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, 2003

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	**02139**
Cambridge, Massachusetts	**(Zip Code)**
(Address of principal executive offices)	

(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 $33,159,937 as of June 30, 2003. As of March 15, 2004, the registrant had 85,018,496 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 17, 2004	Items 10, 11, 12, 13 and 14 of Part III

FORM 10-K

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Hybridon® and GEM® are our registered trademarks. Amplivax™, CpR™, Cyclicon™, IMO™, IMOxine™, YpG™, and YpR™ are also our trademarks. Other trademarks appearing in this annual report are the property of their respective owners.

PART I.

Item 1. *Business*

Overview

We are engaged in the discovery and development of novel therapeutics using synthetic DNA. Our activities are primarily based on two technology platforms:

- Our immunomodulatory oligonucleotide, or IMO, technology modulates responses of the immune system using synthetic DNA containing specific sequences that mimic bacterial DNA.

- Our antisense technology uses synthetic DNA to block the production of disease causing proteins at the cellular level.

Drug Development Strategy

In the near term, we are focusing our internal drug development efforts on developing the two lead drug candidates in our pipeline, HYB2055 and GEM231.

- HYB2055 is the lead clinical drug candidate in our IMO program. We are developing HYB2055 for oncology applications under the name IMOxine. In May 2003, we commenced a phase 1 clinical trial of IMOxine in the United States in patients with refractory solid tumor cancers. If this trial is completed when anticipated and the results are favorable, we plan to commence a phase 2 clinical trial of IMOxine in the second or third quarter of 2004. The phase 2 clinical trial of IMOxine and any future trials of IMOxine may involve the evaluation of IMOxine as a monotherapy for the treatment of solid tumor cancer and/or in combination with other anticancer agents, including chemotherapeutics, antibodies, and vaccines/antigens.

In March 2003, we commenced a phase 1 clinical trial of HYB2055 in the United Kingdom in 28 healthy volunteers, which we completed during the third quarter of 2003. The goal of this trial was to study the safety and immunological activity of HYB2055 over a broad range of dosing levels. In the trial, HYB2055 was well tolerated by the volunteers, who did not experience any significant treatment-related adverse effects. In addition, in the trial HYB2055 demonstrated biological activity in the volunteers, including transient activation of lymph nodes and effects on immune cells in the blood.

We are also developing HYB2055 for use as an adjuvant for vaccines and monoclonal antibodies. We are developing HYB2055 under the name Amplivax for these applications. In October 2003, we licensed Amplivax to another company for use in its development of a potential therapeutic and prophylactic vaccine for HIV infection. We anticipate that this company will initiate a phase 1 clinical trial of the vaccine during the first half of 2004. We plan to seek additional licensees for Amplivax in the future.

- GEM231 is a 2nd generation antisense compound for treating solid tumor cancers. GEM231 is designed to inhibit Protein Kinase A, or PKA, a protein which has been shown to be present at increased levels in the cells of many human cancers. We are currently conducting 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®. If the pharmacokinetic data and other findings from this phase 1/2 clinical trial are favorable, we plan to commence a phase 2 clinical trial of this drug combination in the second half of 2004.

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. We also believe that our antisense technology may prove useful to pharmaceutical and biotechnology companies that are seeking to

collaborate on the development of antisense drug candidates that down-regulate gene targets discovered by, or proprietary to, such companies. We have already entered into six collaboration and licensing agreements for our antisense technology and one for our IMO technology. We are seeking to enter into additional agreements for both our IMO and 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 — 2nd generation IMO (HYB2055)	Cancer	phase 1
Amplivax[1] — 2nd generation IMO (HYB2055) being used as an adjuvant in combination with REMUNE®, an immune-based HIV therapeutic vaccine, in the development of a vaccine candidate	HIV	preclinical lead candidate
Antisense		
GEM231 — 2nd generation antisense drug candidate targeted to PKA	Cancer	phase 1/2
GEM92 — 2nd generation antisense drug candidate targeted to a specific region of HIV-1	HIV	phase 1
MBI 1121[2] — 2nd generation antisense drug candidate targeted to human papillomavirus, an infectious disease	Human Papillomavirus	phase 1
GEM640 (AEG35156)[3] — 2nd generation antisense drug candidate targeted to the XIAP gene, a gene which has been implicated in the resistance of cancer cells to chemotherapy	Cancer	preclinical lead candidate
GEM220 — 2nd generation antisense drug candidate targeted to VEGF, a growth factor that contributes to the growth of new blood vessels	Cancer	preclinical lead candidate
GEM240 — 2nd generation antisense compound targeted to Mdm2, a protein found in increased levels in many human cancers	Cancer	preclinical lead candidate

1. Being developed by The Immune Response Corporation in collaboration with us.

2. Being developed by Micrologix Biotech, Inc. in collaboration with us.

3. Being developed by Aegera Therapeutics, Inc. in collaboration with us.

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 2nd generation IMO compounds, may offer a number of potential advantages over earlier immunostimulatory oligonucleotides.

We are designing our IMO compounds to be used as monotherapies in the treatment of conditions such as cancer, infectious diseases and allergic asthma and other allergies, as well as in combination therapies with chemotherapeutics, 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. 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 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 on the surface or inside of 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 lead 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 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, this response is notoriously weak. The benefits of immunostimulation by bacterial DNA in cancer patients have been long recognized. We believe IMO compounds may strengthen the immune response to cancer cells. In preclinical studies in animals, IMO compounds have been shown to delay and suppress tumor growth.

- *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. 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 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.

- *Combinations with Vaccines and Antibody Therapies.* In preclinical studies in mice, the immune response triggered by IMO compounds increased the production of specific antibodies. As a result, we believe that IMO compounds have the potential to be used in combination with, or as an adjuvant to, vaccines or antibody therapies.

IMO Chemistry

Based on our over ten years of expertise in synthetic oligonucleotide chemistry, we have developed a portfolio of IMO compounds containing different proprietary synthetic motifs and different site-specific sequences. In our preclinical studies and initial clinical trials of our IMO compounds, 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 can create IMO compounds which are optimized for the treatment of different diseases.

HYB2055 Drug Discovery and Development

HYB2055 is the lead clinical candidate in our IMO program. 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 are developing HYB2055 for oncology applications under the name IMOxine. We filed an Investigational New Drug Application, or IND, for HYB2055 with the FDA which became effective March 6, 2003. In May 2003, we commenced a phase 1 clinical trial of IMOxine in the United States designed to evaluate HYB2055 initially in up to 24 patients with refractory solid tumor cancers. This trial is being conducted at the Lombardi Comprehensive Cancer Center at Georgetown University Medical Center. We expect to complete enrollment of our 24th patient in this trial in April 2004 and may enroll additional patients to expand further our understanding of this drug candidate.

In November 2003, we presented at a scientific conference preliminary results from the phase 1 IMOxine trial based on data available as of October 2003. As of October 2003, we had administered HYB2055 to 14 patients in the trial. IMOxine was well tolerated in all of these patients with injection site reactions, fatigue and fever being the most frequently reported adverse events. In addition, in five of the first eight patients evaluated for disease status eight weeks after the first treatment and one of the first three patients evaluated for disease status 16 weeks after the first treatment, the disease had not progressed. If the results of this trial continue to be favorable and this trial is completed when anticipated, we plan to commence a phase 2 clinical trial of IMOxine in the second or third quarter of 2004. The phase 2 clinical trial of IMOxine and any future trials of IMOxine may involve the evaluation of IMOxine as a monotherapy for the treatment of solid tumor cancer and/or in combination with other anticancer agents, including chemotherapeutics, antibodies, and vaccines/antigens.

In March 2003, we commenced a phase 1 clinical trial of HYB2055 in the United Kingdom in 28 healthy volunteers, which we completed during the third quarter of 2003. The goal of this trial was to study the safety and immunological activity of HYB2055 over a broad range of dosing levels. In the trial, HYB2055 was well tolerated by the volunteers, who did not experience any significant treatment-related adverse effects. In addition, in the trial HYB2055 demonstrated biological activity in the volunteers, including transient activation of lymph nodes and effects on immune cells in the blood.

In addition to cancer applications, we are also developing HYB2055 for use as an adjuvant for vaccines and monoclonal antibodies. We are developing HYB2055 under the name Amplivax for these applications. In October 2003, we licensed Amplivax to The Immune Response Corporation for use in its development of a potential therapeutic and prophylactic vaccine for HIV infection. We anticipate that Immune Response will initiate a phase 1 clinical trial of this vaccine during the first half of 2004. We plan to seek additional licensees for Amplivax in the future.

We believe that HYB2055 may also have use as a monotherapy for treatment of infectious diseases, allergic asthma and other allergies. We intend to explore the potential of these uses either on our own, or with collaborators through submission of additional INDs.

Antisense Technology

Introduction

The heart, brain, liver and other organs in the human body function together to support life. Each cell within these organs produces proteins that affect how that cell functions within the organ, and ultimately how efficiently each organ functions within the body.

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 or mutant proteins or produces 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 by infection with a virus. 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. Most traditional drugs are designed to interact with and inhibit the function of protein molecules that are already present in the body and causing or supporting disease. In contrast, antisense technology involves the design of drugs to intervene at the earlier genetic level to inhibit production of disease-causing or disease-supporting proteins.

The full complement of human genes, known as the human genome, contains the information required to produce all human proteins. A copy of the complete human genome is present in each cell, and each cell makes proteins based on its copy of the genome. The information that controls a cell's production of a specific protein is contained in the gene relating to that protein. Each gene is made up of two intertwined strands of DNA that form a structure called a "double helix." Each strand of DNA consists of a string of individual DNA building blocks called nucleotides, arranged in a specific sequence. It is the sequence of nucleotides that contains genetic information. One of the paired strands of the double helix contains the information that directs the composition of a specific protein, and is called the "coding" strand. The other strand, the "non- coding" strand, contains a different but complementary sequence of nucleotides.

Cells make proteins in a two-stage process. First, the cell creates a molecule of messenger RNA 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 DNA in the double helix. This messenger RNA strand is called the "sense" sequence. In the next step, the cell produces proteins based on the information contained in the "sense" sequence.

Conventional Drugs

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, often with as few as two or three points of contact with the target molecule. Once the binding takes place, the disease-causing activity of the target molecule is interrupted.

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 drug interaction with molecules other than the target molecule. This lack of selectivity can result in unwanted side effects, potentially requiring lower doses of the drug, and thus, decreasing effectiveness.

Another characteristic of conventional drugs is that developing them is a time-consuming and expensive process. For every compound that is found to be effective and have tolerable side effects, thousands may be investigated and rejected. In the traditional drug discovery process, this may take many years and millions of dollars.

Antisense Drugs

A synthetic DNA molecule with a sequence exactly complementary to a portion of the sense sequence of the messenger RNA of a specific gene can bind to and inhibit the function of that messenger RNA. This exact complement of the sense messenger RNA sequence is referred to as an antisense sequence or antisense oligonucleotide. By inhibiting the function of the relevant messenger RNA, it is possible to decrease or eliminate the production of disease-causing or disease-supporting proteins. Moreover, the nucleotide sequence of an antisense synthetic DNA complementary to its target sequence on the messenger RNA can be designed in a manner such that the antisense synthetic DNA forms a large number of bonds at the target site, typically 30 or more, as compared to as few as two to three bonds for conventional drugs. This allows the oligonucleotide to form a strong bond with the messenger RNA.

Antisense drug development technology involves the design and synthesis of synthetic DNA to bind and inhibit the activity of messenger RNA which codes for the production of disease-associated proteins. 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. 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.

In recent years there has been a dramatic increase in the understanding of the role of genes in producing proteins associated with disease. This knowledge has come from many sources, including the human genome project and the work being done by academic institutions and pharmaceutical companies all over the world. As a consequence, we believe that the pharmaceutical industry is increasingly becoming an environment that is rich in potential gene-based drug targets and that the challenge for the future will be to create drugs effective against these newly discovered gene 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 and to improve the potential pharmaceutical effects of that synthetic DNA by chemical modification.

Hybridon Antisense Technology

We were founded in 1989 to exploit the pioneering work of Paul Zamecnik, M.D., a member of our board of directors, who is regarded by many as the father of antisense. Our initial efforts in the antisense field and the efforts of other companies in the area focused on the development of synthetic oligonucleotides with a DNA backbone that would withstand degradation by enzymes. A DNA backbone is the linkage between the sugars and the bases known as nucleosides that form a strand of DNA. Oligonucleotides which contain a natural backbone are not suitable for use as drugs because they are rapidly degraded by enzymes before they reach their intended target.

In order to increase the stability of oligonucleotides against these enzymes, we and other companies developed oligonucleotides which are chemically modified by replacing certain oxygen atoms on the backbone with sulfur atoms. We refer to oligonucleotides with this modification as 1st generation antisense compounds. To date, the FDA has approved only one 1st generation antisense compound, which one of our competitors in the antisense field developed and which is currently marketed by Novartis to treat a viral infection through local delivery. Another competitor has submitted an NDA for a 1st generation antisense drug for the treatment of cancer.

More recently, we have focused our research and development efforts on developing more advanced chemistries that enable us to alter the chemical makeup of the backbone of a synthetic DNA compound in a manner designed to improve upon the characteristics of the backbone of synthetic DNA developed using 1st generation antisense chemistry without adversely affecting the compound's ability to inhibit the production of disease-associated proteins. We refer to compounds with these advanced chemistries as 2nd generation antisense compounds.

