitative Disclosures About Market Risk***

Historically, our primary exposures have been related to nondollar-denominated operating expenses in Europe. As of December 31, 2004, we have no assets and liabilities related to nondollar-denominated currencies.

We maintain investments in accordance with our investment policy. The primary objectives of our investment activities are to preserve principal, maintain proper liquidity to meet operating needs and maximize yields. Although our investments are subject to credit risk, our investment policy specifies credit quality standards for our investments and limits the amount of credit exposure from any single issue, issuer or type of investments. We do not own derivative financial investment instruments in our investment portfolio.

Based on a hypothetical ten percent adverse movement in interest rates, the potential losses in future earnings, fair value of risk sensitive financial instruments, and cash flows are immaterial, although the actual effects may differ materially from the hypothetical analysis.

Item 8. ***Financial Statements and Supplementary Data***

All financial statements required to be filed hereunder are filed as listed under Item 15(a) and are incorporated herein by this reference.

Item 9. ***Changes in and Disagreements with Accountants on Accounting and Financial Disclosure***

None.

Item 9A. ***Controls and Procedures***

(a) *Evaluation of Disclosure Controls and Procedures.* Our management, with the participation of our chief executive officer and our chief financial officer, evaluated the effectiveness of our disclosure controls and procedures as of December 31, 2004. The term "disclosure controls and procedures," as defined in Rules 13a-15(e) and 15d-15(e) under the Exchange Act, means controls and other procedures of a company that are designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is recorded, processed, summarized and reported, within the time periods specified in the SEC's rules and forms. Disclosure controls and procedures include, without limitation, controls and procedures designed to ensure that information required to be disclosed by a company in the reports that it files or submits under the Exchange Act is accumulated and communicated to the company's management, including its principal executive and principal financial officers, as appropriate to allow timely decisions regarding required disclosure. Management recognizes that any controls and procedures, no matter how well designed and operated, can provide only reasonable assurance of achieving their objectives and management necessarily applies its judgment in evaluating the cost-benefit relationship of possible controls and procedures. Based on the evaluation of our disclosure controls and procedures as of December 31, 2004, our chief executive officer and chief financial officer concluded that, as of such date, our disclosure controls and procedures were effective at the reasonable assurance level.

(b) *Changes in Internal Controls.* No change in our internal control over financial reporting occurred during the fiscal quarter ended December 31, 2004 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

Item 9B. ***Other Information.***

On March 24, 2005, the Company filed a Certificate of Increase with the Secretary of State of the State of Delaware pursuant to Section 151 of the Delaware General Corporation Law, increasing the number of authorized shares of the Company's Series C Junior Participating Preferred Stock, $.01 par value per share, from 150,000 shares to 185,000 shares, effective as of March 24, 2005.

On September 16, 2004, the Company granted a bonus of $25,000 to Dr. Sudhir Agrawal, the Company's Chief Executive Officer.

On December 21, 2004, the Company granted a bonus of $29,500 to Dr. Sudhir Agrawal and a bonus of $32,700 to Robert G. Andersen, the Company's Chief Financial Officer.

PART III.

The response to the Part III items incorporate by reference certain sections of our Proxy Statement for our annual meeting of stockholders to be held on June 15, 2005. The 2005 Proxy Statement will be filed with the Securities and Exchange Commission on or before April 29, 2005.

Item 10. ***Directors and Executive Officers of Hybridon***

The response to this item is contained under the following captions in the 2005 Proxy Statement: "Election of Directors" and "Section 16(a) Beneficial Ownership Reporting Compliance," which sections are incorporated herein by reference. See Part I of this Annual Report on 10-K under the caption "Executive Officers and Key Employees of Hybridon."

Information required by this item pursuant to Item 402(h) and 402(i) of Regulation S-K relating to an audit committee financial expert and identification of the audit committee of our board of directors is contained in our 2005 Proxy Statement under the caption "Corporate Governance" and is incorporated herein by reference.

We have adopted a written code of business conduct and ethics that applies to our principal executive officer, principal financial officer, principal accounting officer or controller, or persons performing similar functions. We intend to disclose any amendments to, or waivers from, our code of business conduct and ethics on our website which is located at www.Hybridon.com.

Item 11. ***Executive Compensation***

The response to this item is contained in the 2005 Proxy Statement under the captions: "Certain Transactions," and "Director Compensation" and "Executive Compensation", which sections are incorporated herein by reference.

Item 12. ***Security Ownership of Certain Beneficial Owners and Management and Related Stockholder Matters***

The response to this item is contained in the 2005 Proxy Statement under the caption "Security Ownership of Certain Beneficial Owners and Management" which section is incorporated herein by reference.

Item 13. ***Certain Relationships and Related Transactions***

The response to this item is contained in the 2005 Proxy Statement under the captions "Certain Transactions," and "Director Compensation", which sections are incorporated herein by reference.

Item 14. ***Principal Accountant Fees and Services***

The response to this item is contained in the 2005 Proxy Statement under the caption "Principal Accountant Fees and Services", which section is incorporated herein by reference.

PART IV.

Item 15. ***Exhibits and Financial Statement Schedules***

(a)(1) *Financial Statements.*

(2) We are not filing any financial statement schedules as part of this Annual Report on Form 10-K because they are not applicable or the required information is included in the financial statements or notes thereto.

(3) The list of Exhibits filed as a part of this Annual Report on Form 10-K is set forth on the Exhibit Index immediately preceding such Exhibits and is incorporated herein by this reference.

SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934, as amended, the Registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorized, on this 15th day of March 2005.

Hybridon, Inc.

By: /s/ SUDHIR AGRAWAL
Sudhir Agrawal
Chief Executive Officer

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this report has been signed below by the following persons on behalf of the Registrant and in the capacities and on the dates indicated.

Signature	Title	Date
/s/ JAMES B. WYNGAARDEN James B. Wyngaarden	Chairman of the Board of Directors	March 15, 2005
/s/ SUDHIR AGRAWAL Sudhir Agrawal, D. Phil	President, Chief Executive Officer, Chief Scientific Officer and Director (Principal Executive Officer)	March 15, 2005
/s/ ROBERT G. ANDERSEN Robert G. Andersen	Chief Financial Officer and Vice President of Operations, Treasurer and Secretary (Principal Financial and Accounting Officer)	March 15, 2005
/s/ YOUSSEF EL-ZEIN Youssef El-Zein	Director	March 15, 2005
/s/ C. KEITH HARTLEY C. Keith Hartley	Director	March 15, 2005
/s/ WILLIAM S. REARDON William S. Reardon, C.P.A.	Director	March 15, 2005
/s/ ALISON TAUNTON-RIGBY Alison Taunton-Rigby, Ph.D., OBE	Director	March 15, 2005
/s/ PAUL C. ZAMECNIK, M.D. Paul C. Zamecnik	Director	March 15, 2005

HYBRIDON, INC. AND SUBSIDIARIES

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

December 31, 2004

REPORT OF INDEPENDENT REGISTERED PUBLIC ACCOUNTING FIRM

The Board of Directors and Stockholders of Hybridon, Inc.

We have audited the accompanying consolidated balance sheets of Hybridon, Inc. and subsidiaries as of December 31, 2004 and 2003, and the related consolidated statements of operations, shareholders' equity, and cash flows for each of the three years in the period ended December 31, 2004. These financial statements are the responsibility of the Company's management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with the standards of the Public Company Accounting Oversight Board (United States). Those standards require that we plan and perform the audit to obtain reasonable assurance about whether the financial statements are free of material misstatement. We were not engaged to perform an audit of the Company's internal control over financial reporting. Our audit included consideration of internal control over financial reporting as a basis for designing audit procedures that are appropriate in the circumstances, but not for the purpose of expressing an opinion on the effectiveness of the Company's internal control over financial reporting. Accordingly, we express no such opinion. An audit also includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements, assessing the accounting principles used and significant estimates made by management, and evaluating the overall financial statement presentation. We believe that our audits provide a reasonable basis for our opinion.

In our opinion, the financial statements referred to above present fairly, in all material respects, the consolidated financial position of Hybridon, Inc. and subsidiaries at December 31, 2004 and 2003, and the consolidated results of its operations and its cash flows for each of the three years in the period ended December 31, 2004, in conformity with U.S. generally accepted accounting principles.

/s/ ERNST & YOUNG LLP

Boston, Massachusetts
January 28, 2005

HYBRIDON, INC. AND SUBSIDIARIES

CONSOLIDATED BALANCE SHEETS

	December 31, 2004	December 31, 2003
ASSETS		
Current assets:		
Cash and cash equivalents	$ 5,021,860	$ 7,607,655
Short-term investments	9,391,140	6,060,420
Receivables	293,113	202,936
Prepaid expenses and other current assets	333,316	101,697
Total current assets	15,039,429	13,972,708
Property and equipment, net	351,791	436,813
Total Assets	$ 15,391,220	$ 14,409,521
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 354,736	$ 675,926
Accrued expenses	1,332,150	1,123,058
Current portion of deferred revenue	171,287	127,537
9% convertible subordinated notes payable	—	1,306,000
Total current liabilities	1,858,173	3,232,521
Non-current portion of accrued expenses	240,000	—
Deferred revenue, net of current portion	523,655	651,192
Commitments and contingencies		
Stockholders' equity:		
Preferred stock, $0.01 par value		
Authorized — 5,000,000 shares		
Series A convertible preferred stock		
Designated — 1,500,000 shares		
Issued and outstanding — 655 and 489,205 shares at December 31, 2004 and 2003, respectively		
Liquidation value — $655 at December 31, 2004	7	4,892
Common stock, $0.001 par value		
Authorized — 185,000,000 and 150,000,000 shares at December 31, 2004 and 2003, respectively		
Issued and outstanding — 110,931,529 and 70,482,570 shares at December 31, 2004 and 2003, respectively	110,932	70,483
Additional paid-in capital	311,988,467	294,373,630
Accumulated deficit	(299,293,785)	(283,882,840)
Accumulated other comprehensive loss	(14,989)	(2,995)
Deferred compensation	(21,240)	(37,362)
Total stockholders' equity	12,769,392	10,525,808
Total Liabilities and Stockholders' Equity	$ 15,391,220	$ 14,409,521

The accompanying notes are an integral part of these consolidated financial statements.

HYBRIDON, INC. AND SUBSIDIARIES

CONSOLIDATED STATEMENTS OF OPERATIONS

	Years Ended December 31,		
	2004	2003	2002
Alliance revenue	$ 942,598	$ 896,572	$29,605,930
Operating expenses:			
Research and development	10,305,292	10,817,288	7,877,343
General and administrative	4,273,009	6,923,899	7,054,023
Stock-based compensation from repriced options (1)	(713,074)	542,666	(1,297,445)
Total operating expenses	13,865,227	18,283,853	13,633,921
(Loss) income from operations	(12,922,629)	(17,387,281)	15,972,009
Other income (expense):			
Investment income, net	217,064	190,178	649,554
Interest expense	(29,385)	(117,540)	(150,023)
Gain on sale of securities, net	—	103,585	—
(Loss) income from operations	(12,734,950)	(17,211,058)	16,471,540
Income tax benefit	—	—	500,000
Net (loss) income	(12,734,950)	(17,211,058)	16,971,540
Accretion of preferred stock dividends	(2,675,995)	(5,528,856)	(4,246,282)
Net (loss) income applicable to common stockholders	$(15,410,945)	$(22,739,914)	$12,725,258
(Loss) income per share from operations:			
Basic	$ (0.13)	$ (0.34)	$ 0.36
Diluted	$ (0.13)	$ (0.34)	$ 0.32
Net (loss) income per share applicable to common stockholders:			
Basic	$ (0.16)	$ (0.45)	$ 0.27
Diluted	$ (0.16)	$ (0.45)	$ 0.24
Shares used in computing basic net (loss) income per common share	98,913,927	51,053,415	46,879,232
Shares used in computing diluted net (loss) income per common share	98,913,927	51,053,415	52,984,415
(1) The following summarizes the allocation of stock based compensation from repriced options			
Research and development	$ (516,809)	$ 403,310	$ (925,210)
General and administrative	(196,265)	139,356	(372,235)
Total	$ (713,074)	$ 542,666	$(1,297,445)

The accompanying notes are an integral part of these consolidated financial statements.