Specifically, we have designed and created families of advanced synthetic DNA chemistries, including DNA/ RNA combinations, called hybrid or mixed backbone compounds. The results of our preclinical studies and our GEM231 clinical trials in over 80 patients suggest that by modifying the synthetic backbone of our antisense compounds with different combinations of our advanced chemistries, we can develop 2nd generation antisense compounds with improved properties. In particular, based on these preclinical studies and clinical trials, we believe that 2nd generation antisense compounds based on these advanced chemistries will show 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:

- fewer side effects;
- greater stability in the body, enabling patients to take doses less frequently;
- greater potency, permitting patients to take lower doses; and
- greater potential for multiple routes of administration, including by injection, orally or topically.

Antisense Drug Development and Discovery

Because antisense technology works at a genetic level, we believe that we can use this technology for functional genomics, drug discovery and validation of therapeutic drug targets. We believe that our antisense technology is potentially applicable to a wide variety of therapeutic indications, including cancer, viral and infectious disease, autoimmune and inflammatory disease, respiratory diseases, cardiovascular disease and diabetes because these diseases are often caused by the over-production of proteins which may be down regulated by antisense oligonucleotides. We are focusing our drug development and discovery efforts on developing 2nd generation antisense drugs for cancer and infectious diseases. We currently have two antisense compounds in the clinical phase of development and a number of other compounds in preclinical development.

Clinical Development

GEM231 for the Treatment of Cancer. GEM231 is our lead 2nd generation antisense compound for treating solid tumor cancers. 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, and high levels of PKA have been shown to correlate with unfavorable clinical outcomes in patients with breast, colon and ovarian cancers.

We are currently conducting a phase 1/2 clinical trial of GEM231 as a combination therapy with irinotecan, a marketed anticancer therapy. We chose to evaluate the combination of GEM231 and irinotecan based on promising preclinical data relating to this combination as a treatment of solid tumor cancers. Specifically, in xenograft models of several types of human cancer, GEM231 caused a pronounced potentiation of irinotecan anti-tumor activity. We are conducting the current phase 1/2 trial combining GEM231 and irinotecan at Vanderbilt University Medical Center and the University of Chicago Medical Center. In the clinical trial, we are evaluating the safety of GEM231 and irinotecan in combination and measuring the concentration of extracellular PKA, or ECPKA, in plasma as a potential biomarker for GEM231 antisense activity. A biomarker is a biological parameter monitored as a possible indicator of drug activity. In July 2003, we presented data from early patients in the trial indicating that ECPKA levels had been reduced during treatment in a statistically significant manner. We expect to complete enrollment of this combination treatment trial in the second quarter of 2004.

Prior to conducting the current phase 1/2 trial combining GEM231 and irinotecan, we conducted other phase 1 clinical trials of GEM231, both as a monotherapy and in combination with paclitaxel and docetaxel, two other marketed chemotherapeutics. We believe that our first phase 1 clinical trial of GEM231, which evaluated GEM231 as a monotherapy, involved the first systemic administration of a 2nd generation antisense compound to oncology patients. In these trials, we evaluated the safety of GEM231 as a monotherapy and of the combination of GEM231 and these chemotherapeutics in multiple doses in oncology patients, including the maximum tolerated dose of GEM231 for both single doses and multiple doses. In the trials of GEM231 as a monotherapy, GEM231 was generally well tolerated, with mild to moderate fatigue being the most frequently observed side effect. Even in high doses, GEM231 did not show some of the side effects normally associated with most current cancer treatments or with 1st generation antisense compounds. In the combination trials, patients experienced more serious side effects such as diarrhea, vomiting and bone marrow suppression. However, these more serious side effects are characteristic of the side effects of the chemotherapeutics administered in the combination trials. As a result and given that we did not observe these results in the monotherapy trials, we believe that these more serious side effects can be attributed to the chemotherapeutics and not GEM231.

If the pharmacokinetic data and other findings from the GEM231/ irinotecan clinical trial are favorable, we plan to commence a phase 2 clinical trial of this drug combination in the second half of 2004.

GEM92 for the Treatment of HIV-1. GEM92 is a 2nd generation antisense compound that is targeted to a specific region of the genome of the human immunodeficiency virus HIV-1 known as the *gag* region. Based on the clinical experience we gained with GEM91, our 1st generation antisense compound that also targeted same *gag* region of HIV-1, we created chemical modifications designed to improve the side effects profile and to enhance the stability of the compound, including the potential for oral administration. In 1997,

we conducted a phase 1 study in the United Kingdom to investigate the safety and pharmacokinetics of single doses of GEM92, given at three different dose levels by the oral route and one dose level as a 2-hour intravenous infusion. All doses given in the study were well tolerated by the subjects. Further, GEM92 was detected in the blood after both oral dosing and injection, suggesting that GEM92 could be developed as an oral drug. We are not presently advancing the development of GEM92. However, we continue to monitor trends in HIV treatment and may recommence our development efforts for GEM92, either alone or with another company, if we determine that the appropriate market opportunity exists for GEM92 if it is successfully developed.

Preclinical Development

We have a number of antisense compounds in the preclinical testing phase of development. The two principal antisense compounds that we have in preclinical development are:

- GEM220, a 2nd generation antisense compound directed against Vascular Endothelial Growth Factor or VEGF. VEGF is a growth factor that contributes to the growth of new blood vessels, which is a process called angiogenesis. In diseases such as cancer, the growth of new blood vessels is critical to the growth of tumors. Because GEM220 is designed to inhibit VEGF, we believe GEM220 may inhibit angiogenesis in tumors and in other disease states such as macular degeneration and psoriasis.

- GEM240, a 2nd generation antisense compound designed to inhibit mdm2. Mdm2 is a protein found in increased levels in many human cancers. Mdm2 binds to the tumor suppressor proteins p53 and p21, which results in reduced suppression of tumor cells and thereby contributes to the growth of cancer cells. In animal studies, GEM240 has been shown to decrease levels of mdm2 in many types of cancer cells, including colon cancer cells, breast cancer cells and brain cancer cells, and in turn to stabilize p53 and p21 levels in these cells. Recently, mdm2 has been shown in animal models to bind directly to p21 independent of p53. Since approximately 50% of all human cancers have mutated forms of p53, direct regulation of p21 by mdm2 may represent an important tumor suppression mechanism in the absence of functional p53.

Cancer Therapy Potentiation

As part of our efforts to develop antisense drugs that could be used as a component of cancer combination therapies, we discovered that the combination of oligonucleotide compounds with some prodrug anticancer therapies could enhance or potentiate the antitumor activity of the prodrug included in the combination. Prodrugs are compounds metabolized by the body after administration to produce their most active forms.

We have focused most of our efforts in this area on the combination of an antisense oligonucleotide with irinotecan. Irinotecan is a prodrug that is altered primarily in the liver to generate an active product designated as SN38. SN38 is considered to be the molecule responsible for most of the antitumor activity of irinotecan. SN38 is also implicated in production of the major clinical side effects of irinotecan. When we tested irinotecan in animals in combination with several different oligonucleotides, we noted both incremental non-antisense and antisense specific tumor activity. In addition, in over ten animal tumor models, the co-administration of GEM231 with irinotecan resulted in enhanced and prolonged suppression of tumor growth in comparison with irinotecan alone.

As part of our ongoing phase 1/2 clinical trial of GEM231 described above, we are studying the pharmacokinetics of irinotecan when administered in combination with GEM231 because changes in pharmacokinetics may be an indicator of potentiation of irinotecan by GEM231 in patients with solid tumors.

Research and Development

For the years ended December 31, 2003, 2002 and 2001, we spent approximately $10.8 million, $7.9 million and $4.9 million, respectively, on research and development activities. Our collaborators sponsored only a nominal portion of these research and development activities in 2003, 2002 and 2001.

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 February 2004, we owned or exclusively licensed 102 issued U.S. patents and 84 U.S. patent applications and 163 corresponding foreign patents and over 220 corresponding foreign 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 2021.

The composition of matter patents covering GEM231 expire at various dates ranging from 2010 to 2019. We have applied for composition of matter patents covering HYB2055 but no patents have been issued to date 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 UMass 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.

Several of the issued U.S. patents and several issued foreign patents licensed by us from the University of Massachusetts Medical Center broadly claim the use of our hybrid antisense oligonucleotides and ribozymes. The other issued U.S. patents covered by the license agreement include claims covering composition and uses of oligonucleotides based on advanced chemistries, and compositions of certain modified oligonucleotides that are useful for diagnostic tests or assays. 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, and
- an exclusive license agreement with Dr. Yoon S. Cho-Chung covering patents and patent applications relating to Protein Kinase A.

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. 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 February 2003, Isis made such a payment to us in connection with two 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 four collaboration and license arrangements involving the use of our IMO or antisense technologies and specified indications.

- *Aegera Therapeutics Inc.* We are a party to an agreement with Aegera 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 that it has completed preclinical toxicology studies of AEG35156/ GEM640 and that it expects to initiate phase 1 clinical trials in the first quarter of 2004. Under the terms of the license we may receive up to $7,725,000 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.

- *The Immune Response Corporation.* We are 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 to Amplivax that we granted to Immune Response in the agreement, 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.

- *Micrologix Biotech Inc.* We are a party to an agreement with Micrologix 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 Micrologix 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 $5,750,000 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.

Under these arrangements, we typically license to our collaborators our antisense chemistry and delivery patents and patent applications on a non-exclusive basis, and any antisense 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.

MethylGene Inc.

In 1996, we and three Canadian institutional investors formed MethylGene Inc. In connection with the formation of MethylGene, we made a cash investment in MethylGene and granted to MethylGene an exclusive, royalty-free worldwide license to antisense patents, patent applications and technology owned or exclusively licensed by us from University of Massachusetts Medical Center and McGill University to develop and market the following:

- antisense compounds which inhibit the production of DNA methyltransferase for any indication;
- other methods of inhibiting DNA methyltransferase for any indication; and
- antisense compounds to inhibit up to two additional molecular targets for any indication.

In consideration for our initial cash investment and the license, we received shares of capital of MethylGene. In 2001, we sold all of our shares in MethylGene to an institutional investor and a group of Canadian institutional investors for an aggregate sale price of $7.2 million resulting in a gain of $6.9 million. We are not entitled to any additional consideration under our agreement with MethylGene.

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, unless the 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. We cannot be sure 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 are party to a supply agreement with Avecia Biotechnology, which was formally known as Boston Biosystems Inc., under which we may purchase our requirements for oligonucleotide compounds from Avecia at a preferential price. We are purchasing all of the oligonucleotides we are using in our ongoing clinical trials and pre-clinical testing from Avecia under this agreement. We are currently negotiating with Avecia a new agreement to replace the existing agreement which is due to expire at the end of March 2004. We expect that we will enter into a longer term arrangement with Avecia or new arrangements with 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, Genta, 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. In particular,

- Isis has six compounds presently in clinical trials, one of which is in late-stage clinical trials. Of these compounds, four are being studied for the treatment of cancer or infectious diseases.

- Genta, together with its partner Aventis, have submitted a New Drug Application to the FDA for an oligonucleotide compound proposed for the treatment of melanoma and are in late-stage clinical trials of the same compound for the treatment of other cancers.

- Dynavax has a CpG DNA compound in clinical trials for four indications. These indications include the treatment of cancer and infectious disease.

- Coley has a CpG DNA compound in clinical trials for three indications. These indications include treatment of cancer and infectious disease.

Many of our competitors, particularly the pharmaceutical and large 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 16, 2004, we employed 25 individuals full-time, including 19 employees in research and development. Eleven of our employees have an M.D. and/or a Ph.D. 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***

On December 4, 2003, at a special meeting of stockholders, our stockholders voted to approve 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% per annum to 1.0% per annum; 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 of our common stock that would otherwise be issuable upon conversion under our Certificate of Incorporation for a 60-day period following the filing of a Certificate of Amendment to Restated Certificate of Incorporation effecting the amendments.

The approval of the amendments to our Certificate of Incorporation required the affirmative vote of the holders of:

- a majority of the outstanding shares of common stock entitled to vote at the special meeting; and
- a majority of the outstanding shares of series A convertible preferred stock entitled to vote at the special meeting.

The amendments to our Certificate of Incorporation were approved as follows:

	For	Against	Abstain	Broker Non-Votes
Holders of common stock	42,893,620	365,539	150,061	—
Holders of series A convertible preferred stock	698,031	8,170	—	—

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 February 29, 2004:

Name	Age	Position
Stephen R. Seiler	47	Chief Executive Officer and Director
Sudhir Agrawal, D. Phil	50	President, Chief Scientific Officer and Director
Robert G. Andersen	53	Chief Financial Officer, Vice President of Operations, Treasurer and Secretary
R. Russell Martin, M.D.	68	Senior Vice President of Drug Development, Chief Medical Officer
Jinyan Tang, Ph.D.	60	Vice President of Chemistry

Stephen R. Seiler was appointed our Chief Executive Officer and elected to our board of directors on September 1, 2001. Prior to joining us, Mr. Seiler served as Executive Vice President, Planning Investment & Development at Elan Corporation plc from 1995 to 2001. While at Elan, Mr. Seiler took part in and oversaw activities in a wide range of areas including acquisitions, divestitures and in and out licensing. From 1991 to

1995, Mr. Seiler worked as an Investment Banker at Paribas Capital Markets in both London and New York. He was founder and head of Paribas's pharmaceutical industry investment banking group. In that capacity, he initiated and worked on a wide variety of transactions including initial public offerings, privatizations, mergers and acquisitions, debt and equity offerings and derivative transactions. Mr. Seiler received a J.D. from Georgetown University with Honors in 1980 and a B.A. summa cum laude in History from the University of Notre Dame in 1977. He is a member of the Board of Associates of the Whitehead Institute. He is also a member of the bar in New York, Arizona, and Missouri.