HYBRIDON, INC. AND SUBSIDIARIES

CONSOLIDATED STATEMENTS OF STOCKHOLDERS' EQUITY (DEFICIT)

	Series A Convertible Preferred Stock		Common Stock		Additional Paid-In Capital	Accumulated Deficit	Accumulated Other Comprehensive Loss	Deferred Compensation	Total Stockholders' Equity (Deficit)
	Number of Shares	$0.01 Par Value	Number of Shares	$0.001 Par Value					
Balance, December 31, 2001	640,166	$ 6,402	45,632,525	$ 45,632	$273,870,458	$(273,868,184)	$ —	$(87,582)	$ (33,274)
Exercise of common stock options and warrants	—	—	1,162,172	1,162	458,514	—	—	—	459,676
Issuance of stock under the Isis Agreement	—	—	1,005,499	1,006	1,263,664	—	—	—	1,264,670
Issuance of stock options to employees	—	—	—	—	6,150	—	—	(6,150)	—
Amortization of deferred compensation	—	—	—	—	—	—	—	49,325	49,325
Conversion of 8% notes into stock	—	—	52,637	53	31,529	—	—	—	31,582
Preferred stock dividends	42,107	421	—	—	4,245,861	(4,246,282)	—	—	—
Conversion of preferred into common stock	(3,911)	(39)	92,024	92	(53)	—	—	—	—
Stock-based compensation from repriced options	—	—	—	—	(1,297,445)	—	—	—	(1,297,445)
Comprehensive income:									
Unrealized loss on marketable securities	—	—	—	—	—	—	(1,944)	—	(1,944)
Net income	—	—	—	—	—	16,971,540	—	—	16,971,540
Total comprehensive income	—	—	—	—	—	—	—	—	16,969,596
Balance, December 31, 2002	678,362	6,784	47,944,857	47,945	278,578,678	(261,142,926)	(1,944)	(44,407)	17,444,130
Sale of common stock	—	—	20,053,022	20,053	13,031,797	—	—	—	13,051,850
Repurchase of common stock	—	—	(4,643,034)	(4,643)	(3,477,632)	—	—	—	(3,482,275)
Exercise of common stock options and warrants	—	—	173,860	174	91,963	—	—	—	92,137
Issuance of stock options and stock for services	—	—	75,882	76	82,288	—	—	—	82,364
Amortization of deferred compensation	—	—	—	—	—	—	—	7,045	7,045
Preferred stock dividends	44,777	447	—	—	5,528,409	(5,528,856)	—	—	—
Conversion of preferred into common stock	(233,934)	(2,339)	6,877,983	6,878	(4,539)	—	—	—	—
Stock-based compensation from repriced options	—	—	—	—	542,666	—	—	—	542,666
Comprehensive income:									
Unrealized loss on marketable securities	—	—	—	—	—	—	(1,051)	—	(1,051)
Net loss	—	—	—	—	—	(17,211,058)	—	—	(17,211,058)
Total comprehensive loss	—	—	—	—	—	—	—	—	(17,212,109)
Balance, December 31, 2003	489,205	4,892	70,482,570	70,483	294,373,630	(283,882,840)	(2,995)	(37,362)	10,525,808
Sale of common stock	—	—	25,723,200	25,723	15,377,566	—	—	—	15,403,289
Exercise of common stock options and warrants	—	—	246,175	246	154,497	—	—	—	154,743
Issuance of stock options and stock for services	—	—	109,844	110	129,338	—	—	—	129,448
Amortization of deferred compensation	—	—	—	—	—	—	—	16,122	16,122
Preferred stock dividends	20	—	—	—	2,675,995	(2,675,995)	—	—	—
Conversion of preferred into common stock	(488,570)	(4,885)	14,369,740	14,370	(9,485)	—	—	—	—
Stock-based compensation from repriced options	—	—	—	—	(713,074)	—	—	—	(713,074)
Comprehensive income:									
Unrealized loss on marketable securities	—	—	—	—	—	—	(11,994)	—	(11,994)
Net loss	—	—	—	—	—	(12,734,950)	—	—	(12,734,950)
Total comprehensive loss	—	—	—	—	—	—	—	—	(12,746,944)
Balance, December 31, 2004	655	$ 7	110,931,529	$110,932	$311,988,467	$(299,293,785)	$(14,989)	$(21,240)	$ 12,769,392

The accompanying notes are an integral part of these consolidated financial statements.

HYBRIDON, INC. AND SUBSIDIARIES

CONSOLIDATED STATEMENTS OF CASH FLOWS

	Years Ended December 31,		
	2004	2003	2002
Cash Flows from Operating Activities:			
Net (loss) income	$(12,734,950)	$(17,211,058)	$ 16,971,540
Adjustments to reconcile net loss to net cash used in operating activities —			
Realized gain on marketable securities	—	(103,585)	—
Stock repurchase expense	—	1,857,214	—
Stock-based compensation	(713,074)	542,666	(1,297,445)
Depreciation and amortization expense	288,464	280,596	552,115
Issuance of stock options and stock for services	129,448	82,364	—
Amortization of deferred compensation	16,122	7,045	49,325
Amortization of deferred financing costs	—	—	10,586
Issuance of common stock and warrants	—	—	1,264,669
Non cash interest expense	—	—	21,882
Changes in operating assets and liabilities —			
Receivables	(90,177)	203,377	(131,450)
Prepaid expenses and other current assets	(231,619)	90,073	(145,364)
Accounts payable and accrued expenses	127,903	139,565	144,892
Deferred revenue	(83,787)	(266,771)	(28,422,685)
Net cash used in operating activities	(13,291,670)	(14,378,514)	(10,981,935)
Cash Flows from Investing Activities:			
Purchases of held-to-maturity securities	—	—	(14,582,249)
Purchases of available-for-sale securities	(18,635,747)	(17,681,672)	(8,219,615)
Proceeds from sale of available-for-sale securities	12,300,000	15,343,377	4,800,000
Proceeds from sale of held-to-maturity securities	—	—	3,047,725
Proceeds from maturities of held-to-maturity securities	2,850,000	14,080,000	7,816,000
Purchases of property and equipment	(60,410)	(53,943)	(371,584)
Net cash (used in) provided by investing activities	(3,546,157)	11,687,762	(7,509,723)
Cash Flows from Financing Activities:			
Sale of common stock and warrants, net of issuance costs	15,403,289	13,051,850	—
Repurchase of common stock	—	(5,339,489)	—
Proceeds from exercise of common stock options and warrants	154,743	92,137	459,676
Payments on debt	(1,306,000)	—	(284,102)
Payments on capital lease	—	(33,591)	(79,711)
Net cash provided by financing activities	14,252,032	7,770,907	95,863
Net (decrease) increase in cash and cash equivalents	(2,585,795)	5,080,155	(18,395,795)
Cash and cash equivalents, beginning of period	7,607,655	2,527,500	20,923,295
Cash and cash equivalents, end of period	$ 5,021,860	$ 7,607,655	$ 2,527,500

The accompanying notes are an integral part of these consolidated financial statements.

(1) Organization

Hybridon, Inc. (the Company) was incorporated in the State of Delaware on May 25, 1989. The Company is engaged in the discovery, development and commercialization of novel therapeutics based on synthetic DNA for the treatment of cancer, asthma/allergies and infectious diseases. Hybridon's activities are primarily focused on the development of its immunomodulatory oligonucleotide, or IMO, technology. Our IMO compounds are synthetic DNA-based sequences that are designed to mimic bacterial DNA and be recognized by a specific protein receptor called Toll-like Receptor 9, or TLR9, which triggers the activation and modulation of the immune system. The Company has also been a pioneer in the development of antisense technology, which uses synthetic DNA to block the production of disease causing proteins at the cellular level. In 2003 and 2004, Hybridon devoted substantially all of its research and development efforts on developing its IMO technology and products and expects to continue to focus its research and development efforts in 2005 and in future years to its IMO technology and products. The Company plans to continue to seek to enter into collaborations with third parties for the development and commercialization of products based on its antisense technology.

Since inception, the Company has been primarily engaged in research and development and manufacturing. To date almost all revenues received by the Company have been from collaboration and licensing agreements. In addition, the Company generated revenues from the sale of synthetic DNA and reagent products manufactured by Hybridon Specialty Products Division, or HSP, prior to selling HSP in September 2000.

The Company has incurred operating losses in most fiscal years and had an accumulated deficit of $299.3 million at December 31, 2004. The Company had cash, cash equivalents and short-term investments of $14.4 million at December 31, 2004. Based on its current operating plan, the Company believes that these funds will be sufficient to fund operations into January 2006, although the Company could reduce planned activities if it needed to conserve such funds. Therefore, the accompanying financial statements have been prepared assuming that the Company will continue as a going concern.

The Company does not expect to generate significant additional funds internally until it successfully completes development and obtains marketing approval for products, either alone or in collaboration with third parties, which the Company expects will take a number of years. In addition, it has no committed external sources of funds. As a result, in order for the Company to continue to pursue its clinical and preclinical development programs and continue its operations beyond January 2006, the Company must raise additional funds in 2005 from debt, equity financings or from collaborative arrangements with biotechnology or pharmaceutical companies. There can be no assurance that the requisite funds will be available in the necessary time frame or on terms acceptable to the Company. If the Company is unable to raise sufficient funds, the Company may be required to delay, scale back or eliminate some or all of its operating plans and possibly relinquish rights to portions of the Company's technology or products. In addition, increases in expenses or delays in clinical development may adversely impact the Company's cash position and require further cost reductions. No assurance can be given that the Company will be able to operate profitably on a consistent basis, or at all, in the future.

(2) Summary of Significant Accounting Policies

(a) Use of Estimates

The preparation of financial statements in conformity with accounting principles generally accepted in the United States requires management to make estimates and assumptions that affect the reported amounts of assets and liabilities and disclosure of contingent assets and liabilities at the date of the financial statements and the reported amounts of revenues and expenses during the reporting period. Actual results could differ from those estimates.

The Company is subject to a number of risks and uncertainties similar to those of other companies of the same size within the biotechnology industry, such as uncertainty of clinical trial outcomes, uncertainty of additional funding and history of operating losses.

(b) Cash Equivalents and Short-Term Investments

The Company considers all highly liquid investments with maturities of 90 days or less when purchased to be cash equivalents. Cash and cash equivalents at December 31, 2004 and 2003 consist of cash and money market funds.

The Company accounts for investments in accordance with Statement of Financial Accounting Standards (SFAS) No. 115, *Accounting for Certain Investments in Debt and Equity Securities.* Management determines the appropriate classification of marketable securities at the time of purchase. In accordance with SFAS No. 115, investments that the Company has the positive intent and ability to hold to maturity are classified as "held to maturity" and reported at amortized cost, adjusted for amortization of premiums and accretion of discounts to maturity, which approximates fair market value. Such amortization is included in "Investment income, net" on the accompanying consolidated statements of operations. Investments that the Company does not have the positive intent to hold to maturity are classified as "available-for-sale" and reported at fair market value. Unrealized gains and losses associated with "available-for-sale" investments are recorded in "Accumulated other comprehensive loss" on the accompanying consolidated balance sheet. The amortization of premiums and accretion of discounts and interest and dividends are included in "Investment income, net" on the accompanying consolidated statements of operations for all securities. Any realized gains and losses and declines in value judged to be other than temporary are included in "Gain on sale of securities, net". The cost of securities sold is based on the specific identification method. The Company recorded $103,585 of realized gains in "Gain on sale of securities, net" on the accompanying consolidated statement of operations from available-for-sale securities sold in 2003. For the years ended December 31, 2004, 2003 and 2002, there were no realized losses or permanent declines in value included in "Gain on sale of securities, net" for any securities.