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 and as a director since March 1993. 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 200 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.

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 since 1997, our Treasurer since March 1998 and our Chief Financial Officer since February 2000. Prior to joining us, Mr. Andersen served in 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. R. Russell Martin joined us in 1994 and has served as our Senior Vice President of Drug Development since 1998. He served as our Vice President of Drug Development from 1996 through 1998 and our Vice President of Clinical Research from 1994 through 1996. Prior to joining us, Dr. Martin served in a variety of positions at Bristol-Myers Squibb from 1983 to 1993, most recently as Vice President of Infectious Diseases Clinical Research. Prior to joining the pharmaceutical industry, Dr. Martin was associate professor at Indiana University School of Medicine and Professor of Medicine, Microbiology and Immunology at Baylor College of Medicine from 1971 to 1983. Dr. Martin received a M.D. degree from the Medical College of Georgia in 1960 and an A.B. degree in American Studies from Yale University in 1956. He is a Fellow of the American College of Physicians and of the Infectious Diseases Society of America.

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, 2002 through December 4, 2003 and on the American Stock Exchange from December 5, 2003 through December 31, 2003:

	High	Low
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
2002		
First Quarter	$1.85	$1.23
Second Quarter	1.49	0.92
Third Quarter	1.23	0.59
Fourth Quarter	1.25	0.62

The number of common stockholders of record on March 2, 2004 was 462.

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. The indenture under which we issued 9% convertible subordinated notes in April 1997 limits our ability to pay dividends or make other distributions on our common stock or to pay cash dividends on our convertible preferred stock until such notes are repaid. As of March 2, 2004, 9% notes in the aggregate principal amount of $1.3 million remained outstanding. The 9% notes are due in April 2004.

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. As of February 29, 2004, we have only paid these dividends in shares of series A convertible preferred stock.

Sales of Unregistered Securities

On December 10, 2003 the Company issued 18,840 shares of common stock, through the cashless exercise of 39,999 warrants to purchase common stock at an exercise price of $0.73 per share, to an "accredited investor" without registration under the Securities Act of 1933, as amended, in reliance on the exemption from registration for the newly issued common stock provided by Section 4(2) of the Securities Act of 1933.

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,				
	2003	2002	2001	2000	1999
	(In thousands, except per share data)				
Statement of Operations Data:					
Revenues:					
Alliance revenue	$ 870	$ 29,560	$ 988	$ 179	$ 600
Royalty and other income	27	46	134	83	123
Service revenue	—	—	—	82	365
Total revenues	897	29,606	1,122	344	1,088
Operating expenses:					
Research and development	10,817	7,877	4,868	3,620	5,783
General and administrative	6,924	7,054	5,051	3,184	3,664
Stock-based compensation from repriced options	543	(1,297)	1,762	—	—
Total operating expenses	18,284	13,634	11,681	6,804	9,447
(Loss) income from operations	(17,387)	15,972	(10,559)	(6,460)	(8,359)
Other income (expense):					
Investment income, net(1)	190	650	577	229	92
Interest expense(1)	(118)	(150)	(1,319)	(2,154)	(683)
Loss on conversion of 8% convertible subordinated notes payable(1)	—	—	(1,412)	—	—
Gain on sale of securities, net(1)	104	—	5,217	—	—
(Loss) income from continuing operations	(17,211)	16,472	(7,496)	(8,385)	(8,950)
Income (loss) from discontinued operations(2)	—	—	2,663	5,462	(1,553)
(Loss) income before income taxes	(17,211)	16,472	(4,833)	(2,923)	(10,503)
Income tax benefit (provision)	—	500	(500)	—	—
Net (loss) income	(17,211)	16,972	(5,333)	(2,923)	(10,503)
Accretion of preferred stock dividend	(5,529)	(4,246)	(8,342)	(4,087)	(4,232)
Net (loss) income applicable to common stockholders	$ (22,740)	$ 12,726	$ (13,675)	$ (7,010)	$ (14,735)
Basic net income (loss) per common share from:					
Continuing operations	$ (0.34)	$ 0.36	$ (0.26)	$ (0.48)	$ (0.57)
Discontinued operations	—	—	0.09	0.31	(0.10)
Net (loss) income per share	(0.34)	0.36	(0.17)	(0.17)	(0.66)
Accretion of preferred stock dividends	(0.11)	(0.09)	(0.27)	(0.23)	(0.27)
Net (loss) income per share applicable to common stockholders	$ (0.45)	$ 0.27	$ (0.44)	$ (0.40)	$ (0.93)
Diluted net (loss) income per common share from:					
Continuing operations	$ (0.34)	$ 0.32	$ (0.26)	$ (0.48)	$ (0.57)
Discontinued operations	—	—	0.09	0.31	(0.10)
Net (loss) income per share	(0.34)	0.32	(0.17)	(0.17)	(0.66)
Accretion of preferred stock dividends	(0.11)	(0.08)	(0.27)	(0.23)	(0.27)
Net (loss) income per share applicable to common stockholders	$ (0.45)	$ 0.24	$ (0.44)	$ (0.40)	$ (0.93)
Shares used in computing basic net (loss) income per common share(3)	51,053	46,879	30,820	17,418	15,811

Shares used in computing diluted net (loss) income per common share(3)	51,053	52,984	30,820	17,418	15,811
Balance Sheet Data:					
Cash, cash equivalents and short-term investments	$ 13,668	$ 19,175	$ 31,834	$ 3,532	$ 2,552
Working capital (deficit)	10,740	17,638	27,259	(4,238)	(6,534)
Total assets	14,410	21,249	32,309	10,001	10,717
Restricted cash	—	—	—	5,000	—
Capital lease obligations, current portion	—	34	—	—	—
9% convertible subordinated notes payable	1,306	1,306	1,306	1,306	1,306
8% convertible subordinated notes payable	—	—	288	8,046	6,100
Series A convertible preferred stock	5	7	6	6	7
Accumulated deficit	(283,883)	(261,143)	(273,868)	(260,193)	(253,183)
Total stockholders' equity (deficit)	10,526	17,444	(33)	(7,530)	(6,072)

(1) Amounts included in the years ending prior to December 31, 2003 have been reclassified as described in Note 2(d) of notes to consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K.

(2) Consolidated financial statements reflect the financial results of HSP as a discontinued operation for the years ended December 31, 2001, 2000 and 1999. Reported revenues, expenses and cash flows exclude the operating results of discontinued operations.

(3) Computed on the basis described in Note 13 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, 2003. 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 2003	Sep. 30 2003	Jun. 30 2003	Mar. 31 2003	Dec. 31 2002	Sep. 30 2002	Jun. 30 2002	Mar. 31 2002
	(In thousands, except per share data)							
Statement of Operations Data:								
Revenues	108	334	120	335	40	28,176	699	691
Operating expenses:								
Research and development	2,986	2,567	2,858	2,406	2,270	2,794	1,567	1,246
General and administrative	1,475	943	1,282	3,224	1,219	3,351	1,342	1,142
Stock-based compensation from repriced options	(98)	506	129	6	(116)	(438)	(480)	(263)
Total operating expenses	4,363	4,016	4,269	5,636	3,373	5,707	2,429	2,125
(Loss) income from operations	(4,255)	(3,682)	(4,149)	(5,301)	(3,333)	22,469	(1,730)	(1,434)
Investment income(1)	43	28	36	82	120	156	178	196
Interest expense(1)	(29)	(29)	(29)	(29)	(36)	(38)	(38)	(38)
Gain on sale of investment, net(1)	—	—	104	—	—	—	—	—
Income (loss) before provision for income taxes	(4,241)	(3,683)	(4,038)	(5,248)	(3,249)	22,587	(1,590)	(1,276)
Income tax credit	—	—	—	—	—	—	—	500
Net (loss) income	(4,241)	(3,683)	(4,038)	(5,248)	(3,249)	22,587	(1,590)	(776)
Accretion of preferred stock dividend	(2,127)	(1,138)	(1,194)	(1,071)	(1,074)	(1,073)	(1,059)	(1,040)
Net (loss) income applicable to common stockholders	$ (6,368)	$ (4,821)	$ (5,232)	$ (6,319)	$ (4,323)	$21,514	$ (2,649)	$ (1,816)
Basic net (loss) income per share applicable to common stockholders	$ (0.10)	$ (0.10)	$ (0.12)	$ (0.14)	$ (0.09)	$ 0.45	$ (0.06)	$ (0.04)
Diluted net (loss) income per share applicable to common stockholders	$ (0.10)	$ (0.10)	$ (0.12)	$ (0.14)	$ (0.09)	$ 0.34	$ (0.06)	$ (0.04)
Shares used in computing (loss) income per common share(2)								
Basic	64,119	50,704	43,485	45,700	47,575	47,527	46,708	45,670
Diluted	64,119	50,704	43,485	45,700	47,575	66,950	46,708	45,670

(1) Amounts included in the fiscal quarters ending prior to December 31, 2003 have been reclassified as described in Note 2(d) of notes to consolidated financial statements appearing elsewhere in this Annual Report on Form 10-K.

(2) Computed on the basis described in Note 13 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 and development of novel therapeutics using synthetic DNA. Our activities are primarily based on two technology platforms:

- Our immunomodulatory oligonucleotide, or IMO, technology modulates responses of the immune system using synthetic DNA containing specific sequences that mimic bacterial DNA.

- Our antisense technology uses synthetic DNA to block the production of disease causing proteins at the cellular level.

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 manufactured synthetic DNA and reagent products within our Hybridon Specialty Products Division, or HSP, prior to our selling HSP in September 2000.

We have incurred total losses of $283.9 million through December 31, 2003 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 2004, we expect that our research and development expenses will be similar to those in 2003 as we continue to advance our products through clinical development. We expect our general and administrative expenses in 2004, however, to be significantly less than in 2003 which included a one-time expense 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.

At a special meeting of stockholders held on December 4, 2003, our common and preferred stockholders approved amendments to our Certificate of Incorporation that reduced the liquidation preference and annual dividend rate on our series A convertible preferred stock. The amendments also provided that during a 60-day period ended February 2, 2004 shares of our series A convertible preferred stock could be converted into a number of shares of common stock that was 25% greater than the number of shares that would otherwise be issuable upon conversion. During the 60-day period, holders of 722,092 shares of our series A convertible preferred stock, or 99.9% of the series A convertible preferred stock outstanding, converted their shares into 21,238,028 shares of common stock, leaving 635 shares of series A convertible preferred stock outstanding following the end of the special conversion period on February 2, 2004. These remaining shares of series A convertible preferred stock have, as a class, a liquidation preference of $643.

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 to our consolidated financial statements, 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 and 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. 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, 2003, 2002 and 2001

Revenues

Total revenues decreased by $28.7 million from $29.6 million in 2002 to $0.9 million in 2003. Total revenues increased by $28.5 million from $1.1 million in 2001 to $29.6 million in 2002. The significant difference in revenues among these years 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. Offsetting this decrease in 2003 revenues were research revenues and revenue earned from a milestone under a collaboration and license agreement with Aegera and sublicense income received from Isis.

Research and Development Expenses

Research and development expenses increased by $2.9 million, or 37%, from $7.9 million in 2002 to $10.8 million in 2003 and increased by $3.0 million, or 62%, from $4.9 million in 2001 to $7.9 million in 2002. The increase in 2003 was primarily attributable to the initiation in 2003 of clinical trials of HYB2055, expanded clinical trials of GEM231 and increased costs relating to the filing of patents related to new discoveries. The increase in 2002 from 2001 was primarily attributable to advancement of our drug development program in 2002, including the commencement of clinical trials of GEM231 and the expansion of pre-clinical activity related to our IMO technology, as well as additional payroll costs in 2002 associated with employees that we hired in 2002 for our scientific discovery and development teams and reflecting the full-year costs of employees that we hired in 2001. Research and development expenses in 2001 related primarily to the preclinical development of our IMO technology, including HYB2055. Although we participated in several clinical trials of GEM231, the trials were hospital sponsored and the costs for these

trials were primarily borne by third parties whose drugs were being tested in the trials in combination with GEM231.

Our two primary research and development projects relate to HYB2055 and GEM231:

- In 2003 and 2002, we incurred approximately $2.3 and $1.8 million, respectively, in direct expenses in connection with developing HYB2055. These direct expenses included payments to independent contractors and vendors for preclinical studies, drug manufacturing and related costs and patent preparation costs and related filing fees and exclude internal costs such as payroll and overhead. In March 2003, we commenced a phase 1 clinical trial of HYB2055 in the United Kingdom in 28 healthy volunteers, which we completed during the third quarter of 2003. In May 2003, we commenced a phase 1 clinical trial of HYB2055 in the United States in patients with refractory solid tumor cancers. If this trial is completed when anticipated and the results are favorable, we plan to commence a phase 2 clinical trial of IMOxine in the second or third quarter of 2004.