There were no long-term investments as of December 31, 2004 and 2003. Available for sale securities are classified as short-term regardless of the maturity date if the Company plans to use them to fund operations within one year of the balance sheet date. Auction securities are highly liquid equity and debt securities that have floating interest or dividend rates that reset periodically through an auctioning process that sets rates based on bids. Issuers include municipalities, closed-end bond funds and corporations. These securities can either be debt or preferred shares. At December 31, 2004 and 2003, the Company's short-term investments consisted of the following all of which are classified as available-for-sale securities:

	December 31, 2004			
	Cost	Gross Unrealized Losses	Gross Unrealized Gains	Estimated Fair Value
Corporate bonds due in one year or less	$2,006,129	$ 1,979	$—	$2,004,150
Government bonds due in one year or less	3,000,000	13,010	—	2,986,990
Auction Securities	4,400,000	—	—	4,400,000
Total	$9,406,129	$14,989	$—	$9,391,140

	December 31, 2003			
	Cost	Gross Unrealized Losses	Gross Unrealized Gains	Estimated Fair Value
Corporate bonds:				
Due in one year or less	$ 520,545	$1,045	$—	$ 519,500
Due in one to two years	2,042,870	1,950	—	2,040,920
Auction Securities	3,500,000	—	—	3,500,000
Total	$6,063,415	$2,995	$—	$6,060,420

Although unrealized losses exist as of December 31, 2004, the Company does not believe they are other-than-temporary based on the nature of the investment and the lack of any adverse events.

(c) Depreciation and Amortization

Depreciation and amortization are computed using the straight-line method based on the estimated useful lives of the related assets, as follows:

Asset Classification	Estimated Useful Life
Leasehold improvements	Life of lease
Laboratory equipment and other	3 - 5 years

(d) Reclassification and Additional Disclosures

Certain amounts in the prior years consolidated financial statements have been reclassified and certain additional disclosures have been made to such financial statements as discussed below.

(e) Revenue Recognition

In December 2003, the Securities and Exchange Commission issued Staff Accounting Bulletin (SAB) No. 104, *Revenue Recognition*, which codifies, revises and rescinds certain sections of SAB No. 101, *Revenue Recognition*, in order to make this interpretive guidance consistent with current authoritative accounting and auditing guidance and SEC rules and regulations. The changes noted in SAB No. 104 did not have a material effect on the Company's consolidated results of operations, consolidated financial position or consolidated cash flows. The Company's revenue recognition policy complies with SAB No. 101 as modified by SAB No. 104. Alliance revenues are comprised of payments under various collaboration and licensing agreements for research and development, including reimbursement of third party expenses, milestone payments, license fees, sublicense fees, and royalty payments.

The Company recognizes license fees and other upfront fees, not specifically tied to a separate earnings process, ratably over the term of the contract or the term in which the Company must fulfill an obligation to aid in the research or use of the licensed technology.

The Company recognizes service and research and development revenue when the services are performed.

For payments that are specifically associated with a separate earnings process, the Company recognizes revenue when the specific performance obligation is completed. Performance obligations typically consist of significant milestones in the development life cycle of the related technology, such as initiation of clinical trials, filing for approval with regulatory agencies and approvals by regulatory agencies.

Royalty income represents amounts earned under certain collaboration and license agreements and is recognized as earned, which generally occurs upon receipt of quarterly royalty statements from the licensee or, in the case of a contractually-stated minimum annual royalty arrangement, the greater of the amount actually earned or the guaranteed minimum amount.

(f) Financial Instruments

SFAS No. 107, *Disclosures About Fair Value of Financial Instruments*, requires disclosure of the estimated fair values of financial instruments. The Company's financial instruments consist of cash and cash equivalents, short-term investments, and receivables. The estimated fair values of these financial instruments approximates their carrying values as of December 31, 2004 and 2003, respectively. The estimated fair values have been determined through information obtained from market sources and management estimates. As of December 31, 2004 and 2003, the Company does not have any derivatives or any other financial instruments as defined by SFAS No. 133, *Accounting for Derivative and Hedging Instruments.*

(g) Comprehensive Income (Loss)

The Company applies SFAS No. 130, *Reporting Comprehensive Income.* Comprehensive income (loss) is defined as the change in equity of a business enterprise during a period from transactions and other events and circumstances from nonowner sources. Comprehensive income or loss for the years ended December 31, 2004, 2003 and 2002 is comprised of reported net income or loss and the change in net unrealized losses on investments during each year which is included in "Accumulated other comprehensive loss" on the accompanying consolidated balance sheet.

(h) Net (Loss) Income per Common Share

The Company applies SFAS No. 128, *Earnings per Share.* Under SFAS No. 128, basic and diluted net (loss) income per common share is computed using the weighted average number of shares of common stock outstanding during the period. In addition, diluted net income per common share is calculated to give effect of stock options, convertible preferred stock and convertible debt (where the effect is not antidilutive) resulting in lower net income per share. The dilutive effect of outstanding stock options is reflected by the application of the treasury stock method under SFAS No. 128. Diluted net loss per common share is the same as basic net loss per common share for the years ended December 31, 2004 and 2003 as the effects of the Company's potential common stock equivalents are antidilutive (see Note 11).

(i) Segment Reporting

SFAS No. 131, *Disclosures About Segments of an Enterprise and Related Information*, establishes standards for reporting information regarding operating segments in annual financial statements and requires selected information for those segments to be presented in interim financial reports issued to stockholders. SFAS No. 131 also establishes standards for related disclosures about products and services and geographic areas. To date, the Company has viewed its operations and manages its business as one operating segment. Accordingly, the Company operates in one segment, which is the business of discovering and developing novel therapeutics through the application of synthetic DNA. As a result, the financial information disclosed herein represents all of the material financial information related to the Company's principal operating segment. For all of the periods presented, all of the Company's revenues were generated in the United States. As of December 31, 2004 and 2003, all assets were located in the United States.

(j) Stock-Based Compensation

The Company applies the disclosure only provisions of SFAS No. 123, *Accounting for Stock-Based Compensation*, as amended by the disclosure requirements of FASB Statement No. 148, *Accounting for Stock-Based Compensation — Transition and Disclosure.* The Company continues to account for employee stock compensation at intrinsic value, in accordance with Accounting Principles Board (APB) Opinion No. 25, *Accounting for Stock Issued to Employees* and related interpretations, with disclosure of the effects of fair value accounting on net income or net loss and related per share amounts on a pro forma basis.

The Company has computed the pro forma disclosures required by SFAS No. 123 for all stock options granted to employees after January 1, 1995, using the Black-Scholes option-pricing model. The assumptions used for the years ended December 31, 2004, 2003, and 2002 are as follows:

	2004	2003	2002
Average risk free interest rate	4.18%	3.30%	4.23%
Expected dividend yield	—	—	—
Expected lives	6 years	6 years	6 years
Expected volatility	90%	90%	90%
Weighted average grant date fair value of options granted during the period (per share)	$ 0.40	$ 0.79	$ 0.70

For the years ended December 31, 2004, 2003 and 2002, the weighted average per share grant date fair value and exercise price per share of option grants to employees in relation to market price of the stock on the date of the grant is as follows:

	Exercise Price		
	Equals Market Price	Exceeds Market Price	Is Less than Market Price
2004 Option Grants			
Weighted average grant date fair value of options granted during the period	$0.41	$0.36	$ —
Weighted average exercise price of options granted during the period	$0.54	$0.52	$ —
2003 Option Grants			
Weighted average grant date fair value of options granted during the period	$0.79	$ —	$ —
Weighted average exercise price of options granted during the period	$1.05	$ —	$ —
2002 Option Grants			
Weighted average grant date fair value of options granted during the period	$0.62	$1.12	$1.11
Weighted average exercise price of options granted during the period	$0.82	$1.54	$1.40

The Black-Scholes option-pricing model was developed for use in estimating the fair value of traded options, which have no vesting restrictions and are fully transferable. In addition, option-pricing models require the input of highly subjective assumptions including expected stock price volatility. Because the Company's employee stock options have characteristics significantly different from those of traded options, and because changes in the subjective input assumptions can materially affect the fair value estimate, in

management's opinion, the existing models do not necessarily provide a reliable single measure of the fair value of its employee stock options.

The pro forma effect of applying SFAS No. 123 for the three years ended December 31, 2004 would be as follows:

	2004	2003	2002
Net (loss) income applicable to common stockholders, as reported	$(15,410,945)	$(22,739,914)	$12,725,258
Less: stock-based compensation (income) expense included in reported net (loss) income	(713,074)	542,666	(1,297,445)
Add: stock-based employee compensation expense determined under fair value based method for all awards	(1,711,953)	(1,078,898)	(1,586,526)
Pro forma net (loss) income applicable to common stockholders, as adjusted for the effect of applying SFAS No. 123	$(17,835,972)	$(23,276,146)	$ 9,841,287
Basic net (loss) income per common share —			
As reported	$ (0.16)	$ (0.45)	$ 0.27
Pro forma	$ (0.18)	$ (0.46)	$ 0.21
Diluted net (loss) income per common share —			
As reported	$ (0.16)	$ (0.45)	$ 0.24
Pro forma	$ (0.18)	$ (0.46)	$ 0.19

The effects on years ended December 31, 2004, 2003 and 2002 pro forma net (loss) income and net (loss) income per share of expensing the estimated fair value of stock options are not necessarily representative of the effects on reported net (loss) income for future years because of the vesting period of the stock options and the potential for issuance of additional stock options in future years.

(k) Concentration of Credit Risk

Financial instruments that subject the Company to credit risk primarily consist of cash and cash equivalents and short-term investments. The Company's credit risk is managed by investing its cash and cash equivalents and marketable securities in highly rated money market instruments and debt securities. Due to these factors, no significant additional credit risk is believed by management to be inherent in the Company's assets. As of December 31, 2004, approximately 99% of the Company's cash, cash equivalents, and investments are held at one financial institution.

(l) New Accounting Pronouncement

In December 2004, the FASB issued SFAS No. 123 (revised 2004), *"Share-Based Payment"*, which is a revision of SFAS No. 123, *"Accounting for Stock-Based Compensation"*. SFAS No. 123(R) supersedes APB Opinion No. 25, *"Accounting for Stock Issued to Employees"*, and amends SFAS No. 95, *"Statement of Cash Flows"*. Generally, the approach in SFAS No. 123(R) is similar to the approach described in SFAS No. 123. However, SFAS No. 123(R) requires all share-based payments to employees, including grants of employee stock options, to be recognized in the income statement based on their fair values. Pro forma disclosure is no

longer an alternative. The new standard will be effective for the Company in the quarter beginning July 1, 2005.

As permitted by SFAS 123, the Company currently accounts for share-based payments to employees using APB 25's intrinsic value method and, as such, generally, except for marking to market the repriced options discussed in Note 7(e), the Company recognizes no compensation cost for employee stock options. Accordingly, the adoption of SFAS 123(R)'s fair value method may have a material impact on the Company's results of operations, although it will have no impact on the Company's overall financial position. The impact of adopting SFAS 123(R) cannot be predicted at this time because it will depend on levels of share-based payments granted in the future. However, had the company adopted SFAS 123(R) in a prior period, the impact of applying that standard would have approximated the impact of SFAS 123 as described in the disclosure of pro forma net loss and net loss per share in Note 2(j) to these financial statements. The Company is currently evaluating the impact of adopting of SFAS 123(R) on its financial position and results of operations, including the valuation methods and support for the assumptions that underlie the valuation of the awards.

(3) Accrued Expenses

At December 31, 2004 and 2003, accrued expenses consist of the following:

	December 31	
	2004	2003
Payroll and related costs	$ 527,000	$ 308,891
Clinical trial expenses	306,596	364,070
Other	498,554	450,097
	$1,332,150	$1,123,058

(4) Property and Equipment

At December 31, 2004 and 2003, net property and equipment at cost consists of the following:

	December 31	
	2004	2003
Leasehold improvements	$ 424,500	$ 407,812
Laboratory equipment and other	1,804,799	1,761,077
Total property and equipment, at cost	2,229,299	2,168,889
Less: Accumulated depreciation and amortization	1,877,508	1,732,076
Property and equipment, net	$ 351,791	$ 436,813

For the years ended December 31, 2004 and 2003, laboratory equipment and other includes approximately $113,000 of office equipment financed under capital leases with accumulated depreciation of approximately $57,000 and $34,000, respectively.

Depreciation expense, which includes amortization of assets recorded under capital leases, was approximately $145,000, $152,000 and $93,000 in 2004, 2003 and 2002, respectively.

(5) Debt

(a) 9% Convertible Subordinated Notes Payable

On April 1, 2004, the Company's 9% convertible subordinated notes payable (the 9% Notes) matured. As a result, the Company paid $1,306,000 to the note holders in payment of the principal amount outstanding under the notes plus accrued interest through the maturity date of $58,770. Under the terms of the 9% Notes, the Company made semi-annual interest payments on the outstanding principal balance through the maturity date of April 1, 2004. The Company currently has no debt outstanding.

(b) 8% Convertible Notes Payable

Upon maturity of the Company's 8% convertible notes payable (the 8% Notes) on November 30, 2002, $31,582 of the 8% Notes plus accrued interest were converted into 52,637 shares of common stock. The Company paid approximately $284,000 to the holders of the remaining 8% Notes in payment of the outstanding principal and accrued interest thereon.

(6) Collaboration and License Agreements

(a) Collaboration and License Agreement with VasGene Therapeutics, Inc.

On October 29, 2004, the Company and VasGene Therapeutics Inc. entered into reciprocal Collaboration and License Agreements pursuant to which both parties agreed to collaborate on the research and development of VEGF antisense products. The Company intends to pursue the treatment of ophthalmologic and other non-cancer diseases that are susceptible to treatment based on localized administration under one agreement, and VasGene intends to pursue the treatment of cancer and other non-ophthalmologic diseases that are susceptible to treatment through systemic administration under the other agreement. The Company is entitled to receive milestone payments, royalties, and sublicensing payments. Additionally, the Company may be entitled to reimbursement of research services performed in accordance with the terms of the agreement at the request of VasGene. The Company may have to pay VasGene royalties and sublicensing payments. VasGene may also be entitled to reimbursement of research services that it performs under the agreement at the Company's request. The milestones, if fully achieved, could result in payments to the Company of $8.0 million for each non-cancer VEGF antisense product developed by VasGene. Milestone payments would be triggered by the achievement of specific events in the development and commercial launch process.

(b) Collaboration and License Agreement with Alnylam Pharmaceuticals, Inc.

On August 2, 2004, the Company and Alnylam Pharmaceuticals, Inc. entered into a collaboration and license agreement pursuant to which the Company granted to Alnylam an exclusive license to a series of patents and patent applications relating to the therapeutic use of oligonucleotides that inhibit the production of the protein Vascular Endothelial Growth Factor (VEGF). Under the license, Alnylam's rights are limited to targeting VEGF for ocular indications with RNAi molecules. The Company is entitled to receive an up-front payment, annual license fees, milestone payments, royalties and sublicensing payments from Alnylam under the terms of the agreement. The up-front payment, license fees and milestone payments payable to the Company under the agreement could total approximately $4.4 million if all the milestones are achieved. Milestone payments are triggered by the achievement of specific events in the development process.

(c) Collaboration and License Agreement with The Immune Response Corporation.

On October 8, 2003, the Company entered into a collaboration and license agreement with The Immune Response Corporation to develop Amplivax as an adjuvant for use in combination with Immune Response's REMUNE vaccine candidate for the prevention and treatment of HIV-1. Under the terms of the agreement,

the Company granted Immune Response, during an exclusivity period, a worldwide license to Amplivax as an HIV vaccine adjuvant for the prevention and treatment of HIV. In order to maintain the exclusivity of the license to Amplivax that the Company granted to Immune Response in the agreement, Immune Response must make payments to the Company at specified times under the agreement. The Company is also entitled to reimbursement for time and materials and amounts payable to third parties for contracted services at cost plus an additional contractually stated percentage. In addition, the Company may receive certain specified fees, royalties on sales of the REMUNE vaccine combined with Amplivax and a percentage of sublicense income received by Immune Response.

(d) Collaboration and License Agreement with Aegera Therapeutics Inc.

On September 13, 2002, the Company and Aegera Therapeutics Inc. entered into a Collaboration and License Agreement (the Collaboration) to research, develop, and optimize a 2nd generation antisense drug targeted to the XIAP gene, a gene which has been implicated in the resistance of cancer cells to chemotherapy. In addition, Hybridon licensed to Aegera, on a non-exclusive basis, rights to the Company's portfolio of 2nd generation antisense chemistries and oral antisense delivery intellectual property owned or licensed by the Company. In consideration for research, development and optimization work to be performed by the Company under the Collaboration and the license of technology by the Company, Aegera paid the Company an upfront license fee and a prepaid milestone. In addition, Aegera agreed to pay the Company additional research payments, milestone payments upon the achievement of specified development milestones, and royalties on product sales and sublicensing, if any. Future anticipated payments under the Collaboration could total approximately $7.7 million if all of the milestones are achieved. Aegera is responsible for the development costs of the drug candidate.

(e) Collaboration and License Agreement with Migenix Inc.

On September 11, 2002, the Company and Migenix Inc. (formerly Micrologix Biotechnology, Inc.) entered into a Collaboration and License Agreement to develop an antisense drug candidate (MBI1121) for the treatment of human papillomavirus (HPV). The Company licensed Migenix the exclusive worldwide rights to a family of patents, claims of which cover a number of antisense oligonucleotides targeted to the HPV genome and non-exclusive rights to a portfolio of antisense chemistries owned or licensed by the Company. In consideration, Migenix agreed to pay the Company a license fee, paid in two installments, milestone payments upon the achievement of specified milestones, and royalties on product sales and sublicensing, if earned. The total license fee and milestone payments could amount to approximately $5.8 million, if all the milestones are achieved.

As part of the collaboration and license agreement, the Company and Migenix entered into a stock purchase agreement relating to the payment of the remaining portion of the license fee and certain future milestone payments under which Migenix issued to the Company shares of preferred stock of Migenix. Under the terms of the agreement, upon a specified date or the achievement of a milestone, a portion of the shares of preferred stock would, at the option of Migenix, either (i) be converted into common stock of Migenix at a conversion rate based on an average market price or (ii) be redeemed by Migenix for a cash amount equal to the payment due in respect of such date or milestone. The Company became entitled to receive the final installment of the license fee on April 17, 2003 and was issued 379,139 shares of Migenix common stock upon conversion of a portion of the preferred stock. The Company classified the common stock as available-for-sale. In the second quarter of 2003, the Company sold all the shares it received from Migenix for approximately $343,000 and recorded a realized gain of approximately $103,000. License fee revenue is being recorded over the current estimated development term of the drug candidate, MBI1121.

(f) Collaboration and License Agreement with Isis Pharmaceuticals, Inc.

On May 24, 2001, the Company and Isis Pharmaceuticals, Inc. (Isis) entered into a Collaboration and License Agreement (the Isis Agreement). Under the Isis Agreement, the Company granted Isis a license, with the right to sublicense, to the Company's antisense chemistry and delivery patents and patent applications. Isis also agreed to pay the Company a portion of specified sublicense income it receives from specified types of sublicenses of the Company's patents and patent applications. The Company has retained the right to use the patents and patent applications in its own drug discovery and development efforts and in collaboration with third parties. In consideration of the license granted by the Company, Isis paid $15.0 million in cash and issued 857,143 shares of its common stock having an aggregate fair market value on the dates on which title to the shares was received of $17.3 million. An additional $4.5 million installment was due in 2003; this obligation was subsequently canceled as part of the August 2002 amendment to the Isis Agreement described below.

Isis granted the Company a license to use specified antisense patents and patent applications, principally Isis' suite of RNase H patents. The Company has the right under the Isis Agreement to use these patents and patent applications in its drug discovery and development efforts and in specified types of collaborations with third parties. In consideration of this license, the Company originally agreed to pay Isis a total of $6.0 million in cash or in shares of its common stock in three equal annual installments of $2.0 million beginning in 2002. In May 2002, the Company made its first payment to Isis consisting of approximately $716,000 in cash and 1,005,499 shares of common stock having a fair market value of approximately $1.2 million on the date of issuance. The Company also agreed to pay Isis a nominal annual maintenance fee and a modest royalty on sales of products covered by specified patents and patent applications sublicensed to the Company by Isis. The actual number of shares of Hybridon stock that was issuable to Isis under the Isis Agreement was based on certain market conditions, as defined in the Isis Agreement, but was intended to have a fair market value of $6.0 million, if the stock remained in a certain price range as defined in the Isis Agreement; this obligation was subsequently cancelled as part of the August 2002 amendment to the Isis Agreement described below.

Prior to August 14, 2002, the Company interpreted its obligations under the Isis Agreement not to be inconsequential and perfunctory. As a result, for the year ended December 31, 2001, the Company recognized revenue under the Isis Agreement, net of amortization of the Company's payments to Isis, over the 10-year term of the Isis Agreement expiring in 2011. On August 14, 2002, the Company and Isis entered into an amendment to the Isis Agreement. As part of the amendment, each party agreed to cancel the remaining tranche payments due to the other under the Isis Agreement. In addition, the Company and Isis agreed to more specifically define and limit each party's future collaborative obligations under the Isis Agreement. As a result of the amendment, the Company was able to specifically limit the nature of its obligation and related cost of compliance under the Isis Agreement and to determine that such amended obligation and cost was inconsequential. In accordance with SAB 101, the Company recognized all previously deferred revenue under the Isis Agreement at the time of the amendment. Revenue for 2002 included approximately $29.5 million which was the previously deferred portion, at the time of the amendment, of the $32.3 million of cash and Isis stock received by the Company in 2001. Revenue for 2003 includes sublicense income received from Isis in connection with sublicenses of the Company's patents and patent applications granted by Isis to third parties. General and administrative expenses for the year ended December 31, 2002 include the $2.2 million previously unrecognized portion of the $2.4 million in direct expenses related to the Isis Agreement.

(g) License Agreement with University of Massachusetts Medical Center

The Company has a licensing agreement with the University of Massachusetts Medical Center (UMass), under which the Company has received exclusive licenses to technology in specified patents and patent applications. The Company is required to make royalty payments based on future sales of products employing

the technology or falling under claims of a patent, as well as a specified percentage of sublicense income received related to the licensed technology. Additionally, the Company is required to pay an annual maintenance fee through the life of the patents.

(7) Stockholders' Equity

(a) Common Stock

Pursuant to the terms of a unit purchase agreement dated as of May 5, 1998, the Company issued and sold a total of 9,597,476 shares of common stock (the "Put Shares") at a price of $2.00 per share. Under the terms of the unit purchase agreement, the initial purchasers (the "Put Holders") of the Put Shares have the right (the "Put Right") to require the Company to repurchase the Put Shares. The Put Right may not be exercised by any Put Holder unless: 1) the Company liquidates, dissolves or winds up its affairs pursuant to applicable bankruptcy law, whether voluntarily or involuntarily; 2) all of the Company's indebtedness and obligations, including without limitation the indebtedness under the Company's then outstanding notes, has been paid in full; and 3) all rights of the holders of any series or class of capital stock ranking prior and senior to the common stock with respect to liquidation, including without limitation the Series A convertible preferred stock, have been satisfied in full. The Company may terminate the Put Right upon written notice to the Put Holders if the closing sales price of its common stock exceeds $4.00 per share for the twenty consecutive trading days prior to the date of notice of termination. Because the Put Right is not transferable, in the event that a Put Holder has transferred Put Shares since May 5, 1998, the Put Right with respect to those shares has terminated. As a consequence of the Put Right, in the event the Company is liquidated, holders of shares of common stock that do not have Put Rights with respect to such shares may receive smaller distributions per share upon the liquidation than if there were no Put Rights outstanding.

In February 2003, the Company repurchased 2,415,880 Put Shares (see Note 14). As of December 31, 2004, 1,087,124 of the Put Shares continued to be held in the name of Put Holders. The Company cannot determine at this time what portion of the Put Rights of the remaining 6,094,472 Put Shares have terminated.

(b) Warrants

The Company has the following warrants outstanding and exercisable for the purchase of common stock at December 31, 2004:

Expiration Date	Shares	Weighted Exercise Price Per Share
March 31, 2006	500,000	$0.50
January 1, 2007	100,000	1.65
August 28, 2008	2,368,629	0.73
August 28, 2008	7,308,684	1.00
April 20, 2009	3,041,964	1.14
August 27, 2009	2,197,200	0.67
	15,516,477	
Weighted average exercise price per share		$0.93

During 2002, the Company issued warrants to purchase 100,000 shares of common stock to a financial advisor which it valued at approximately $98,000 using the Black-Scholes pricing model and charged to

general and administrative expense during the year. The warrants that expire in 2008 and 2009 are described in Notes 8(d) and 15.

(c) Stock Options

The 1990 Stock Option Plan provided for the grant of incentive stock options and nonqualified stock options. All options granted under this plan and outstanding are fully vested. No additional options are being granted under the 1990 Option Plan. As of December 31, 2004, options to purchase a total of 53,334 shares of common stock remained outstanding under the 1990 Option Plan.