- In 2003 and 2002, we incurred approximately $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 and exclude internal costs such as payroll and overhead. 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 and 2003. We are currently conducting a phase 1/2 clinical trial of GEM231 as a combination therapy with irinotecan. We expect to complete enrollment of this combination treatment trial in the second quarter of 2004. If the pharmacokinetic data and other findings from this phase 1/2 clinical trial are favorable, we plan to commence a phase 2 clinical trial of this drug combination in the second half of 2004.

Because these projects are in the early stage of development and given the technological and regulatory hurdles likely to be encountered in the development and commercialization of our products, the future timing and costs of our various research and development programs are uncertain.

General and Administrative Expenses

General and administrative expenses decreased by approximately $0.1 million, or 2%, from $7.0 million in 2002 to $6.9 million in 2003 and increased by $2.0 million, or 40%, from $5.1 million in 2001 to $7.1 million in 2002. 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 differences in the years primarily reflect 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 2003 or 2001. The impact of the 2002 Isis expenses on the difference between 2003 and 2002 expenses 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. Operating results include an expense of approximately $0.5 million in 2003 as a result of 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. In 2001, we incurred a stock-based compensation expense of $1.8 million, which resulted from an increase 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.

Investment Income, net

Investment income decreased by approximately $0.4 million from $0.6 million in 2002 to $0.2 million in 2003, and remained relatively constant at $0.6 million in 2001 and 2002. 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 $0.1 million from $0.2 million in 2002 to $0.1 million in 2003, and decreased by $1.1 million from $1.3 million in 2001 to $0.2 million in 2002. The decrease from 2002 to 2003 was attributable to the maturity of our 8% notes in November 2002. The decrease from 2001 to 2002 was primarily attributable to the conversion of $7.6 million of our 8% notes into series B convertible preferred stock in March 2001 and our repayment of a $6.0 million of indebtedness evidenced by a $6.0 million note payable, which we made to six shareholders during the second and third quarters of 2001.

Loss on Conversion of 8% Notes

We recorded a loss of $1.4 million in 2001 resulting from the exchange of our Series B preferred stock for 8% notes.

Gain on Sale of Securities, net

Gain on sale of securities increased by $0.1 million from $0 in 2002 to $0.1 million in 2003, and decreased by $5.2 million from $5.2 million in 2001 to $0 in 2002. The increase from 2002 to 2003 is primarily attributable a $0.1 million gain on the sale of shares of Micrologix common stock which we received as payment under our agreement with Micrologix. The decrease from 2001 to 2002 was primarily attributable to the inclusion in 2001 of a net gain of $6.9 million from the sale of our MethylGene shares offset by a realized loss of $1.4 million attributable to a loss in value of the shares of Isis common stock received in 2001 under our agreement with Isis.

Income (Loss) from Discontinued Operations

We recognized income from discontinued operations of $2.7 million for 2001. The 2001 income primarily reflects the receipt of a $3.0 million contingent payment from the buyer of our former HSP division.

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 sixty-day period between December 4, 2003 and February 2, 2004 inclusive.

During the sixty-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 stock to common stock.

There was also a 25% special conversion period for the series B convertible preferred stockholders during 2001 which resulted in the conversion of 100% of our series B convertible preferred stock at that time.

The preferred stock dividends for each of the three years ended December 31, 2003 were as follows:

	Preferred Stock Dividends		
	2003	2002	2001
Accretion of dividends expected to be paid:			
Series A Preferred Stock	$3,402,856	$4,246,282	$4,020,635
Series B Preferred Stock	—	—	221,300
Accretion of dividend that would have been paid on April 1, 2004 if preferred shares were not converted in January and February 2004	570,000	—	—
Market value of 25% additional shares issued upon conversion	1,556,000	—	4,100,000
Total preferred stock dividend	$5,528,856	$4,246,282	$8,341,935

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 2003 of $1.6 million and during 2001 of $4.1 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 $73,055,654 at December 3, 2003 to $494,912 at December 31, 2003 and $643 at February 2, 2004.

The expected series A convertible preferred stock dividend in 2004 is as follows:

Accretion of dividend expected to be paid	$ 654
Reversal of previous dividend accretion that will not be paid due to 2004 conversions	(570,000)
Market value of 25% additional shares issued upon conversion in 2004	3,245,492
Total preferred stock dividend	$2,676,146

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, 2003, we had approximately $241.0 million and $4.4 million of net operating loss and tax credit carryforwards, respectively. 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, 2003, have resulted in ownership changes, as defined under the Tax Act, which will limit our ability to utilize a portion of our available net operating loss 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 by Hybridon Specialty Products, or 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 2003, we raised approximately $14.6 million in gross proceeds from a private placement of 20,053,022 shares of our common stock and warrants to purchase 6,015,934 of our common stock to institutional and accredited investors. 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 through 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, excluding the proceeds of any exercise of the warrants and after deducting payments to selected dealers and placement agents and other expenses, totaled $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, 2003, we had approximately $13.7 million in cash and cash equivalents and investments, a net decrease of approximately $6.4 million from December 31, 2002. We used $14.4 million of cash in operating activities during 2003, principally to fund our research and development expenses and our general and administrative expenses. The $14.4 million primarily consists of our $17.2 million net loss for the period, as adjusted to exclude the $1.9 million charge to operating expenses for the premium over fair market value that we paid in repurchasing shares of our common stock in the first quarter of 2003, as well as non-cash expenses including depreciation and amortization and stock-based compensation.

The net cash provided by investing activities during 2003 reflects our sale of approximately $15.3 million in “available-for-sale” securities, including the stock we received from Micrologix, under our collaboration and license agreement with Micrologix, and the proceeds of approximately $14.1 million from securities that matured in 2003, offset by our purchase of $17.7 million of “available-for-sale” securities.

The net cash provided by financing activities during 2003, reflects the $13.1 million in net proceeds that we raised in the August 2003 private placement and use by us of $5.3 million of our cash in February 2003 to repurchase from certain stockholders approximately 4.6 million shares of our common stock at a price of $1.15 per share. Cash from other financing activities included proceeds from the exercise of stock options.

Funding Requirements

We have incurred operating losses in most fiscal years and had an accumulated deficit of $283.9 million at December 31, 2003. We had cash, cash equivalents and short-term investments of $13.7 million at December 31, 2003. Although, based on our current operating plan, we believe that these funds will be sufficient to fund operations through December 2004, we may be required to reduce planned activities in order to conserve such funds. We are assuming that we will continue 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 December 2004, we must raise additional funds in 2004 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 filed a shelf registration statement on Form S-3 with the SEC, which became effective in the first quarter of 2004. This shelf registration statement permits us to offer, from time to time, up to 20,000,000 shares of common stock, including shares of common stock issuable upon exercise of warrants.

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, 2003, our contractual obligations were as follows:

	Payments Due by Period			
Contractual Obligations	Total	Less than 1 year	1-3 years	4-5 years
Debt	$1,306,000	$1,306,000	$ —	$ —
Lease Commitments	2,037,000	611,000	1,222,000	204,000
Employment Agreements	2,899,250	1,118,000	1,691,250	90,000
Consulting & Collaboration Agreements	142,515	142,515	—	—
Total	$6,384,765	$3,177,515	$2,913,250	$294,000

As of December 31, 2003, our outstanding indebtedness consisted of 9% convertible subordinated notes in the aggregate principal amount of $1.3 million. These notes mature in April 2004 and are unsecured. We expect to repay these notes when they become due in April 2004 out of our existing cash resources. 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 2004.

FORWARD-LOOKING STATEMENTS

This annual report contains certain 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 wherever they appear in this annual report. In addition, any forward-looking statements represent our estimates only as of the date 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 statements, 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 and elsewhere from time to time.

Risks Relating to Our Business, Strategy and Industry

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. In 2003, we commenced phase 1 clinical trials of HYB2055, our lead 2nd generation IMO compound, in oncology patients and in healthy volunteers, and we are currently conducting a phase 1/2 clinical trial of GEM231, our lead 2nd generation antisense compound for the treatment of solid tumor cancer. 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. Furthermore, we, one of our collaborators, an IRB, or a regulatory agency with jurisdiction over the trials, may suspend clinical trials at any time if the subjects or patients participating in such trials are being exposed to unacceptable health risks, or for other reasons. As an example, in 1997, after reviewing the results from the clinical trial of GEM91, our lead 1st generation antisense compound 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. 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.

Delays in planned patient enrollment may result in increased costs and prolonged clinical development.

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,
- 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 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 not granted marketing approval to any products based on antisense technology or IMO-like technology and no such products are currently being marketed, except for one antisense product that is currently being marketed by another company for the treatment of cytomegalovirus retinitis, an infectious disease, in patients with AIDs. As a result, it may be more difficult for us to achieve 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 Stephen Seiler and Sudhir Agrawal. Mr. Seiler, our Chief Executive Officer, has extensive experience in the pharmaceutical industry and as an investment banker and provides strategic leadership for us. The loss of Mr. Seiler's services would be detrimental to the execution of our strategic plan. Dr. Agrawal serves as our President and Chief Scientific Officer. Dr. Agrawal has made significant contributions to the field of nucleic acid chemistry and is named as an inventor on over 200 U.S. patents and patent applications. 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.

We are a party to employment agreements with each of Mr. Seiler and Dr. Agrawal, but each of these agreements may be terminated by us or the employee for any reason or no reason at any time upon notice to the other party. We do not carry key man life insurance on Mr. Seiler or 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 five compounds. In 1997, we determined not to continue clinical development of GEM91. The other four compounds are still in development. Currently, we are conducting clinical trials of two of these compounds, GEM231 and HYB2055.

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, 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 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 the year. As of December 31, 2003, we had incurred operating losses of approximately $283.9 million. We expect to continue to incur substantial operating losses in future periods. 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 HSP prior to our selling that division in September 2000. We cannot be certain whether or when we will become profitable because of the significant uncertainties with respect to our ability to generate revenues from the sale of products and from any potential strategic alliances.

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 through the end of December 2004. However, we will need to raise additional funds to operate our business beyond such time.

Additional financing may not be available to us when we need it or may not be available to us on favorable terms. 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. 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.

If we raise additional funds by issuing equity securities, our then existing stockholders will experience dilution. In addition, the terms of the financing may adversely affect the holdings or the rights of existing stockholders.

Our former independent public accountant, Arthur Andersen LLP, has been found guilty of a federal obstruction of justice charge. Arthur Andersen LLP has not consented to the inclusion of its audit report with respect to our consolidated financial statements in this annual report, and you may be unable to exercise effective remedies against it in any legal action.

Our former independent public accountant, Arthur Andersen LLP, provided us with auditing services for prior fiscal periods through December 31, 2001, including issuing an audit report with respect to our audited consolidated financial statements as of and for the year ended December 31, 2001, which report is included in this Annual Report of Form 10-K. On June 15, 2002, a jury in Houston, Texas found Arthur Andersen LLP guilty of a federal obstruction of justice charge arising from the federal government's investigation of Enron Corp. On August 31, 2002, Arthur Andersen LLP ceased practicing before the Securities and Exchange Commission.

We were unable to obtain Arthur Andersen LLP's consent to include its report with respect to our audited consolidated financial statements as of and for the year ended December 31, 2001 in this Annual Report on Form 10-K, or in any other filing that we may make with the SEC. As a result, you may not have an effective remedy against Arthur Andersen LLP in connection with a material misstatement or omission with respect to our audited consolidated financial statements that are included in this Annual Report on Form 10-K or any other filing that we may make with the SEC. In addition, even if you were able to assert such a claim, as a result of its conviction and other lawsuits, Arthur Andersen LLP may fail or otherwise have insufficient assets to satisfy claims made by investors or by us that might arise under federal securities laws or otherwise relating to any alleged material misstatement or omission with respect to our audited consolidated financial statements.

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 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 event, we might not be able to develop or commercialize products covered by the licenses.

We are party to eleven 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 2021. 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 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. In addition, in 2003, we became involved in an interference declared by the United States Patent and Trademark Office 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.

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

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.

Our current manufacturing agreement with Avecia expires in March 2004. If we are unable to renew this agreement on satisfactory terms or on a timely basis, we may need to seek a new contract manufacturer. If 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. If we have not entered into a collaborative arrangement with respect to a product and need to market it 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 enter into arrangements with 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 we fail to obtain an adequate level of reimbursement for our products by third party payors, there may be no commercially viable markets for our products.

The availability and levels of reimbursement by governmental and other third party payors such as health maintenance organizations, Medicaid, medical insurance companies, medical plan administrators, pharmacy benefit managers, physician and hospital alliances and other physician organizations affect the market for healthcare products. These third party payors continually attempt to contain or reduce the costs of healthcare by challenging the prices charged for medical products and services. If reimbursement for our products is unavailable or limited in scope or amount, our business could be materially harmed.

In both the United States and some foreign jurisdictions, there have been a number of legislative and regulatory proposals to change the healthcare system in ways that could affect our ability to sell our products profitability. In the United States, new legislation has been proposed at the federal and state levels that would result in significant changes to the healthcare system, either nationally or at the state level. Moreover, in December 2003, President Bush signed into law new Medicare prescription drug coverage legislation. Starting in January 2004, the legislation will change the methodology used to calculate reimbursement for drugs in a manner intended to reduce the amount that is subject to reimbursement. Further federal and state proposals and healthcare reforms are likely. Our results of operations could be materially adversely affected by the Medicare prescription drug coverage legislation, by the possible effect of this legislation on amounts that private insurers will pay and by other healthcare reforms that may be enacted or adopted in the future. In addition, this legislation and other proposals and reforms could adversely affect our ability to raise capital or obtain collaborators.