The 1995 Stock Option Plan provides for the grant of incentive stock options and nonqualified stock options. Options granted under this plan generally vest over three to five years, and expire no later than 10 years from the date of grant. A total of 700,000 shares of common stock may be issued upon the exercise of options granted under this plan. The maximum number of shares with respect to which options may be granted to any employee under the 1995 Option Plan shall not exceed 500,000 shares of common stock during any calendar year. The Compensation Committee of the Board of Directors has the authority to select the employees to whom options are granted and determine the terms of each option, including (i) the number of shares of common stock subject to the option; (ii) when the option becomes exercisable; (iii) the option exercise price, which in the case of incentive stock options must be at least 100% and 110% in the case of incentive stock options granted to a stockholder owning in excess of 10% of the Company's common stock, of the fair market value of the common stock as of the date of grant and (iv) the duration of the options which in the case of incentive stock options may not exceed 10 years. As of December 31, 2004, options to purchase a total of 442,954 shares of common stock remained outstanding under the 1995 Stock Option Plan.

Under the 1995 Director Stock Option Plan, a total of 800,000 shares of common stock may be issued upon the exercise of options. Under the terms of the Director Plan options to purchase 3,750 shares of common stock are granted to each non-employee director on the first day of each calendar quarter and options to purchase 25,000 shares of common stock are granted to non-employee directors upon appointment to the Board. All options vest on the first anniversary of the date of grant. As of December 31, 2004, options to purchase a total of 242,250 shares of common stock remained outstanding under the Director Plan.

Under the 1997 Stock Incentive Plan, options generally vest over three to five years, and expire no later than 10 years from the date of grant. A total of 13,500,000 shares of common stock may be issued upon the exercise of options granted under the plan. The maximum number of shares with respect to which options may be granted during any calendar year to any employee under the 1997 Stock Incentive Plan is determined by dividing 1,500,000 by the fair market value of a share of the Company's common stock at the time of grant, and may not exceed an overall per participant annual limit of 5,000,000 shares. The Compensation Committee of the Board of Directors has the authority to select the employees to whom options are granted and determine the terms of each option, including (i) the number of shares of common stock subject to the option; (ii) when the option becomes exercisable; (iii) the option exercise price, which in the case of incentive stock options must be at least 100% (110% in the case of incentive stock options granted to those holding 10% or more of the voting power of the Company) of the fair market value of the common stock as of the date of grant and (iv) the duration of the option, which in the case of incentive stock options may not exceed 10 years. As of December 31, 2004, options to purchase a total of 9,583,876 shares of common stock remained outstanding under the 1997 Stock Incentive Plan.

As of December 31, 2004, options to purchase 2,411,414 shares of common stock remain available for grant under the 1995 Stock Option Plan, the 1995 Director Plan and the 1997 Stock Incentive Plan.

Stock option activity for the years ended December 31, 2004, 2003, and 2002 is summarized as follows:

	Number of Shares	Exercise Price Per Share	Weighted Average Price Per Share
Outstanding, December 31, 2001	14,477,114	$0.50 - $2.00	$0.74
Granted	786,500	0.50 - 1.54	0.92
Exercised	(889,687)	0.50 - 0.56	0.50
Terminated	(66,667)	0.50 - 2.00	0.51
Outstanding, December 31, 2002	14,307,260	0.50 - 2.00	0.77
Granted	596,000	0.70 - 1.15	1.05
Exercised	(96,841)	0.50 - 0.56	0.50
Terminated	(86,500)	0.50 - 2.00	0.87
Outstanding, December 31, 2003	14,719,919	0.50 - 2.00	0.78
Granted	2,084,750	0.52 - 1.14	0.53
Exercised	(85,784)	0.50 - 0.82	0.59
Terminated	(159,178)	0.50 - 1.54	1.13
Outstanding, December 31, 2004	16,559,707	$0.50 - $2.00	$0.75
Exercisable, December 31, 2002	8,739,045	$0.50 - $2.00	$0.74
Exercisable, December 31, 2003	10,357,565	$0.50 - $2.00	$0.75
Exercisable, December 31, 2004	12,883,125	$0.50 - $2.00	$0.76

	Options Outstanding			Options Exercisable	
Exercise Prices	Number	Weighted Average Remaining Contractual Life (Years)	Weighted Average Exercise Price Per Share	Number	Weighted Average Exercise Price Per Share
$ 0.50	2,622,028	3.66	$0.50	2,602,888	$0.50
0.52	1,965,000	9.92	0.52	—	—
0.56	2,497,192	6.24	0.56	2,490,939	0.56
0.57 - 0.79	1,196,000	7.50	0.74	1,010,311	0.74
0.82 - 0.83	2,353,750	6.59	0.83	1,221,250	0.83
0.84	3,152,500	6.57	0.84	3,151,250	0.84
0.93 - 1.10	1,469,487	5.81	1.06	1,436,487	1.06
1.12 - 2.00	1,303,750	6.77	1.23	970,000	1.26
	16,559,707	6.48	0.75	12,883,125	0.76

In accordance with EITF No. 96-18, *Accounting for Equity Instruments That Are Issued to Other Than Employees for Acquiring, or in Conjunction with Selling Goods or Services*, the Company recognizes the fair value of non-employee options as they vest using the Black-Scholes option pricing model. The Company has recorded compensation expense of $1,082, $1,082, and $2,079 in 2004, 2003 and 2002, respectively, related to grants to non-employees.

(d) Employee Stock Purchase Plan

The 1995 Employee Stock Purchase Plan (the Stock Purchase Plan) was adopted in October 1995 and amended in June 2003. Under the Stock Purchase Plan up to 500,000 shares of common stock may be issued to participating employees of the Company, as defined, or its subsidiaries. Participation is limited to employees that would not own 5% or more of the total combined voting power or value of the stock of the Company after the grant.

On the first day of a designated payroll deduction period, the "Offering Period", the Company will grant to each eligible employee who has elected to participate in the Stock Purchase Plan an option to purchase shares of common stock as follows: the employee may authorize an amount, a whole percentage from 1% to 10% of such employee's regular pay, to be deducted by the Company from such pay during the Offering Period. On the last day of the Offering Period, the employee is deemed to have exercised the option, at the option exercise price, to the extent of accumulated payroll deductions. Under the terms of the Stock Purchase Plan, the option price is an amount equal to 85% of the fair market value per share of the common stock on either the first day or the last day of the Offering Period, whichever is lower. In no event may an employee purchase in any one Offering Period a number of shares that is more than 15% of the employee's annualized base pay divided by 85% of the market value of a share of common stock on the commencement date of the Offering Period. The Compensation Committee may, in its discretion, choose an Offering Period of 12 months or less for each of the Offerings and choose a different Offering Period for each Offering.

Offering periods are three months in duration and commence on March 1, June 1, September 1, and December 1. In 2004, 2003 and 2002, the Company issued 92,215, 58,179 and 25,185 shares of common stock, respectively, under the Stock Purchase Plan.

(e) Repricing

In September 1999, the Company's Board of Directors authorized the repricing of options to purchase 5,251,827 shares of common stock to $0.50 per share, which represented the market value on the date of the repricing. These options are subject to variable plan accounting, as defined in FASB Interpretation No. 44 (FIN 44). The Company will remeasure the intrinsic value of the repriced options, through the earlier of the date of exercise, cancellation or expiration, at each reporting date. A decrease in the intrinsic value of these options over 2004 and 2002 resulted in credits of approximately $713,000 and $1,297,000 to stock compensation expense for the years ended December 31, 2004 and 2002, respectively. For the year ended December 31, 2003, the Company recognized approximately $543,000 as stock compensation expense from repriced options. As of December 31, 2004, options to purchase 2,403,256 shares are subject to variable plan accounting.

(f) Preferred Stock

The Restated Certificate of Incorporation of the Company permits its Board of Directors to issue up to 5,000,000 shares of preferred stock, par value $0.01 per share, in one or more series, to designate the number of shares constituting such series, and fix by resolution, the powers, privileges, preferences and relative, optional or special rights thereof, including liquidation preferences and dividends, and conversion and redemption rights of each such series. During 1998, the Company designated 1,500,000 shares as Series A convertible preferred stock which is described below in Note (7)(g). As of December 31, 2004 and 2003, there were 655 and 489,205 shares, respectively, of Series A convertible preferred stock outstanding. As discussed in Note (13), during 2002 the Company designated 100,000 shares of Series C junior participating preferred stock. In 2003, the Company designated an additional 50,000 shares of Series C junior participating preferred stock. There were no shares of Series C junior participating preferred stock issued or outstanding at December 31, 2004 and 2003.

(g) Series A Convertible Preferred Stock

On December 4, 2003, stockholders approved amendments to the Company's Restated Certificate of Incorporation that:

- reduced the liquidation preference of the Company's Series A convertible preferred stock from $100 per share to $1 per share;
- reduced the annual dividend on the Company's Series A convertible preferred stock from 6.5% to 1%; and
- increased the number of shares of the Company's common stock issuable upon conversion of the Company's Series A convertible preferred stock by 25% over the number of shares that would otherwise be issuable for a sixty-day conversion period between December 4, 2003 and February 2, 2004 inclusive.

During the sixty-day conversion period, the conversion ratio was increased so that the Series A convertible preferred shareholders could receive approximately 29.41 shares of common stock for each share of Series A convertible preferred stock converted instead of the stated conversion rate of 23.53 shares.

During the conversion period, 99.9% of the Series A convertible preferred stock was converted to common stock. The combined effects of the amendments to the Company's Restated Certificate of Incorporation and the Series A convertible preferred stock conversions are as follows:

	December 3, 2003	December 31, 2003	February 2, 2004
Shares:			
Preferred stock outstanding	722,727	489,205	635
Common stock issued from conversions (cumulative)	—	6,868,288	21,238,028
Common stock outstanding	63,595,442	70,482,570	84,900,627
Series A preferred liquidation preference	$73,055,654	$ 494,912	$ 643
Annual dividend amount	$ 4,697,726	$ 937,643	$ 864

The financial statement recognition of the Series A preferred stock conversion is shown below:

	Preferred Stock Dividends		
	2004	2003	2002
Accretion of dividends expected to be paid on Series A Preferred Stock	$ 503	$3,402,856	$4,246,282
Accretion of dividend that would have been paid on April 1, 2004 and reversal since preferred shares were converted in January and February 2004	(570,000)	570,000	—
Market value of 25% additional shares issued upon conversion	3,245,492	1,556,000	—
Total preferred stock dividend	$2,675,995	$5,528,856	$4,246,282

As shown above, $1.6 million of the 25% additional shares issued during the sixty-day conversion period was recorded as additional dividends (a) in the calculation of net loss applicable to common stockholders in the 2003 statement of operations and (b) in the 2003 statement of stockholders' equity. The remaining $3.2 million of the 25% additional shares were issued between January 1, 2004 and February 2, 2004 and was recorded as additional dividends (a) in the calculation off "Net (loss) applicable to common stockholders" in

the 2004 statement of operations and (b) in the 2004 statement of stockholders equity. As a result of the amendment to the Company's Certificate of Incorporation and the Series A convertible preferred stock conversions, the preferred stock liquidation preference was reduced from $73,055,654 at December 3, 2003 to $494,912 at December 31, 2003 and $643 at February 2, 2004.

The dividends are now payable semi-annually in arrears at the rate of 1% per annum, at the election of the Company, either in cash or additional duly authorized, fully paid and nonassessable shares of Series A preferred stock. In the event of liquidation, dissolution or winding up of the Company, after payment of debts and other liabilities of the Company, the holders of the Series A convertible preferred stock then outstanding will be entitled to a distribution of $1 per share out of any assets available to shareholders. The Series A preferred stock is non-voting. All remaining shares of Series A preferred stock rank as to payment upon the occurrence of any liquidation event senior to the common stock. Shares of Series A preferred stock are convertible, in whole or in part, at the option of the holder into fully paid and nonassessable shares of common stock at $4.25 per share, subject to adjustment as defined.

(8) Commitments and Contingencies

(a) Lease Commitments

The Company leases its headquarters facility on Vassar Street in Cambridge, Massachusetts, under a lease that has a 10-year term, which commenced on May 1, 1997. Future minimum commitments as of December 31, 2004, under existing lease agreements through the lease term, are approximately:

December 31,	Operating Leases
2005	611,000
2006	611,000
2007	204,000
	$1,426,000

During 2004, 2003, and 2002, facility rent expense for continuing operations, net of sublease income, was approximately $282,000, $397,000 and $282,000, respectively.

(b) External Collaborations

The Company funds research efforts of various academic collaborators and consultants in connection with its research and development programs. Total future fixed commitments under these agreements are estimated at approximately $79,000 for 2005.

In July 2004, the Company signed an agreement with PAREXEL International (PAREXEL) to manage the phase 2 clinical trial of IMOxine in patients with renal cell carcinoma. Under the agreement, the Company may pay PAREXEL up to $4.4 million in connection with this trial. As of December 31, 2004, the Company had paid approximately $0.7 million to PAREXEL under the agreement and expensed approximately $0.4 million in "Research and development" on the accompanying consolidated statement of operations.

(c) Contract Obligations

In August 2004, Dr. Sudhir Agrawal, the Company's President and Chief Scientific Officer, was appointed to the additional position of Chief Executive Officer, replacing Stephen R. Seiler who resigned as

CEO and a director of the Company. The Company has expensed approximately $0.7 million for amounts to be paid to Mr. Seiler through September 1, 2006 under his employment agreement.

(d) Related-Party Agreements with Affiliates of Stockholders and Directors

In 2004, the Company paid Pillar Investment Ltd., which is controlled by a director of the Company, a total of $281,000 for commissions relating to the Company's August 2004 financing. In conjunction with the financing, the Company also issued Pillar Investment Ltd., as additional commissions, warrants to purchase 432,520 shares of common stock at an exercise price of $0.67 per share. These warrants have a Black-Scholes value of approximately $155,000. Optima Life Sciences Limited, which is controlled by Pillar Investment Ltd., purchased 2,768,100 shares of common stock and warrants to purchase 553,620 additional shares of common stock at an exercise price of $0.67 per share in the financing.

In 2003, the Company paid Pillar S.A. and Pillar Investment Ltd. a total of $550,000 for (i) consulting services relating to international investor relations (ii) consulting services related to the repurchase of the Company's common stock from certain stockholders and (iii) commissions relating to the Company's August 2003 private placement. In conjunction with the private placement, the Company also issued Pillar Investment Ltd., as additional compensation for services provided as a placement agent in the private placement, warrants to purchase 587,709 shares of common stock at an exercise price of $1.00 per share. The amounts payable to Pillar in cash and warrants for the August 2003 private placement were less on a percentage basis than the comparable fees paid to the other placement agent involved in the private placement. Optima Life Sciences Limited, which is controlled by Pillar Investment Ltd., purchased 5,500,381 shares of common stock and warrants to purchase 1,650,114 additional shares of common stock in the private placement.

Drs. James Wyngaarden and Paul Zamecnik, Chairman of the Board of Directors and a director of the Company, respectively, participated in the August 2003 private placement offering under the same terms as other investors. Dr. Wyngaarden purchased 34,246 shares of common stock and warrants to purchase 10,274 shares of common stock at an exercise price of $1.00 per share; Dr. Zamecnik purchased 68,493 shares of common stock and warrants to purchase 20,548 shares of common stock at an exercise price of $1.00 per share.

In addition to the fees described above, the Company also paid other directors consulting fees of $35,875, $65,000 and $20,000 in 2004, 2003 and 2002, respectively.

(e) Contingencies

In the fourth quarter of 2002, the United States Patent and Trademark Office (the PTO) declared an interference involving a patent application exclusively licensed by the Company from the University of Massachusetts Medical Center, or UMMC (formerly the Worcester Foundation for Biological Research), and three patents issued to the National Institutes of Health. An interference proceeding is a proceeding to determine who was the first to invent and thus who is entitled to patent a claimed invention. The PTO's initial declaration of interference named UMMC, and indirectly the Company, as the senior party. In the fourth quarter of 2004, the PTO redeclared and restyled the interference subsequently naming UMMC, and indirectly the Company, as the junior party in the interference. See Note 16.

On July 8, 2003, the PTO declared a second interference between another patent exclusively licensed to the Company from UMMC and a patent application assigned jointly to the University of Montreal and Massachusetts Institute of Technology. The PTO's declaration of interference in the second proceeding named UMMC, and indirectly the Company, as the junior party. Under the terms of the license agreement with UMMC, the Company is responsible for the prosecution and maintenance of the patents and patent

applications at issue and is acting on behalf of UMMC in connection with the interference proceedings. Based upon priority of filing, the PTO issued judgment against UMMC, and indirectly the Company. As a result, UMMC, and indirectly the Company, are not entitled to certain claims of the UMMC patent involved.

The Company is not practicing nor does it intend to practice any of the intellectual property involved in either interference. Consequently, if the remaining matter is not resolved in a way beneficial to the Company, the Company does not believe that it will have a negative impact on the Company's business. If UMMC is successful in the patent interferences, the Company may be entitled to a portion of any sublicense income resulting from the patents that are the subject of the interferences.

(9) Income Taxes

The Company applies SFAS No. 109, *Accounting for Income Taxes.* Accordingly, a deferred tax asset or liability is determined based on the difference between the financial statement and tax basis of assets and liabilities, as measured by the enacted tax rates expected to be in effect when these differences reverse. At December 31, 2004, the Company had cumulative net operating loss and tax credit carryforwards for federal income tax purposes of approximately $254.9 million and $4.6 million, respectively, available to reduce federal taxable income and federal income taxes, respectively. These carryforwards expire through 2024. The Tax Reform Act of 1986 contains provisions which limit the amount of net operating loss and credit carryforwards that companies may utilize in any one year in the event of cumulative changes in ownership over a three-year period in excess of 50%. The Company has completed several financings since the effective date of the Tax Reform Act of 1986, which as of December 31, 2004, have resulted in ownership changes in excess of 50%, as defined under the Act and which will limit the Company's ability to utilize its net operating loss and tax credit carryforwards. The Company has not prepared an analysis to determine the effect of the ownership change limitation on its ability to utilize its net operating loss and tax credit carryforwards. Ownership changes in future periods may place additional limits on the Company's ability to utilize net operating loss and tax credit carryforwards.

As of December 31, 2004 and 2003, the components of the deferred tax assets are approximately as follows:

	2004	2003
Operating loss carryforwards	$ 101,946,064	$ 97,330,439
Tax credit carryforwards	4,603,431	4,362,658
Other	679,106	692,546
	107,228,601	102,385,643
Valuation allowance	(107,228,601)	(102,385,643)
	$ —	$ —

The Company has provided a valuation allowance for its deferred tax asset due to the uncertainty surrounding the ability to realize this asset. During 2001, the Company accrued $500,000 for Alternative Minimum Tax (AMT) of which $450,000 was paid prior to December 31, 2001. The National Economic Stabilization and Recovery Act, enacted in March 2002, has temporarily rescinded the AMT as it applies to the Company. The Company received a $450,000 refund and recognized a $500,000 credit to operations during 2002 in accordance with SFAS No. 109, *Accounting for Income Taxes.*

(10) Employee Benefit Plan

The Company has an employee benefit plan under Section 401(k) of the Internal Revenue Code. The plan allows employees to make contributions up to a specified percentage of their compensation. Under the plan, the Company may, but is not obligated to, match a portion of the employees' contributions up to a defined maximum. The Company is currently contributing up to 3% of employee base salary, by matching 50% of the first 6% of annual base salary contributed by each employee. Approximately $82,000, $74,000, and $58,000 of 401(k) benefits were charged to continuing operations during 2004, 2003, and 2002, respectively.

(11) Income (Loss) Per Share

The following table sets forth the computation of basic and diluted (loss) income per share:

	Years Ended December 31,		
	2004	2003	2002
Numerator:			
(Loss) income from operations	$(12,734,950)	$(17,211,058)	$16,971,540
Accretion of preferred stock dividend	(2,675,995)	(5,528,856)	(4,246,282)
Numerator for basic (loss) income applicable to common shareholders	(15,410,945)	(22,739,914)	12,725,258
Effect of dilutive securities:			
Interest expense related to convertible debt	—	—	21,896
Numerator for diluted (loss) income applicable to common shareholders	$(15,410,945)	$(22,739,914)	$12,747,154
Denominator for basic (loss) income per share:			
Weighted average shares outstanding	98,913,927	51,053,415	46,879,232
Effect of dilutive securities:			
Common stock options and warrants	—	—	5,647,539
Convertible debt	—	—	457,644
Denominator for diluted (loss) income per share	98,913,927	51,053,415	52,984,415
(Loss) income per share — basic			
(Loss) income from operations	$ (0.13)	$ (0.34)	$ 0.36
Accretion of preferred stock dividends	(0.03)	(0.11)	(0.09)
Net (loss) income per share applicable to common stockholders	$ (0.16)	$ (0.45)	$ 0.27
(Loss) income per share — diluted			
(Loss) income from operations	$ (0.13)	$ (0.34)	$ 0.32
Accretion of preferred stock dividends	(0.03)	(0.11)	(0.08)
Net (loss) income per share applicable to common stockholders	$ (0.16)	$ (0.45)	$ 0.24

For the years ended December 31, 2004 and 2003, diluted net loss per share from operations is the same as basic net loss per common share, as the effects of the Company's potential common stock equivalents are antidilutive. Total antidilutive securities were 32,091,596 and 39,545,229 at December 31, 2004 and 2003, respectively, and consist of stock options, warrants, and convertible preferred stock. Antidilutive securities for the year ended December 31, 2003 also includes convertible debt instruments (on an as-converted basis). As of December 31, 2002, 22,383,725 shares were not included in diluted net income per share as the effects of certain convertible debt, convertible preferred stock, warrants, and certain stock options are antidilutive.

(12) Supplemental Disclosure of Cash Flow Information

Supplemental disclosure of cash flow information for the periods presented are as follows:

	Years Ended December 31,		
	2004	2003	2002
Supplemental disclosure of cash flow information:			
Cash paid for interest	$ 58,770	$ 117,540	$ 121,278
Cash (received) paid for taxes	$ —	$ —	$ (450,000)
Supplemental disclosure of non cash financing and investing activities:			
Exchange of 8% convertible notes payable for common stock	$ —	$ —	$ 31,582
Accretion (reversal) of Series A preferred stock dividends	$ (569,497)	$3,972,856	$4,246,282
Dividend from induced conversion of Series A preferred stock	$3,245,492	$1,556,000	$ —
Issuance of stock options and stock for services	$ 129,448	$ 82,364	$ —
Interest paid in kind on 8% Notes	$ —	$ —	$ 27,657
Conversion of Series A preferred stock into common stock	$ 14,370	$ 6,878	$ 92
Issuance of warrants in connection with consulting services	$ —	$ —	$ 98,000
Cashless exercise of stock warrants	$ 7	$ 19	$ 247
Deferred compensation relating to issuance of stock options	$ —	$ —	$ 6,150
Equipment acquired under capital lease	$ —	$ —	$ 113,303

(13) Shareholder Rights Plan

The Company adopted a shareholder rights plan in December 2001. Under the rights plan, one right was distributed as of the close of business on January 7, 2002 on each then outstanding share of the Company's common stock. The rights will automatically trade with the underlying common stock and ordinarily will not be exercisable. The rights will only become exercisable if a person acquires beneficial ownership of, or commences a tender offer for, fifteen percent or more of the Company's common stock, unless, in either case, the transaction was approved by the Company's board of directors.

If the rights become exercisable, the type and amount of securities receivable upon exercise of the rights would depend on the circumstances at the time of exercise. Initially, each right would entitle the holder to purchase one one-thousandth of a share of the Company's newly created Series C junior participating preferred stock for an exercise price of $13.00. If a person acquires fifteen percent or more of the Company's common stock in a transaction that was not approved by the Company's board of directors, then each right, other than those owned by the acquiring person, would instead entitle the holder to purchase $26.00 worth of the Company's common stock for the $13.00 exercise price. If the Company is involved in a merger or other transaction with another company in which the Company is not the surviving corporation, or transfers more than 50% of its assets to another company, in a transaction that was not approved by the Company's board of directors, then each right, other than those owned by the acquiring person, would instead entitle the holder to purchase $26.00 worth of the acquiring company's common stock for the $13.00 exercise price.