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. Investors may lose all or a significant portion of their investment.

The stock market has experienced significant price and volume fluctuations, and the market prices of biotechnology companies have been highly volatile. In addition, broad market and industry fluctuations that are not within our control may adversely affect the trading price of our common stock.

Because our common stock has historically been traded at low volume levels, any large purchase or sale of our common stock could have a significant impact on the price of our common stock. During the period from January 1, 2002 to March 1, 2004, the closing sale price of our common stock ranged from a high of $1.85 per share to a low of $0.60 per share. As a result, 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, 2003, 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) immediately after the signature page to this report on Form 10-K, and are incorporated herein by this reference.

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

We previously reported the information required to be reported in this Item in our Current Report on Form 8-K dated April 25, 2002, which we filed with the Securities and Exchange Commission on May 1, 2002.

Our consolidated financial statements as of and for the fiscal year ended December 31, 2001 were audited by Arthur Andersen LLP, independent accountants. On August 31, 2002, Arthur Andersen ceased practicing before the SEC. Therefore, Arthur Andersen did not participate in the preparation of this Annual Report on Form 10-K, did not reissue its audit report with respect to the financial statements included in this Annual Report on Form 10-K and did not consent to the inclusion of its audit report in this Annual Report on Form 10-K. As a result, holders of our securities, and investors evaluating offers and purchasing securities pursuant to a prospectus incorporating by reference this Annual Report on Form 10-K, may have no effective remedy against Arthur Andersen in connection with a material misstatement or omission in the financial statements to which Arthur Andersen's audit report relates. In addition, even if such holders or investors were able to assert such a claim, because it has ceased operations, Arthur Andersen may fail or otherwise have insufficient assets to satisfy claims made by such persons that might arise under federal securities laws or otherwise with respect to Arthur Andersen's audit report.

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

(a) Evaluation of Disclosure Controls and Procedures. Our management, with the participation of our Chief Executive Officer, or CEO, and Chief Financial Officer, or CFO, evaluated the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-15(e) and 15d-15(e) under the Securities Exchange Act) as of December 31, 2003. Based on this evaluation, our CEO and CFO concluded that, as of December 31, 2003, our disclosure controls and procedures were (1) designed to ensure that material information relating to us, including our consolidated subsidiaries, is made known to our CEO and CFO by

others within those entities, particularly during the period in which this report was being prepared and (2) effective, in that they provide reasonable assurance that information required to be disclosed by us in the reports that we file or submit under the Securities Exchange Act is recorded, processed, summarized and reported within the time periods specified in the Securities and Exchange Commission's rules and forms.

(b) Changes in Internal Controls. No change in our internal control over financial reporting (as defined in Rules 13a-15(f) and 15d-15(f) under the Securities Exchange Act) occurred during the fiscal quarter ended December 31, 2003 that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

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 17, 2004. The 2004 Proxy Statement will be filed with the Securities and Exchange Commission on or before April 30, 2004.

Item 10. *Directors and Executive Officers of Hybridon*

The response to this item is contained under the following captions in the 2004 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 2004 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 2004 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 2004 Proxy Statement under the caption "Security Ownership of Certain Beneficial Owners and Management," and "Securities Authorized for Issuance Under Equity Compensation Plans", which sections are incorporated herein by reference.

Item 13. *Certain Relationships and Related Transactions*

The response to this item is contained in the 2004 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 2004 Proxy Statement under the caption "Principal Accountant Fees and Services", which section is incorporated herein by reference.

PART IV.

Item 15. ***Exhibits, Financial Statement Schedules and Reports on Form 8-K***

(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.

(b) *Reports on Form 8-K.*

On November 26, 2003 we filed a Current Report on Form 8-K reporting the approval of our application to list our common stock on the American Stock Exchange.

On December 5, 2003, we filed a Current Report on Form 8-K regarding the results of a special meeting of stockholders held on December 4, 2003, at which the stockholders approved amendments to our Restated Certificate of Incorporation. In addition, we stated that our Common Stock would begin trading on the American Stock Exchange beginning on December 5, 2003 under the trading symbol "HBY".

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 19th day of March 2004.

Hybridon, Inc.

By: /s/ STEPHEN R. SEILER

Stephen R. Seiler
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, M.D.	Chairman of the Board of Directors	March 19, 2004
/s/ STEPHEN R. SEILER Stephen R. Seiler	Chief Executive Officer and Director (Principal Executive Officer)	March 19, 2004
/s/ SUDHIR AGRAWAL Sudhir Agrawal, D. Phil	President, Chief Scientific Officer and Director	March 19, 2004
/s/ ROBERT G. ANDERSON Robert G. Andersen	Chief Financial Officer and Vice President of Operations, Treasurer and Secretary (Principal Financial and Accounting Officer)	March 19, 2004
/s/ YOUSSEF EL-ZEIN Youssef El-Zein	Director	March 19, 2004
/s/ C. KEITH HARTLEY C. Keith Hartley	Director	March 19, 2004
/s/ WILLIAM S. REARDON William S. Reardon, C.P.A.	Director	March 19, 2004
/s/ PAUL C. ZAMECNIK Paul C. Zamecnik, M.D.	Director	March 19, 2004

HYBRIDON, INC. AND SUBSIDIARIES

INDEX TO CONSOLIDATED FINANCIAL STATEMENTS

December 31, 2003

REPORT OF INDEPENDENT AUDITORS

The Board of Directors and Stockholders

Hybridon, Inc.

We have audited the accompanying balance sheets of Hybridon, Inc. as of December 31, 2003 and 2002, and the related statements of operations, stockholders' equity (deficit), and cash flows for the years then ended. 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. The financial statements of Hybridon, Inc. for the year ended December 31, 2001 were audited by other auditors who have ceased operations and whose report dated February 21, 2002, expressed an unqualified opinion on those statements before the restatement adjustments described in Note 2.

We conducted our audits in accordance with auditing standards generally accepted in the 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. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as 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 financial position of Hybridon, Inc. at December 31, 2003 and 2002 and the results of its operations and its cash flow for the years then ended in conformity with accounting principles generally accepted in the United States.

As discussed above, the financial statements of Hybridon, Inc. for the year ended December 31, 2001 were audited by other auditors who have ceased operations. As described in Note 2(d), in 2003 the Company (a) reclassified investment income from revenue to other income and (b) reclassified interest expense from operating expenses to other expenses. In 2002 the Company (a) reclassified the proceeds from the 2001 sale of certain securities designated as trading securities from cash flows from investing activities to cash flows from operating activities and (b) disclosed separately the weighted average grant date fair value and exercise price of stock options granted with exercise prices equal to, exceeding or less than market price on the grant date in 2001. The 2001 financial statements have been revised to reflect the reclassification and additional disclosures described above. We audited the adjustments that were applied in 2001 to reflect the reclassifications and the additional disclosures in 2001 as described below.

With respect to the investment income and interest expense adjustment, we (a) agreed the amounts reclassified to the amounts originally presented in the 2001 Consolidated Statement of Operations as a component of revenues and expenses, respectively and (b) tested the mathematical accuracy of the (loss) income from continuing operations in the reclassified 2001 Consolidated Statement of Operations. With respect to the trading securities adjustment, we (a) agreed the 2001 receipt of 857,143 shares of Isis Pharmaceuticals, Inc. ("Isis") common stock to the Company's 2001 independent broker statement; and (b) agreed the 2001 proceeds of $15,619,475 from the sale of the aforementioned shares of Isis common stock to the Company's 2001 independent broker statement and agreed such amount to the amount presented as proceeds from sale of trading securities in the 2001 Consolidated Statement of Cash Flows. With respect to the stock option grants, we (a) agreed the separately reported weighted average grant date fair value and exercise price of stock options granted in 2001 reported in Note 2(k) to a schedule prepared by the Company from its underlying records; (b) agreed the information contained in the aforementioned schedule to the signed minutes of the 2001 Board of Directors and Compensation Committee meetings; and (c) reconciled the number of stock options listed as granted within the aforementioned schedule to the number of stock options listed as granted in Note 9(d).

In our opinion, such adjustments and additional disclosures are appropriate and have been properly applied. However, we were not engaged to audit, review, or apply any procedures to the 2001 financial statements of the Company other than with respect to such adjustments described in Note 2(d) and, accordingly, we do not express an opinion or any other form of assurance on the 2001 financial statements taken as a whole.

/s/ ERNST & YOUNG LLP

Boston, Massachusetts

January 24, 2004, except for Note 18
as to which the date is February 2, 2004

THE FOLLOWING REPORT IS A COPY OF A REPORT PREVIOUSLY ISSUED BY ARTHUR ANDERSEN LLP AND HAS NOT BEEN REISSUED BY ARTHUR ANDERSEN LLP.

REPORT OF INDEPENDENT PUBLIC ACCOUNTANTS

To Hybridon, Inc.:

We have audited the accompanying consolidated balance sheets of Hybridon, Inc. (a Delaware corporation) as of December 31, 2001 and 2000, and the related consolidated statements of operations, stockholders' equity (deficit) and cash flows for each of the three years in the period ended December 31, 2001. These financial statements are the responsibility of Hybridon, Inc.'s management. Our responsibility is to express an opinion on these financial statements based on our audits.

We conducted our audits in accordance with auditing standards generally accepted in the 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. An audit includes examining, on a test basis, evidence supporting the amounts and disclosures in the financial statements. An audit also includes assessing the accounting principles used and significant estimates made by management, as well as 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 financial position of Hybridon, Inc. and subsidiaries as of December 31, 2001 and 2000, and the results of their operations and their cash flows for each of the three years in the period ended December 31, 2001, in conformity with accounting principles generally accepted in the United States.

/s/ ARTHUR ANDERSEN LLP

Boston, Massachusetts

February 21, 2002

HYBRIDON, INC. AND SUBSIDIARIES

CONSOLIDATED BALANCE SHEETS

	December 31,	
	2003	2002
ASSETS		
Current assets:		
Cash and cash equivalents	$ 7,607,655	$ 2,527,500
Short-term investments	6,060,420	16,647,417
Receivables	202,936	406,313
Prepaid expenses and other current assets	101,697	191,770
Total current assets	13,972,708	19,773,000
Long-term investments	—	941,069
Property and equipment, net	436,813	534,764
Total Assets	$ 14,409,521	$ 21,248,833
LIABILITIES AND STOCKHOLDERS' EQUITY		
Current liabilities:		
Accounts payable	$ 675,926	$ 831,192
Accrued expenses	1,123,058	828,227
Current portion of capital lease	—	33,591
Current portion of deferred revenue	127,537	442,333
9% convertible subordinated notes payable	1,306,000	—
Total current liabilities	3,232,521	2,135,343
9% convertible subordinated notes payable	—	1,306,000
Deferred revenue, net of current portion	651,192	363,360
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 — 489,205 and 678,362 shares at December 31, 2003 and 2002, respectively		
Liquidation value — $494,912 at December 31, 2003	4,892	6,784
Common stock, $0.001 par value		
Authorized — 150,000,000 shares		
Issued and outstanding — 70,482,570 and 47,944,857 shares at December 31, 2003 and 2002, respectively	70,483	47,945
Additional paid-in capital	294,373,630	278,578,678
Accumulated deficit	(283,882,840)	(261,142,926)
Accumulated other comprehensive loss	(2,995)	(1,944)
Deferred compensation	(37,362)	(44,407)
Total stockholders' equity	10,525,808	17,444,130
Total Liabilities and Stockholders' Equity	$ 14,409,521	$ 21,248,833

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

HYBRIDON, INC. AND SUBSIDIARIES

CONSOLIDATED STATEMENTS OF OPERATIONS

	Years Ended December 31,		
	2003	2002	2001
Revenues:			
Alliance revenue	$ 869,975	$29,560,211	$ 987,556
Royalty and other income	26,597	45,719	134,225
Total revenues	896,572	29,605,930	1,121,781
Operating expenses:			
Research and development	10,817,288	7,877,343	4,868,035
General and administrative	6,923,899	7,054,023	5,051,344
Stock-based compensation from repriced options (1)	542,666	(1,297,445)	1,761,657
Total operating expenses	18,283,853	13,633,921	11,681,036
(Loss) income from operations	(17,387,281)	15,972,009	(10,559,255)
Other income (expense):			
Investment income, net	190,178	649,554	577,267
Interest expense	(117,540)	(150,023)	(1,319,387)
Loss on conversion of 8% convertible subordinated notes payable	—	—	(1,411,876)
Gain on sale of securities, net	103,585	—	5,217,451
(Loss) income from continuing operations	(17,211,058)	16,471,540	(7,495,800)
Income from discontinued operations	—	—	2,662,597
(Loss) income before provision for income taxes	(17,211,058)	16,471,540	(4,833,203)
Income tax benefit (provision)	—	500,000	(500,000)
Net (loss) income	(17,211,058)	16,971,540	(5,333,203)
Accretion of preferred stock dividends	(5,528,856)	(4,246,282)	(8,341,935)
Net (loss) income applicable to common stockholders	$(22,739,914)	$12,725,258	$(13,675,138)
(Loss) income per share from continuing operations:			
Basic	$ (0.34)	$ 0.36	$ (0.26)
Diluted	$ (0.34)	$ 0.32	$ (0.26)
Net (loss) income per share:			
Basic	$ (0.45)	$ 0.27	$ (0.44)
Diluted	$ (0.45)	$ 0.24	$ (0.44)
Shares used in computing basic net (loss) income per common share	51,053,415	46,879,232	30,820,098
Shares used in computing diluted net (loss) income per common share	51,053,415	52,984,415	30,820,098
(1) The following summarizes the allocation of stock based compensation from repriced options			
Research and development	$ 403,310	$ (925,210)	$ 1,060,404
General and administrative	139,356	(372,235)	701,253
Total	$ 542,666	$ (1,297,445)	$ 1,761,657