The Company's board of directors may redeem the rights for $0.001 per right at any time until ten business days after a person acquires fifteen percent or more of the Company's outstanding common stock. Unless the rights are redeemed or exchanged earlier, they will expire on December 10, 2011.

(14) Repurchase of Common Shares

On February 14, 2003, the Company repurchased 4,643,034 shares of its common stock at a price of $1.15 per share. The fair market value of the common stock was $0.75 per share on the date of the transaction

resulting in a premium of approximately $1,857,000 in the aggregate. The Company charged this premium to general and administrative expense in 2003. The repurchased stock was retired on March 13, 2003.

(15) Financing

In August 2004, the Company raised approximately $5.1 million in gross proceeds from a private placement to institutional and overseas investors. In the private placement, the Company sold 8,823,400 shares of common stock and warrants to purchase 1,764,680 shares of common stock. The warrants to purchase common stock have an exercise price of $0.67 per share and will expire if not exercised on or prior to August 27, 2009. The warrants may be exercised by cash payment only. On or after February 27, 2005, the Company may redeem the warrants if the closing sales price of the common stock for each day of any 20 consecutive trading day period is greater than or equal to $1.34 per share. The redemption price will be $0.01 per share of common stock underlying the warrants. The Company may exercise its right to redeem the warrants by providing 30 days prior written notice to the holders of the warrants. The net proceeds to the Company from the offering, excluding the proceeds of any future exercise of the warrants, totaled approximately $4.7 million.

In April 2004, the Company raised approximately $11.8 million in gross proceeds through a registered direct offering. In the offering, the Company sold 16,899,800 shares of common stock and warrants to purchase 3,041,964 shares of common stock to institutional and other investors. The warrants to purchase common stock have an exercise price of $1.14 per share and are exercisable at any time on or after October 21, 2004 and on or prior to April 20, 2009. The warrants may be exercised by cash payment only. On or after October 21, 2005, the Company may redeem the warrants if the closing sales price of the common stock for each day of any 20 consecutive trading day period within 30 days prior to providing advance notice of redemption is greater than or equal to $2.60 per share. The redemption price will be $0.01 per share of common stock underlying the warrants. The Company may exercise its right to redeem the warrants by providing 30 days prior written notice to the holders of the warrants. The net proceeds to the Company from the offering, excluding the proceeds of any future exercise of the warrants, totaled approximately $10.7 million.

In August 2003, the Company raised approximately $14.6 million in gross proceeds from a private placement to institutional and accredited investors. In the private placement, the Company sold 20,053,022 shares of common stock and warrants to purchase 6,015,934 shares of common stock. The warrants to purchase common stock have an exercise price of $1.00 per share and will expire if not exercised by August 28, 2008. The warrants may be exercised by paying cash or by invoking a cashless exercise feature. The Company may redeem the warrants at a price of $0.05 per share of common stock issuable upon exercise of the warrants if the average closing sales price of the common stock for a ten consecutive trading day period is greater than or equal to $2.00 per share. The net proceeds to the Company from the offering, excluding the proceeds of any future exercise of the warrants, totaled approximately $13.1 million. In addition, the Company issued warrants to selected dealers and placement agents which assisted with the private placement. These include warrants to purchase 2,458,405 shares of common stock at an exercise price of $0.73 per share and warrants to purchase 1,325,342 shares of common stock at an exercise price of $1.00 per share. These warrants have a Black-Scholes value of $2.8 million and will expire if not exercised by August 28, 2008. These warrants may be exercised by paying cash or through a cashless exercise feature. The Company does not have the right to redeem these warrants.

(16) Subsequent Event

On January 15, 2005, the Company and UMMC entered into an Interference Settlement Agreement with the NIH with respect to the interference proceeding discussed in the first paragraph of Note 8(e). The agreement is subject to approval of the Board of Patent Appeals and Interferences.

Exhibit Index

Exhibit Number	Description	Filed with this Form 10-K	Incorporated by Reference		
			Form or Schedule	Filing Date with SEC	SEC File Number
3.1	Restated Certificate of Incorporation of Hybridon, Inc., as amended.	X			
3.2	Amended and Restated Bylaws of Hybridon, Inc.		S-1	November 6, 1995	33-99024
4.1	Specimen Certificate for shares of Common Stock, $.001 par value, of Hybridon, Inc.		S-1	December 8, 1995	33-99024
4.2	Indenture dated as of March 26, 1997 between Forum Capital Markets LLC and Hybridon, Inc.		8-K	April 14, 1997	000-27352
4.3	Rights Agreement dated December 10, 2001 by and between Hybridon, Inc. and Mellon Investor Services LLC, as rights agent, as amended.		S-2	October 10, 2003	333-109630
10.1†	License Agreement dated February 21, 1990 and restated as of September 8, 1993 between Hybridon, Inc. and University of Massachusetts Medical Center.		S-1	November 6, 1995	33-99024
10.2†	Patent License Agreement effective as of October 13, 1994 between Hybridon, Inc. and McGill University.		S-1	November 6, 1995	33-99024
10.3†	License Agreement effective as of October 25, 1995 between Hybridon, Inc. and the General Hospital Corporation.		S-1	November 6, 1995	33-99024
10.4†	License Agreement dated as of October 30, 1995 between Hybridon, Inc. and Yoon S. Cho-Chung.		S-1	November 6, 1995	33-99024
10.5	Registration Rights Agreement dated as of February 21, 1990 between Hybridon, Inc., University of Massachusetts Medical Center and Paul C. Zamecnik.		S-1	November 6, 1995	33-99024
10.6††	1990 Stock Option Plan, as amended.		S-1	November 6, 1995	33-99024
10.7††	1995 Stock Option Plan.		S-1	November 6, 1995	33-99024
10.8††	1995 Director Stock Plan.		S-1	November 6, 1995	33-99024
10.9††	1995 Employee Stock Purchase Plan.		S-1	November 6, 1995	33-99024

Exhibit Number	Description	Filed with this Form 10-K	Incorporated by Reference		
			Form or Schedule	Filing Date with SEC	SEC File Number
10.10††	Employment Agreement dated April 1, 2002 between Hybridon, Inc. and Dr. Sudhir Agrawal.		10-Q	May 14, 2002	000-27352
10.11††	Consulting Agreement dated as of March 1, 2003 between Hybridon, Inc. and Dr. Paul C. Zamecnik.		10-K	March 31, 2003	000-27352
10.12†	Amendment No. 1 to License Agreement, dated as of February 21, 1990 and restated as of September 8, 1993, by and between University of Massachusetts Medical Center and Hybridon, Inc., dated as of November 26, 1996.		10-Q	August 14, 1997	000-27352
10.13†	Licensing Agreement dated March 12, 1999 by and between Hybridon, Inc. and Integrated DNA Technologies, Inc.		10-K	April 15, 1999	000-27352
10.14†	Licensing Agreement dated September 7, 1999 by and between Hybridon, Inc. and Genzyme Corporation.		10-Q	November 15, 1999	000-27352
10.15	License Agreement dated September 20, 2000 by and between Hybridon and Boston Biosystems, Inc.		S-1/A	December 29, 2000	333-69649
10.16	Assignment of Coexclusive License dated September 20, 2000 by and between Hybridon and the Public Health Service.		S-1/A	December 29, 2000	333-69649
10.17	Oligonucleotide Purification Patent License Agreement dated September 20, 2000 by and between Hybridon and Boston Biosystems, Inc.		S-1/A	December 29, 2000	333-69649
10.18	Asset Purchase Agreement dated June 29, 2000 by and between Hybridon and Boston Biosystems, Inc.		Schedule 14A	August 15, 2000	000-27352
10.19†	Assignment of Patent Rights dated September 20, 2000 by and between Hybridon and Boston Biosystems, Inc.		S-1/A	December 29, 2000	333-69649
10.20†	PNT Monomer Patent License and Option Agreement dated September 20, 2000 by and between Hybridon and Boston Biosystems, Inc.		S-1/A	December 29, 2000	333-69649

Exhibit Number	Description	Filed with this Form 10-K	Incorporated by Reference		
			Form or Schedule	Filing Date with SEC	SEC File Number
10.21†	Agreement Relating to Patents Forming Part of Acquired Assets but to be Licensed Back to Hybridon for the Purposes of OriGenix Agreements dated September 20, 2000 by and between Hybridon and Boston Biosystems, Inc.		S-1/A	December 29, 2000	333-69649
10.22	Agreement and Mutual Release between Hybridon and MethylGene, Inc. dated March 21, 2001.		10-K	April 13, 2001	000-27352
10.23††	Amended and Restated 1997 Stock Incentive Plan.		10-Q	May 15, 2001	000-27352
10.24†	Collaboration and License Agreement by and between Isis Pharmaceuticals, Inc., and Hybridon, Inc., dated May 24, 2001.		10-Q	August 20, 2001	000-27352
10.25	Amendment No. 1 to the Collaboration and License Agreement, dated as of May 24, 2001 by and between Isis Pharmaceuticals, Inc. and Hybridon, Inc., dated as of August 14, 2002.		10-K	March 31, 2003	000-27352
10.26	Master Agreement relating to the Cross License of Certain Intellectual Property and Collaboration by and between Isis Pharmaceuticals, Inc. and Hybridon, Inc., dated May 24, 2001.		10-Q	August 20, 2001	000-27352
10.27††	Employment Agreement by and between Stephen R. Seiler and Hybridon, Inc. effective as of July 25, 2001.		10-Q	November 14, 2001	000-27352
10.28††	Amendment to Employment Agreement, dated August 20, 2004, by and between Hybridon, Inc. and Stephen R. Seiler.		10-Q	November 12, 2004	001-31918
10.29	Unit Purchase Agreement by and among Hybridon, Inc. and certain persons and entities listed therein, dated April 1, 1998.		10-K	April 1, 2002	000-27352
10.30††	Employment Agreement dated April 1, 2002 between Hybridon, Inc. and Robert G. Andersen.		10-Q	May 14, 2002	000-27352

Exhibit Number	Description	Filed with this Form 10-K	Incorporated by Reference		
			Form or Schedule	Filing Date with SEC	SEC File Number
10.31††	Executive Stock Option Agreement for 3,150,000 Options effective as of July 25, 2001 between Hybridon, Inc. and Stephen R. Seiler.		10-Q	August 14, 2002	000-27352
10.32††	Executive Stock Option Agreement for 490,000 Options effective as of July 25, 2001 between Hybridon, Inc. and Stephen R. Seiler.		10-Q	August 14, 2002	000-27352
10.33††	Executive Stock Option Agreement for 1,260,000 Options effective as of July 25, 2001 between Hybridon, Inc. and Dr. Sudhir Agrawal.		10-Q	October 24, 2002	000-27352
10.34††	Executive Stock Option Agreement for 550,000 Options effective as of July 25, 2001 between Hybridon, Inc. and Dr. Sudhir Agrawal.		10-Q	October 24, 2002	000-27352
10.35††	Executive Stock Option Agreement for 500,000 Options effective as of July 25, 2001 between Hybridon, Inc. and Dr. Sudhir Agrawal.		10-Q	October 24, 2002	000-27352
10.36	Consulting Agreement effective as of October 1, 2002 between Hybridon, Inc. and Pillar, S.A.		10-Q	October 24, 2002	000-27352
10.37†	License Agreement by and between Louisiana State University and Hybridon, Inc., dated July 1, 1998.		10-K	March 31, 2003	000-27352
10.38	Engagement Letter, dated as of April 18, 2003, by and among Hybridon, Inc., Pillar Investment Limited and PrimeCorp Finance S.A.		S-2	October 10, 2003	333-109630
10.39	Registration Rights Agreement, dated as of August 28, 2003 by and among Hybridon, Inc., the Purchasers and the Agents.		S-2	October 10, 2003	333-109630
10.40	Form of Common Stock Purchase Warrant issued to purchasers of units in a private placement on August 28, 2003 and August 29, 2003.		S-2	October 10, 2003	333-109630
10.41	Form of Common Stock Purchase Warrant issued to selected dealers and placement agents on August 28, 2003 in connection with a private placement.		S-2	October 10, 2003	333-109630
10.42	Engagement Letter, dated as of August 27, 2004, by and among Hybridon, Inc. and Pillar Investment Limited.		10-Q	November 12, 2004	001-31918

Exhibit Number	Description	Filed with this Form 10-K	Incorporated by Reference		
			Form or Schedule	Filing Date with SEC	SEC File Number
10.43	Registration Rights Agreement, dated August 27, 2004 by and among Hybridon, Inc., Pillar Investments Limited and Purchasers.		10-Q	November 12, 2004	001-31918
10.44	Form of Warrants issued to investors and the placement agent in connection with Hybridon's August 27, 2004 financing.		10-Q	November 12, 2004	001-31918
10.45	Amendment to the License Agreement dated as of October 30, 1995 by and between Hybridon, Inc. and Yoon S. Cho-Chung, M.D., Ph.D. dated February 4, 2005.	X			
10.46	Summary of Director Compensation of Hybridon, Inc.	X			
10.47	Non-Employee Director Nonstatutory Stock Option Agreement Granted under 1997 Stock Incentive Plan	X			
23.1	Consent of Independent Registered Public Accounting Firm.	X			
31.1	Certification of Chief Executive Officer pursuant to Exchange Act Rules 13a-14 and 15d-14, as adopted pursuant to Section 302 of Sarbanes-Oxley Act of 2002.	X			
31.2	Certification of Chief Financial Officer pursuant to Exchange Act Rules 13a-14 and 15d-14, as adopted pursuant to Section 302 of Sarbanes-Oxley Act of 2002.	X			
32.1	Certification of Chief Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.	X			
32.2	Certification of Chief Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002.	X			

† Confidential treatment granted as to certain portions, which portions are omitted and filed separately with the Commission.

†† Management contract or compensatory plan or arrangement required to be filed as an Exhibit to the Annual Report on Form 10-K.

Exhibit 31.1

Certification of Chief Executive Officer pursuant to Exchange Act Rules 13a-14 and 15d-14, as adopted pursuant to Section 302 of Sarbanes-Oxley Act of 2002

I, Sudhir Agrawal, certify that:

1. I have reviewed this Annual Report on Form 10-K of Hybridon, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) [Not Applicable]

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

/s/ SUDHIR AGRAWAL

Sudhir Agrawal
Chief Executive Officer

Dated: March 15, 2005

Exhibit 31.2

Certification of Chief Financial Officer pursuant to Exchange Act Rules 13a-14 and 15d-14, as adopted pursuant to Section 302 of Sarbanes-Oxley Act of 2002

I, Robert G. Andersen certify that:

1. I have reviewed this Annual Report on Form 10-K of Hybridon, Inc.;

2. Based on my knowledge, this report does not contain any untrue statement of a material fact or omit to state a material fact necessary to make the statements made, in light of the circumstances under which such statements were made, not misleading with respect to the period covered by this report;

3. Based on my knowledge, the financial statements, and other financial information included in this report, fairly present in all material respects the financial condition, results of operations and cash flows of the registrant as of, and for, the periods presented in this report;

4. The registrant's other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-15(e) and 15d-15(e)) for the registrant and have:

a) Designed such disclosure controls and procedures, or caused such disclosure controls and procedures to be designed under our supervision, to ensure that material information relating to the registrant, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this report is being prepared;

b) [Not Applicable]

c) Evaluated the effectiveness of the registrant's disclosure controls and procedures and presented in this report our conclusions about the effectiveness of the disclosure controls and procedures, as of the end of the period covered by this report based on such evaluation; and

d) Disclosed in this report any change in the registrant's internal control over financial reporting that occurred during the registrant's most recent fiscal quarter (the registrant's fourth fiscal quarter in the case of an annual report) that has materially affected, or is reasonably likely to materially affect, the registrant's internal control over financial reporting; and

5. The registrant's other certifying officer and I have disclosed, based on our most recent evaluation of internal control over financial reporting, to the registrant's auditors and the audit committee of the registrant's board of directors (or persons performing the equivalent functions):

a) All significant deficiencies and material weaknesses in the design or operation of internal control over financial reporting which are reasonably likely to adversely affect the registrant's ability to record, process, summarize and report financial information; and

b) Any fraud, whether or not material, that involves management or other employees who have a significant role in the registrant's internal control over financial reporting.

/s/ ROBERT G. ANDERSEN

Robert G. Andersen
Chief Financial Officer

Dated: March 15, 2005

Exhibit 32.1

Certification of Chief Executive Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002

In connection with the Annual Report on Form 10-K of Hybridon, Inc. (the "Company") for the year ended December 31, 2004 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Sudhir Agrawal, Chief Executive Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, that:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

A signed original of this written statement has been provided to Hybridon, Inc. and will be retained by Hybridon, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.

/s/ SUDHIR AGRAWAL

Sudhir Agrawal
Chief Executive Officer

Date: March 15, 2005

Exhibit 32.2

Certification of Chief Financial Officer pursuant to 18 U.S.C. Section 1350, as adopted pursuant to Section 906 of the Sarbanes-Oxley Act of 2002

In connection with the Annual Report on Form 10-K of Hybridon, Inc. (the "Company") for the year ended December 31, 2004 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Robert G. Andersen, Chief Financial Officer of the Company, hereby certifies, pursuant to 18 U.S.C. Section 1350, that:

(1) the Report fully complies with the requirements of Section 13(a) or 15(d) of the Securities Exchange Act of 1934; and

(2) the information contained in the Report fairly presents, in all material respects, the financial condition and results of operations of the Company.

A signed original of this written statement has been provided to Hybridon, Inc. and will be retained by Hybridon, Inc. and furnished to the Securities and Exchange Commission or its staff upon request.

/s/ ROBERT G. ANDERSEN

Robert G. Andersen
Chief Financial Officer

Date: March 15, 2005

BOARD OF DIRECTORS

James B. Wyngaarden, M.D.
Chairman, Hybridon, Inc.
Former Director, Human Genome Organization
Former Director, National Institutes of Health

Yousef El Zein
Vice Chairman, Hybridon, Inc.
Chairman and Chief Executive Officer, Pillar, S.A.

Mohit Agrawal, D. Phil.
President, Chief Executive Officer and
Chief Scientific Officer
Hybridon, Inc.

Keith Hartley
President
Hartley Capital Advisors

William S. Reardon, CPA
Retired Audit Partner
PricewaterhouseCoopers, LLP

Alison Taunton-Rigby, Ph.D., O.B.E.
Founder, President, Chief Executive Officer and Director
BioNovix, Inc.

Paul C. Zamecnik, M.D.
Professor of Oncologic Medicine Emeritus
Harvard Medical School
Senior Scientist
Massachusetts General Hospital

MANAGEMENT & KEY EMPLOYEES

Mohit Agrawal, D. Phil.
President, Chief Executive Officer and
Chief Scientific Officer

Robert G. Andersen
Chief Financial Officer,
Vice President - Operations,
Treasurer and Secretary

Timothy M. Sullivan
Vice President, Development Programs

Kambhar R. Kandimalla, Ph.D.
Senior Director, Research

Erik Whalen
Controller

STOCKHOLDERS' MEETING

The 2005 Annual Meeting of Stockholders will be held at the American Stock Exchange, 86 Trinity Place, NY, NY on June 15, 2005 at 10:00 a.m. A notice of the meeting, proxy statement and proxy voting card, have been mailed to stockholders with this Annual Report.

INVESTOR RELATIONS

Additional copies of this Annual Report, including the Company's Annual Report on Form 10-K for the year ended December 31, 2004, as filed with the Securities and Exchange Commission, are available upon request to:

Investor Relations
Hybridon, Inc.
345 Vassar Street
Cambridge, MA 02139
Company information is available at:
www.hybridon.com or (617) 679 5500

TRANSFER AGENT & REGISTRAR

Mellon Investor Services LLC
Overpeck Centre
85 Challenger Road
Ridgefield Park, NJ 07660-2108
www.melloninvestor.com
(800) 288 9541

OUTSIDE LEGAL COUNSEL

Wilmer Cutler Pickering Hale and Dorr, LLP
60 State Street
Boston, MA 02109

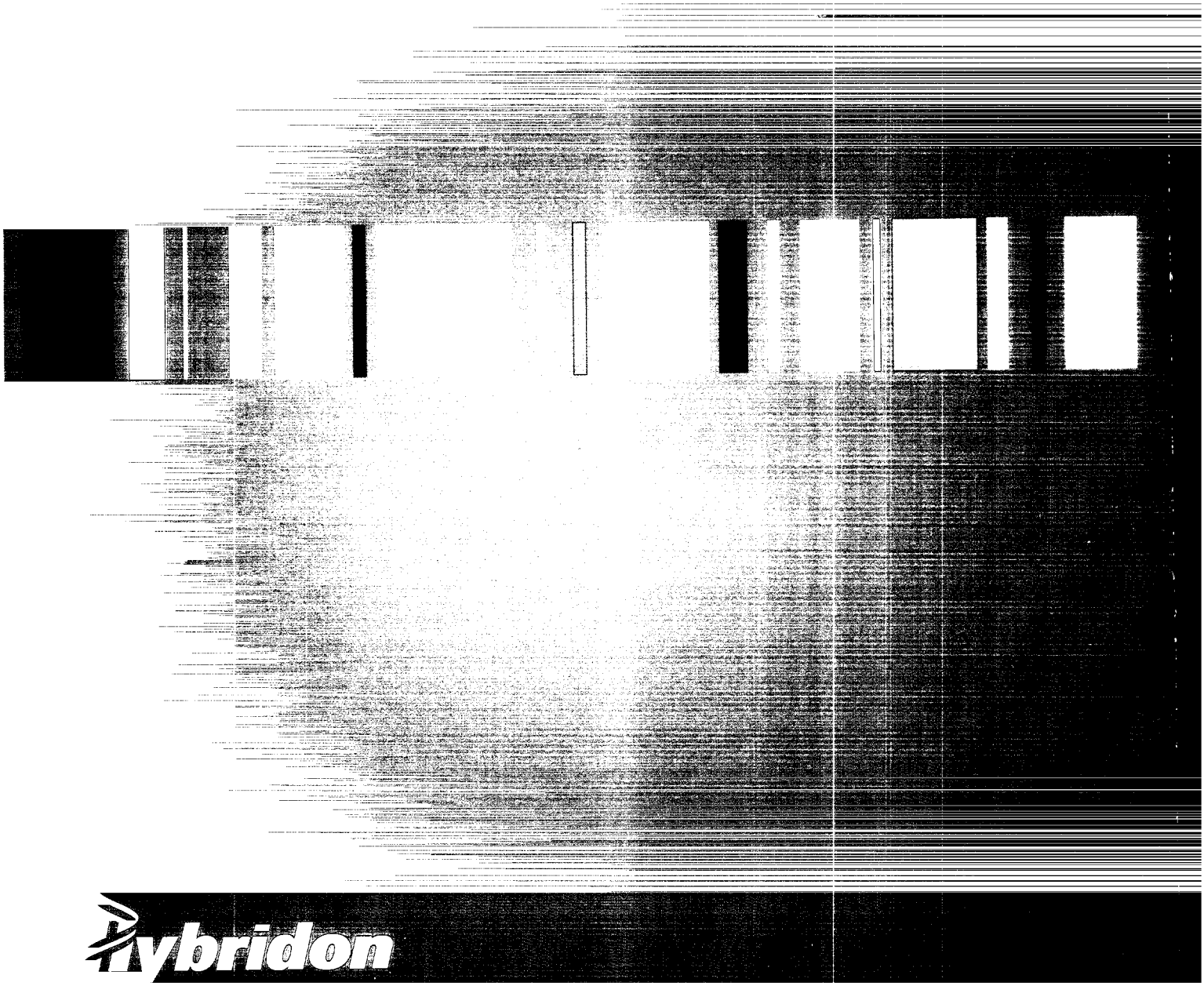
INDEPENDENT AUDITORS

Ernst & Young, LLP
200 Clarendon Street
Boston, MA 02116

COMMON STOCK SYMBOL

AMEX: HBY

Any statements that we may make in this annual report about future expectations, plans and prospects for the Company constitute forward-looking statements for purposes of the safe harbor provisions under The Private Securities Litigation Reform Act of 1995. Actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors, including the risks set forth under the caption "Risk Factors" in Hybridon's Annual Report on Form 10-K for the year ended December 31, 2004. Hybridon disclaims any intention or obligation to update any forward-looking statements.



Hybridon

Hybridon, Inc.
345 Vassar Street
Cambridge, MA 02139
Company information is available at:
www.hybridon.com or (617) 679 5500