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		Series B Convertible Preferred Stock		Common Stock	
	Number of Shares	$0.01 Par Value	Number of Shares	$0.01 Par Value	Number of Shares	$0.001 Par Value
Balance, December 31, 2000	626,170	$ 6,262	—	$ —	18,382,237	$ 18,382
Exercise of common stock options and warrants	—	—	—	—	4,965,715	4,966
Sale of common stock	—	—	—	—	510,000	510
Issuance of stock, stock options and warrants for services	—	—	—	—	298,530	298
Issuance of stock bonus	—	—	—	—	157,471	157
Issuance of stock options to employees	—	—	—	—	—	—
Amortization of deferred compensation	—	—	—	—	—	—
Conversion of 8% notes into stock	—	—	76,046	760	1,140,448	1,140
Preferred stock dividends	40,075	401	2,213	22	—	—
Conversion of preferred into common stock	(26,079)	(261)	(78,259)	(782)	20,178,124	20,179
Stock-based compensation from repriced options	—	—	—	—	—	—
Net loss	—	—	—	—	—	—
Balance, December 31, 2001	640,166	6,402	—	—	45,632,525	45,632
Exercise of common stock options and warrants	—	—	—	—	1,162,172	1,162
Issuance of stock under the Isis Agreement and warrants	—	—	—	—	1,005,499	1,006
Issuance of stock options to employees	—	—	—	—	—	—
Amortization of deferred compensation	—	—	—	—	—	—
Conversion of 8% notes into stock	—	—	—	—	52,637	53
Preferred stock dividends	42,107	421	—	—	—	—
Conversion of preferred into common stock	(3,911)	(39)	—	—	92,024	92
Stock-based compensation from repriced options	—	—	—	—	—	—
Comprehensive income:						
Unrealized loss on marketable securities	—	—	—	—	—	—
Net income	—	—	—	—	—	—
Total comprehensive income	—	—	—	—	—	—
Balance, December 31, 2002	678,362	6,784	—	—	47,944,857	47,945
Sale of common stock	—	—	—	—	20,053,022	20,053
Repurchase of common stock	—	—	—	—	(4,643,034)	(4,643)
Exercise of common stock options and warrants	—	—	—	—	173,860	174
Issuance of stock options and stock for services	—	—	—	—	75,882	76

Amortization of deferred compensation	—	—	—	—	—	—
Preferred stock dividends	44,777	447	—	—	—	—
Conversion of preferred into common stock	(233,934)	(2,339)	—	—	6,877,983	6,878
Stock-based compensation from repriced options	—	—	—	—	—	—
Comprehensive income:						
Unrealized loss on marketable securities	—	—	—	—	—	—
Net loss	—	—	—	—	—	—
Total comprehensive income	—	—	—	—	—	—
Balance, December 31, 2003	489,205	$ 4,892	—	$ —	70,482,570	$ 70,483

[Additional columns below]

[Continued from above table, first column(s) repeated]

	Additional Paid-In Capital	Accumulated Deficit	Accumulated Other Comprehensive Loss	Deferred Compensation	Total Stockholders' Equity (Deficit)
Balance, December 31, 2000	$252,645,636	$(260,193,046)	$ —	$ (7,236)	$ (7,530,002)
Exercise of common stock options and warrants	312,228	—	—	—	317,194
Sale of common stock	427,890	—	—	—	428,400
Issuance of stock, stock options and warrants for services	898,269	—	—	(10,756)	887,811
Issuance of stock bonus	88,419	—	—	—	88,576
Issuance of stock options to employees	112,192	—	—	(112,192)	—
Amortization of deferred compensation	—	—	—	42,602	42,602
Conversion of 8% notes into stock	9,301,791	—	—	—	9,303,691
Preferred stock dividends	8,341,512	(8,341,935)	—	—	—
Conversion of preferred into common stock	(19,136)	—	—	—	—
Stock-based compensation from repriced options	1,761,657	—	—	—	1,761,657
Net loss	—	(5,333,203)	—	—	(5,333,203)
Balance, December 31, 2001	273,870,458	(273,868,184)	—	(87,582)	(33,274)
Exercise of common stock options and warrants	458,514	—	—	—	459,676
Issuance of stock under the Isis Agreement and warrants	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	31,529	—	—	—	31,582
Preferred stock dividends	4,245,861	(4,246,282)	—	—	—
Conversion of preferred into common stock	(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	278,578,678	(261,142,926)	(1,944)	(44,407)	17,444,130
Sale of common stock	13,031,797	—	—	—	13,051,850
Repurchase of common stock	(3,477,632)	—	—	—	(3,482,275)
Exercise of common stock options and warrants	91,963	—	—	—	92,137
Issuance of stock options and stock for services	82,288	—	—	—	82,364
Amortization of deferred compensation	—	—	—	7,045	7,045
Preferred stock dividends	5,528,409	(5,528,856)	—	—	—
Conversion of preferred into common stock	(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 income	—	—	—	—	(17,212,109)
Balance, December 31, 2003	$294,373,630	$(283,882,840)	$ (2,995)	$ (37,362)	$ 10,525,808

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,		
	2003	2002	2001
Cash Flows from Operating Activities:			
Net (loss) income	$(17,211,058)	$ 16,971,540	$ (5,333,203)
Income from discontinued operations	—	—	2,662,597
(Loss) income from continuing operations	(17,211,058)	16,971,540	(7,995,800)
Adjustments to reconcile net loss to net cash used in operating activities —			
Realized (gain) loss on marketable securities	(103,585)	—	1,664,810
Stock repurchase expense	1,857,214	—	—
Stock-based compensation	542,666	(1,297,445)	1,850,233
Depreciation and amortization expense	280,596	552,115	37,703
Issuance of stock options and stock for services	82,364	—	177,786
Amortization of deferred compensation	7,045	49,325	42,602
Amortization of deferred financing costs	—	10,586	162,465
Issuance of common stock and warrants	—	1,264,669	—
Non cash interest expense	—	21,882	912,224
Extraordinary loss on exchange of 8% convertible subordinated notes payable	—	—	1,411,876
Proceeds from trading securities, net	—	—	15,619,475
Gain on sale of property and equipment	—	—	(45,560)
Changes in operating assets and liabilities —			
Receivables	203,377	(131,450)	(243,351)
Prepaid expenses and other current assets	90,073	(145,364)	(6,301)
Accounts payable and accrued expenses	139,565	144,892	(506,387)
Deferred revenue	(266,771)	(28,422,685)	12,654,116
Net cash (used in) provided by continuing operating activities	(14,378,514)	(10,981,935)	25,735,891
Net cash provided by discontinued operations	—	—	3,000,000
Cash Flows from Investing Activities:			
Purchases of held-to-maturity securities	—	(14,582,249)	(13,653,578)
Purchases of available-for-sale securities	(17,681,672)	(8,219,615)	—
Proceeds from sale of available-for-sale securities	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	14,080,000	7,816,000	—
Proceeds from sale and maturities of securities, net	—	—	4,607,995
Purchases of property and equipment	(53,943)	(371,584)	(90,322)
Proceeds from sale of property and equipment	—	—	45,560
Net cash provided by (used in) investing activities	11,687,762	(7,509,723)	(9,090,345)
Cash Flows from Financing Activities:			
Sale of common stock and warrants, net of issuance costs	13,051,850	—	428,400
Repurchase of common stock	(5,339,489)	—	—
Proceeds from exercise of common stock options and warrants	92,137	459,676	317,194
Payments on debt	—	(284,102)	(6,000,000)
Payments on capital lease	(33,591)	(79,711)	—
Decrease in restricted cash	—	—	5,000,000
Net cash provided by (used in) financing activities	7,770,907	95,863	(254,406)
Net increase (decrease) in cash and cash equivalents	5,080,155	(18,395,795)	19,391,140
Cash and cash equivalents, beginning of period	2,527,500	20,923,295	1,532,155
Cash and cash equivalents, end of period	$ 7,607,655	$ 2,527,500	$ 20,923,295

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

HYBRIDON, INC. AND SUBSIDIARIES

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

December 31, 2003

(1) Organization

Hybridon, Inc. (the Company) was incorporated in the State of Delaware on May 25, 1989. The Company is engaged in the discovery and development of novel therapeutics and diagnostics using synthetic DNA. The Company's activities are primarily based on two technologies: immunomodulatory oligonucleotide (IMO) technology, which modulates responses of the immune system using synthetic DNA containing specific sequences that mimic bacterial DNA and antisense technology, which uses synthetic DNA to block the production of disease causing proteins at the cellular level.

Since inception, the Company has been primarily engaged in research and development and manufacturing. To date, all revenues received by the Company have been from collaboration and licensing agreements. In addition, the Company manufactured synthetic DNA and reagent products within its Hybridon Specialty Products Division, or HSP, prior to its disposal in September 2000 (see Note 12).

The Company has incurred operating losses in most fiscal years and had an accumulated deficit of $283.9 million at December 31, 2003. The Company had cash, cash equivalents and short-term investments of $13.7 million at December 31, 2003. Although, based on its current operating plan, the Company believes that these funds will be sufficient to fund operations through December 2004, the Company may be required to reduce planned activities in order 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 December 2004, the Company must raise additional funds in 2004 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.

HYBRIDON, INC. AND SUBSIDIARIES

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

December 31, 2003

(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, 2003 and 2002 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. During 2002, the Company sold three of its securities issued by two corporations which the Company had classified as "held-to-maturity" as of December 31, 2001. The Company sold such securities when the underlying corporations' credit ratings were down-graded. In order to avoid incurring any potential losses, the Company sold these securities for their approximate book value. For the years ended December 31, 2003 and 2002, there were no losses or permanent declines in value included in "Gain on sale of securities, net" for any securities. For the year ended December 31, 2001, losses from the sale of Isis shares were included in "Gain on sale of securities, net." There were no permanent declines in value included in "Gain on sale of securities, net" for the year ended December 31, 2001.

Short-term held-to-maturity investments have maturities of greater than three months and mature within one year of the balance sheet date. There were no long-term held-to-maturity investments as of December 31, 2003 and 2002. 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 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, 2003 and 2002, the Company's investments consisted of the following:

	December 31,	
	2003	2002
Short-term investments		
Held-to-maturity at amortized cost:		
Government bonds	$ —	$10,047,377
Corporate bonds	—	4,136,666
Available-for sale at market value:		
Government bonds	999,420	—
Corporate bonds	1,561,000	463,374
Auction securities	3,500,000	2,000,000
Total short-term investments	6,060,420	16,647,417
Long-term available-for-sale corporate bonds	—	941,069
Total	$6,060,420	$17,588,486

The following is a summary of available-for-sale securities:

	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

	December 31, 2002			
	Cost	Gross Unrealized Losses	Gross Unrealized Gains	Estimated Fair Value
Corporate bonds:				
Due in one year or less	$ 462,346	$ —	$ 1,028	$ 463,374
Due in one to two years	944,041	2,972	—	941,069
Auction Securities	2,000,000	—	—	2,000,000
Total	$3,406,387	$ 2,972	$ 1,028	$3,404,443

Although unrealized losses exist as of December 31, 2003, the Company does not believe they are other-than-temporary based on the nature of the investment and the lack of any adverse events.

HYBRIDON, INC. AND SUBSIDIARIES

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

December 31, 2003

(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.

In accordance with Financial Accounting Standards No. 145, (FAS 145), *Rescission of FASB Statements No. 4, 44 and 64, Amendment of FASB Statement No. 13, and Technical Corrections*, the Company reclassified its $1.4 million loss on the conversion of 8% notes discussed in Note 5(b) from an extraordinary item to Other Expense in the Consolidated Statement of Operations for the year ended December 31, 2001.

The Company reclassified investment income from revenue to other income and interest expense from operating expenses to other expenses in the Consolidated Statements of Operations for the years ended December 31, 2002 and 2001 to conform with the December 31, 2003 presentation.

The Company reclassified auction securities from cash and cash equivalents to short term investments in the Consolidated Balance Sheets for the year ended December 31, 2002 to conform with the December 31, 2003 presentation.

The Company reclassified the proceeds from the 2001 sale of certain securities designated as trading securities (see Note 2(b)) from cash flows from investing activities to cash flows from operating activities in the Consolidated Statement of Cash Flows for the year ended December 31, 2001.

The Company disclosed separately the weighted average grant date fair value and exercise price of stock options granted with exercise prices equal to, exceeding or less than the market price on the grant date in 2001 (see Note 2(k)).

(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.

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, receivables and debt obligations. The estimated fair values of these financial instruments approximates their carrying values as of December 31, 2003 and 2002, respectively. The estimated fair values have been determined through information obtained from market sources and management estimates. As of December 31, 2003 and 2002, 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, 2003 and 2002 is comprised of reported net income or loss and net unrealized losses on investments included in "Accumulated other comprehensive loss" on the accompanying consolidated balance sheet. The Company's comprehensive loss is the same as the reported net loss for the year ended December 31, 2001.

(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, 2003 and 2001 as the effects of the Company's potential common stock equivalents are antidilutive (see Note 13).

(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, 2003 and 2002, all assets were located in the United States.

(j) Derivative Instruments and Hedging

The Company applies SFAS No. 133, *Accounting for Derivative Instruments and Hedging Activities*, as amended by SFAS Nos. 137 and 138. These statements establish accounting and reporting standards for derivative instruments, including derivative instruments embedded in other contracts and for hedging activities. In addition, the Emerging Issues Task Force (EITF) has issued a number of derivative-related tentative and final consensuses. The Company did not own any derivative instruments at December 31, 2003 and 2002.

(k) 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, 2003, 2002, and 2001 are as follows:

	2003	2002	2001
Average risk free interest rate	3.30%	4.23%	4.77%
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)	$ 0.79	$ 0.70	$ 0.59

HYBRIDON, INC. AND SUBSIDIARIES

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

December 31, 2003

For the years ended December 31, 2003, 2002 and 2001, 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
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
2001 Option Grants			
Weighted average grant date fair value of options granted during the period	$0.57	$ 0.36	$ 0.65
Weighted average exercise price of options granted during the period	$0.75	$ 1.06	$ 0.81

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.

HYBRIDON, INC. AND SUBSIDIARIES

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

December 31, 2003

The pro forma effect of applying SFAS No. 123 for the three years ended December 31, 2003 would be as follows:

	2003	2002	2001
Net (loss) income applicable to common stockholders, as reported	$(22,739,914)	$12,725,258	$(13,675,138)
Less: stock-based compensation expense (income) included in reported net (loss) income	542,666	(1,297,445)	1,761,657
Add: stock-based employee compensation expense determined under fair value based method for all awards	(1,078,898)	(1,586,526)	(2,215,259)
Pro forma net (loss) income applicable to common stockholders, as adjusted for the effect of applying SFAS No. 123	$(23,276,146)	$ 9,841,287	$(14,128,740)
Basic net (loss) income per common shares —			
As reported	$ (0.45)	$ 0.27	$ (0.44)
Pro forma	$ (0.46)	$ 0.21	$ (0.46)
Diluted net (loss) income per common shares —			
As reported	$ (0.45)	$ 0.24	$ (0.44)
Pro forma	$ (0.46)	$ 0.19	$ (0.46)

The effects on years ended December 31, 2003, 2002 and 2001 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.

(l) New Accounting Pronouncements

In January 2003, the FASB issued Interpretation No. 46, *"Consolidation of Variable Interest Entities,"* as amended by FASB Staff Position No. FIN 46-6. Interpretation No. 46 provides guidance for identifying a controlling interest in a Variable Interest Entity ("VIE") established by means other than voting interests. Interpretation No. 46 also requires consolidation of a VIE by an enterprise that holds such a controlling interest. The effective date for this Interpretation for the Company will be January 1, 2004. The adoption of this Statement is not expected to have a material impact on the financial statements of the Company.

In May 2003, the FASB issued SFAS No. 150, *"Accounting for Certain Financial Instruments with Characteristics of both Liabilities and Equity."* The Company does not currently have any financial instruments with characteristics of both liabilities and equity. As such, the adoption of this Statement is not expected to have a material impact on the Company's financial statements.

(m) Concentration of Credit Risk

Financial instruments that subject the Company to credit risk primarily consist of cash and cash equivalents and short-term and long-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, 2003, approximately 98% of the Company's cash, cash equivalents, and investments are held at one financial institution.

(3) Accrued Expenses

At December 31, 2003 and 2002, accrued expenses consist of the following:

	December 31	
	2003	2002
Payroll and related costs	$ 308,891	$200,308
Clinical trial expenses	364,070	129,425
Other	450,097	498,494
	$1,123,058	$828,227

(4) Property and Equipment

At December 31, 2003 and 2002, net property and equipment at cost consists of the following:

	December 31	
	2003	2002
Leasehold improvements	$ 407,812	$ 399,359
Laboratory equipment and other	1,761,077	1,715,587
Total property and equipment, at cost	2,168,889	2,114,946
Less: Accumulated depreciation and amortization	1,732,076	1,580,182
Property and equipment, net	$ 436,813	$ 534,764

For the years ended December 31, 2003 and 2002, laboratory equipment and other includes approximately $113,000 of office equipment financed under capital leases with accumulated depreciation of approximately $34,000 and $11,000, respectively. During 2002, the Company wrote off unused, fully depreciated property and equipment that had a cost of approximately $1,321,000. A gain of $45,560 is included in the 2001 statement of operations from a small portion of equipment sold in 2001.

Depreciation expense, which includes amortization of assets recorded under capital leases, was approximately $152,000, $93,000 and $38,000 in 2003, 2002 and 2001, respectively.

(5) Debt

(a) 9% Convertible Subordinated Notes Payable

Under the terms of the 9% Convertible Subordinated Notes Payable (the 9% Notes), the Company must make semi-annual interest payments on the outstanding principal balance through the maturity date of April 1, 2004. The 9% Notes are convertible at any time prior to the maturity date at a conversion price equal to $35.0625 per share. Upon a change of control of the Company, as defined, the Company will be required to offer to repurchase the 9% Notes at 150% of the original issue price. As of December 31, 2003 and 2002, $1,306,000 in principal of the 9% Notes was outstanding.

(b) 8% Convertible Notes Payable

On March 5, 2001, the Company made an offer to the holders of its 8% Notes to exchange their notes at a ratio of one share of a newly-designated class of Series B Convertible Preferred Stock (Series B Preferred

Stock) for each $100 in principal amount of notes tendered. On March 30, 2001, holders of $7.6 million of the Company's 8% Notes exchanged their notes for 76,046 shares of Series B Preferred Stock. The Company recorded a loss of $1.4 million related to the early extinguishment of the 8% Notes. The loss represented the difference between the carrying value of the 8% Notes and the fair value of the Series B Preferred Stock, as determined by the fair market value of the common stock into which the Series B Preferred Stock was convertible and the write-off of deferred financing costs and related legal fees. As a result of the exchange, the holders of the 8% Notes released their claim on $5.0 million of collateral held prior to the exchange.

In 2001, approximately $456,000 of the remaining 8% Notes were converted into 1,140,448 shares of common stock and all of the 78,259 shares of Series B Preferred Stock were converted into 19,564,500 shares of common stock. These conversions were based on a reduced conversion price of $0.40 per share which was agreed to with the holders of Series B Preferred Stock and 8% Note holders as part of the Company's early exercise program discussed in Note 8. In accordance with SFAS No. 84, *Induced Conversions of Convertible Debt*, the Company recorded a charge to interest expense of approximately $353,000. The charge was equal to the fair value of the common stock received less the fair value of common stock that would have been received pursuant to the original conversion terms of the 8% Notes.

Upon maturity of the 8% Notes on November 30, 2002, $31,582 of the remaining 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. There were no 8% Notes outstanding at December 31, 2003 or 2002.

(6) Collaboration and License Agreements

(a) 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 our 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.

Following the receipt of 357,143 shares from Isis in September 2001, the Company entered into a number of hedging contracts to protect against a decline in value of the Isis stock while the Company awaited registration of these shares which was necessary before the Company could sell the Isis stock. In accordance with SFAS No. 133, these hedging contracts were derivative instruments and were included in the balance sheet at fair market value with the corresponding changes in fair value recognized in earnings. In accordance with SFAS No. 115, the Company recorded an unrealized loss on the shares of approximately $902,000 prior to entering into these hedging contracts. On November 1, 2001, the Company received an additional 500,000 shares of Isis common stock. The Company did not enter into any hedging contracts in connection with the receipt of these shares and recorded a realized loss of approximately $457,000 on the sale of these shares in 2001. In addition, the $306,000 in fees associated with the execution of the hedging contracts was also charged to expenses during 2001. As a result, the Company incurred a net loss of $1,665,000 upon the sale of the Isis shares in November 2001 that is included in Gain on sale of securities, net in the accompanying Consolidated Statement of Operations.

HYBRIDON, INC. AND SUBSIDIARIES

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

December 31, 2003

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 SAB101, 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.

(b) Collaboration and License Agreement with Micrologix Biotech Inc.

On September 11, 2002, the Company and Micrologix Biotech 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 Micrologix 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, Micrologix 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 Micrologix 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 Micrologix issued to the Company without further consideration shares of preferred stock of Micrologix. 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 Micrologix, either (i) be converted into common stock of Micrologix at a conversion rate based on an average market price or (ii) be redeemed by Micrologix 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 Micrologix 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 Micrologix 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.

(c) 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, 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 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.

(d) Collaboration and License Agreement with Immune Response Corporation.

On October 8, 2003, the Company entered into a collaboration and license agreement with The Immune Response Corporation to cooperate on the research and development of an HIV vaccine combining Immune Response's whole-killed vaccine technology employed in Remune, an immune-based HIV therapeutic vaccine being evaluated in Phase II clinical trials, and Amplivax, the Company's 2nd generation IMO compound (also known as HYB2055) used as an adjuvant. Under the agreement, Immune Response will reimburse the Company 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 and a percentage of sublicense income received by Immune Response.

(e) 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. As a result of the Agreement with Isis Pharmaceuticals, Inc. (Note 6(a)), in 2001 the Company paid UMass approximately $1,177,000 based on the net consideration received from Isis.

(7) Sale of Investment in MethylGene Inc.

In 2001, the Company sold its ownership interest in MethylGene Inc., a Quebec company, for total proceeds of approximately $7.2 million (US), which was reduced by approximately $300,000 in professional fees. The Company recorded a net gain of approximately $6.9 million included in Gain on sale of securities, net in the accompanying consolidated statement of operations.

HYBRIDON, INC. AND SUBSIDIARIES

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

December 31, 2003

(8) 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 16). As of December 31, 2003, 2,195,005 of the Put Shares continued to be held in the name of Put Holders. The Company cannot determine at this time whether the Put Rights with respect to the remaining 4,986,591 Put Shares have terminated.

(b) Early Exercise Program

In 2001, the Company effected an "early exercise" program (the Early Exercise Program) to exchange its Series B Convertible Preferred Stock, several classes of its warrants, and its remaining 8% Notes for shares of the Company's common stock, in order to simplify the Company's capital structure and to reduce the number of outstanding securities which are exercisable for or convertible into shares of its common stock. The Company offered the holders of its Series B shares the right to convert such shares into common stock at a lower conversion price than that set forth in the Certificate of Designation governing the terms of their Series B Convertible Preferred Stock. The Company offered the holders of various warrants the opportunity to immediately exercise their warrants for the purchase of shares covered by such warrants at a reduced exercise price, either by paying the lower exercise price for such shares in cash or by engaging in a "cashless" transaction, whereby they could receive a reduced number of shares of common stock in exchange for warrants of equivalent value. The value of the warrants was determined by the Company based on advice from the Company's investment bankers. The Company offered the holders of its remaining 8% Notes the opportunity to exchange the 8% Notes for shares of the Company's common stock at a reduced conversion price. The results of the program were as follows:

- All holders of the Company's Series B Convertible Preferred Stock exchanged their shares for 19,564,500 shares of the Company's common stock;
- Holders of warrants priced between $0.60 and $2.40 exchanged their warrants for 4,669,808 shares of the Company's common stock; and
- $456,221 in 8% notes was exchanged for 1,140,448 shares of common stock.

HYBRIDON, INC. AND SUBSIDIARIES

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

December 31, 2003

In accordance with SFAS No. 84, *Induced Conversions of Convertible Debt*, the Company recorded a charge to accumulated deficit of approximately $4,100,000 in connection with the conversion of Series B Preferred Stock. The charge was equal to the fair value of the common stock received less the fair value of common stock that would have been received pursuant to the original conversion terms of the Series B Preferred Stock. This charge was recorded as accretion of preferred stock dividends on the accompanying Consolidated Statements of Operations and as a component of the net loss available to common stockholders.

In accordance with SFAS No. 123, *Accounting for Stock-Based Compensation*, the Company did not record any charges related to the warrant exchange as the fair value of the warrants immediately prior to the exchange was equal to the fair value of the common stock issued to the holders as settlement of the warrants. See Note 5 for the accounting for the conversion of the 8% Notes.

(c) Warrants

The Company has the following warrants outstanding and exercisable for the purchase of common stock at December 31, 2003:

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	9,759,682	0.93
	10,359,682	
Weighted average exercise price per share		$ 0.92

In 2001, the Company issued warrants to purchase 500,000 shares of common stock to an individual who provided consulting services to the Company related to the Isis Agreement. The Company valued these warrants using the Black-Scholes pricing model. The warrants' fair value of approximately $570,000 was accounted for as a direct cost of the Isis Agreement (see Note 6(a)). 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. In 2003, the Company sold warrants to purchase 6,015,934 shares of common stock with an exercise price of $1.00 to investors participating in the private placement offering (see Note 17). As part of the private placement offering, the Company also issued warrants to selected dealers and placement agents which assisted in the offering. Of these warrants, 2,458,405 have an exercise price of $0.73 and 1,325,342 have an exercise price of $1.00.

(d) 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 are fully vested. In October 1995, the Company terminated the issuance of additional options under the 1990 Option Plan. As of December 31, 2003, options to purchase a total of 80,734 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

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

December 31, 2003

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, 2003, options to purchase a total of 436,516 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, 2003, options to purchase a total of 151,000 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, 2003, options to purchase a total of 7,814,376 shares of common stock remained outstanding under the 1997 Stock Incentive Plan.

As of December 31, 2003, options to purchase 4,407,030 shares of common stock remain available for grant under the 1995 Stock Option Plan, the 1995 Director Plan and the 1997 Stock Incentive Plan.

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December 31, 2003

Stock option activity for the years ended December 31, 2003, 2002, and 2001 is summarized as follows:

	Number of Shares	Exercise Price Per Share	Weighted Average Price Per Share
Outstanding, December 31, 2000	5,401,833	$0.50 – $2.00	$ 0.67
Granted	9,515,987	0.50 – 1.18	0.78
Exercised	(295,907)	0.50 – 0.56	0.50
Terminated	(144,799)	0.50 – 0.56	0.51
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
Exercisable, December 31, 2001	6,913,118	$0.50 – $2.00	$ 0.71
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

	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	2,685,990	4.61	$ 0.50	2,666,850	$ 0.50
0.56	2,514,192	7.24	0.56	2,444,292	0.56
0.70 – 0.83	3,530,500	7.86	0.80	1,525,686	0.77
0.84	3,152,500	7.57	0.84	1,418,125	0.84
0.93 – 2.00	2,836,737	7.13	1.15	2,302,612	1.15
	14,719,919	6.96	$ 0.78	10,357,565	$ 0.75

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 measures 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, $2,079 and $13,516 in 2003, 2002 and 2001, respectively, related to grants to non-employees.

(e) 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 2003 and 2002, the Company issued 58,179 and 25,185 shares of common stock, respectively, under the Stock Purchase Plan.

(f) 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. For the years ended December 31, 2003 and 2001, the Company recognized approximately $543,000 and $1,762,000, respectively, as stock compensation expense from repriced options. A decrease in the intrinsic value of these options between January 1, 2002 and December 31, 2002 resulted in the credit of approximately $1,297,000 to stock compensation expense for the year ended December 31, 2002.

(g) 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 (8)(h). During 2001, the Company designated 85,000 shares as Series B convertible preferred stock. As of December 31, 2003 and 2002, there were no shares of Series B convertible preferred stock authorized or outstanding. As discussed in Note (15), 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, 2003 and 2002.

(h) 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. See Note 18 for the financial statement impact of the conversion of the Series A convertible preferred stock.

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.

(9) 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 approximate minimum commitments as of December 31, 2003, under existing lease agreements through the lease term, are as follows:

December 31,	Operating Leases
2004	$ 611,000
2005	611,000
2006	611,000
2007	204,000
	$2,037,000

During 2003, 2002, and 2001, facility rent expense for continuing operations, net of sublease income, was approximately $397,000, $282,000 and $293,000, respectively.

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(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 $143,000 for 2004.

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

In 2003, the Company paid Pillar S.A. and Pillar Investment Ltd., which are controlled by a director of the Company, 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 Limited, 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, in 2003, the Company also paid two other directors approximately $45,000 and $20,000, respectively, for consulting services provided to the Company in 2003. One of these directors was also paid $20,000 in 2003 for consulting services rendered during 2002.

(d) 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 UMass 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 declaration of interference named UMMC, and indirectly the Company, as the senior party. 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. The Company is not practicing nor does it intend to practice any of the intellectual property involved in either interference. Consequently, if the matters are 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.

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December 31, 2003

(10) 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, 2003, the Company had net operating loss and tax credit carryforwards for federal income tax purposes of approximately $241.0 million and $4.4 million, respectively, available to reduce federal taxable income and federal income taxes, respectively. These carryforwards expire through 2023. The Tax Reform Act of 1986 limits 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, 2003, 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 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, 2003 and 2002, the components of the deferred tax assets are approximately as follows:

	2003	2002
Operating loss carryforwards	$ 97,330,439	$ 90,275,000
Tax credit carryforwards	4,362,658	4,158,000
Other	692,546	791,000
	102,385,643	95,224,000
Valuation allowance	(102,385,643)	(95,224,000)
	$ —	$ —

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*.

(11) 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 $74,000, $58,000, and $44,000 of 401(k) benefits were charged to continuing operations during 2003, 2002, and 2001, respectively.

(12) Sale of Hybridon Specialty Products

In September 2000, the Company completed the sale of its Hybridon Specialty Products (HSP) business, which manufactured and marketed oligonucleotides to Avecia Biotechnology, a subsidiary of Avecia, Inc. of Manchester, United Kingdom, for up to $15.0 million. A payment of $3.0 million was held

back by Avecia since, as part of this transaction, the Company had entered into a supply agreement whereby it was committed to make minimum purchases during 2000 and 2001 on a "take or pay" basis if Avecia's third-party sales did not meet specified goals. Hybridon was also required to make quarterly payments to cover purchasing shortfalls, based on an agreed upon formula.

On September 20, 2001, the Company received the $3.0 million contingent payment in full from Avecia. Upon receipt of the $3.0 million payment, the Company applied approximately $1,032,000 toward the satisfaction of the above mentioned purchasing shortfall and recognized the remaining $1,968,000 as income from the sale of the discontinued operations. In November 2001, the Company also received a refund of approximately $695,000 of the Company's minimum payments to Avecia per the terms of the supply agreement. This refund increased the income from discontinued operations during the year ended December 31, 2001 to approximately $2,663,000.

(13) Income (Loss) Per Share

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

	Years Ended December 31,		
	2003	2002	2001
Numerator:			
(Loss) income from continuing operations	$(17,211,058)	$16,971,540	$ (7,995,800)
Income from discontinued operation	—	—	2,662,597
Net (loss) income	(17,211,058)	16,971,540	(5,333,203)
Accretion of preferred stock dividend	(5,528,856)	(4,246,282)	(8,341,935)
Numerator for basic (loss) income applicable to common shareholders	(22,739,914)	12,725,258	(13,675,138)
Effect of dilutive securities:			
Interest expense related to convertible debt	—	21,896	—
Numerator for diluted (loss) income applicable to common shareholders	$(22,739,914)	$12,747,154	$(13,675,138)
Denominator for basic (loss) income per share:			
Weighted average shares outstanding	51,053,415	46,879,232	30,820,098
Effect of dilutive securities:			
Common stock options and warrants	—	5,647,539	—
Convertible debt	—	457,644	—
Denominator for diluted (loss) income per share	51,053,415	52,984,415	30,820,098
(Loss) income per share — basic			
Continuing operations	$ (0.34)	$ 0.36	$ (0.26)
Discontinued operations	—	—	0.09
Net (loss) income per share	(0.34)	0.36	(0.17)
Accretion of preferred stock dividends	(0.11)	(0.09)	(0.27)
Net (loss) income per share applicable to common stockholders	$ (0.45)	$ 0.27	$ (0.44)
(Loss) income per share — diluted			
Continuing operations	$ (0.34)	$ 0.32	$ (0.26)
Discontinued operations	—	—	0.09
Net (loss) income per share	(0.34)	0.32	(0.17)
Accretion of preferred stock dividends	(0.11)	(0.08)	(0.27)
Net (loss) income per share applicable to common stockholders	$ (0.45)	$ 0.24	$ (0.44)

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December 31, 2003

For the years ended December 31, 2003 and 2001, diluted net loss per share from continuing 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 39,545,229 and 40,714,556 for the years ended December 31, 2003 and 2001, respectively, and consist of stock options, warrants, convertible preferred stock and convertible debt instruments (on an as-converted basis). For the year ended 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.

(14) Supplemental Disclosure of Cash Flow Information

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

	Years Ended December 31,		
	2003	2002	2001
Supplemental disclosure of cash flow information:			
Cash paid for interest	$ 117,540	$ 121,278	$ 379,294
Cash (received) paid for taxes	$ —	$ (450,000)	$ 450,000
Supplemental disclosure of non cash financing and investing activities:			
Exchange of 8% convertible notes payable for Series B preferred stock and common stock	$ —	$ 31,582	$ 8,060,779
Accretion of Series A and Series B preferred stock dividends	$3,972,856	$4,246,282	$ 4,241,935
Dividend from induced conversion of Series A and Series B preferred stock	$1,556,000	$ —	$ 4,100,000
Issuance of stock options and stock for services	$ 82,364	$ —	$ 140,358
Interest paid in kind on 8% Notes	$ —	$ 27,657	$ 305,180
Conversion of Series A preferred stock into common stock	$ 6,878	$ 92	$ 614
Conversion of Series B preferred stock into common stock	$ —	$ —	$ 19,565
Issuance of stock options to non-employees, net of terminations	$ —	$ —	$ 10,756
Issuance of warrants in connection with consulting services	$ —	$ 98,000	$ 569,667
Cashless exercise of stock warrants	$ 19	$ 247	$ 4,443
Fair value of ISIS stock received	$ —	$ —	$17,284,288
Deferred compensation relating to issuance of stock options	$ —	$ 6,150	$ 112,192
Equipment acquired under capital lease	$ —	$ 113,303	$ —

(15) 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, 15 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 15 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 15 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.

(16) 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 from two Middle Eastern stockholders and their affiliates. 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 the quarter ending March 31, 2003.

(17) Financing

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 through 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 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 $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.

(18) Subsequent Events

As described in Note 8(h), the sixty-day Series A convertible preferred stock special conversion period ended on February 2, 2004. From January 1, 2004 through February 2, 2004, 488,570 shares of Series A convertible preferred stock were converted into 14,369,740 shares of the Company's common stock at the favorable conversion ratio. As a result of this conversion, $570,000 of dividends accreted during the year ended December 31, 2003 (dividends accrete semi-annually through April 1 and October 1) will be reversed during the year ended December 31, 2004 because the former holders of these shares of Series A convertible preferred stock were no longer entitled to such dividends once their shares of Series A convertible preferred stock were converted into common stock.

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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 (Proforma Unaudited)
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 Dividend	
	4th Quarter 2003	1st Quarter 2004 (Proforma Unaudited)
Accretion of dividend expected to be paid on April 1, 2004	$ 741	$ 159
Accretion of dividend that would have been paid on April 1, 2004 if preferred shares were not converted in January and February 2004	570,000	(570,000)
Market value of 25% additional shares issued upon conversion	1,556,000	3,245,492
Total preferred stock dividend	$ 2,126,741	$ 2,675,651

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 Company anticipates an additional $3.2 million of such dividends in the first quarter of 2004. 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.

In January 2004, the Company filed a shelf registration statement on Form S-3 with the SEC. This shelf registration statement permits the Company to offer, from time to time, up to 20,000,000 shares of common stock, including shares of common stock issuable upon exercise of warrants.

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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.		8-A	December 4, 2003	001-31918
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

Exhibit Number	Description	Filed with this Form 10-K	Incorporated by Reference		
			Form or Schedule	Filing Date with SEC	SEC File Number
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
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	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
10.29††	Employment Agreement dated April 1, 2002 between Hybridon, Inc. and Robert G. Andersen.		10-Q	May 14, 2002	000-27352

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Exhibit Number	Description	Filed with this Form 10-K	Incorporated by Reference		
			Form or Schedule	Filing Date with SEC	SEC File Number
10.30††	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
10.31††	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
10.32††	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
10.33††	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
10.34††	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
10.35	Consulting Agreement effective as of October 1, 2002 between Hybridon, Inc. and Pillar, S.A.		10-Q	October 24, 2002	000-27352
10.36†	License Agreement by and between Louisiana State University and Hybridon, Inc., dated July 1, 1998.		10-K	March 31, 2003	000-27352
10.37	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
10.38	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
10.39	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

Exhibit Number	Description	Filed with this Form 10-K	Incorporated by Reference		
			Form or Schedule	Filing Date with SEC	SEC File Number
10.40	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
23.1	Consent of Ernst & Young LLP.	X			
23.2	Limitation of Remedies Against Arthur Andersen LLP. Please see Item 9 of this Annual Report on Form 10-K.				
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 23.1

CONSENT OF ERNST & YOUNG LLP

We consent to the incorporation by reference in the Registration Statements (Form S-8 Nos. 333-3898, 333-3900, 333-3902, 333-34008 and 333-71938, Form S-2 as amended by Form S3/A No. 333-109630 and Form S-3 No. 333-111903) and the related Prospectuses of Hybridon, Inc. of our report dated January 24, 2004 (except for Note 18, as to which date is February 2, 2004), with respect to the consolidated financial statements of Hybridon, Inc. included in the Annual Report (Form 10-K) for the year ended December 31, 2003.

/s/ Ernst & Young LLP

Boston, Massachusetts
March 18, 2004

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, Stephen R. Seiler, 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) [Paragraph omitted in accordance with SEC transition instructions contained in SEC Release 34-47986]

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/STEPHEN R. SEILER

Stephen R. Seiler
Chief Executive Officer

Dated: March 19, 2004

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) [Paragraph omitted in accordance with SEC transition instructions contained in SEC Release 34-47986]

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 19, 2004

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, 2003 as filed with the Securities and Exchange Commission on the date hereof (the "Report"), the undersigned, Stephen R. Seiler, 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/STEPHEN R. SEILER

Stephen R. Seiler
Chief Executive Officer

Date: March 19, 2004

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, 2003 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 19, 2004