INTROGEN THERAPEUTICS INC
Form 10-K
March 05, 2004

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UNITED STATES SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

Form 10-K

(Mark One)

þ **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

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

For the transition period from to .

Commission file number: 000-21291

Introgen Therapeutics, Inc.

(Exact name of registrant as specified in its charter)

Delaware	**74-2704230**
(State or other jurisdiction of incorporation or organization)	*(I.R.S. Employer Identification Number)*
301 Congress Avenue, Suite 1850 Austin, Texas	**78701**
(Address of principal executive offices)	*(Zip Code)*

Registrant s telephone number, including area code:

(512) 708-9310

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

None

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

Common Stock, $0.001 par value

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 such filing requirements for the past 90 days. Yes þ No o

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. þ

Indicate by check mark whether the Registrant is an accelerated filer (as defined in Securities Exchange Act Rule 12b-2). Yes o No þ

The aggregate market value of the voting stock (common stock) held by non-affiliates of the Registrant, as of the last day of the Registrant s second fiscal quarter, was approximately $61.6 million based upon the last sale price reported on the Nasdaq National Market for June 30, 2003. For purposes of this disclosure, shares of common stock held by persons who hold more than 5% of the outstanding shares of common stock and shares held by executive officers and directors of the Registrant have been excluded because such persons may be deemed to be affiliates. This determination is not necessarily conclusive.

As of March 1, 2004, the Registrant had 26,583,274 shares of common stock, $0.001 par value, issued and outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Certain information required by Items 10, 11, 12, 13 and 14 of Form 10-K is incorporated by reference to the Registrant s proxy statement (2004 Proxy Statement) for the 2004 Annual Stockholders Meeting, which will be filed with the Securities and Exchange Commission within 120 days after the close of the Registrant s fiscal year ended December 31, 2003.

INTROGEN THERAPEUTICS, INC.

ANNUAL REPORT ON FORM 10-K

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Certification of CEO & CFO - Section 906

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PART I

Item 1. *Business*

This Annual Report on Form 10-K contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. These statements include, among others, statements concerning our future operations, financial condition and prospects, and our business strategies. The words believe, expect, anticipate and other similar expressions generally identify forward-looking statements. Investors in our common stock are cautioned not to place undue reliance on these forward-looking statements. These forward-looking statements are subject to substantial risks and uncertainties that could cause our future business, financial condition, or results of operations to differ materially from historical results or currently anticipated results. Investors should carefully review the information contained under the caption Risk Factors in Management s Discussion and Analysis of Financial Condition and Results of Operations and elsewhere in, or incorporated by reference into, this Annual Report on Form 10-K.

Access to Company Information

Our Internet website address is *www.introgen.com.* Our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934 are available free of charge through our website as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities and Exchange Commission. Our website and the information contained therein or connected thereto is not intended to be incorporated into this Annual Report on Form 10-K.

Overview

Introgen Therapeutics, Inc. was incorporated in Delaware in 1993. We are a biopharmaceutical company focused on the discovery, development and commercialization of targeted therapies for the treatment of cancer and other diseases. We are developing product candidates to treat a wide range of cancers using non-integrating gene agents. These agents are designed to increase production of normal cancer-fighting proteins that act to overpower cancerous cells. Our lead product candidate, ADVEXIN therapy, combines the p53 gene with a non-replicating, non-integrating adenoviral gene delivery system that we have developed and extensively tested. The p53 gene is one of the most potent members of a group of naturally occurring tumor suppressor genes, which act to kill cancer cells, arrest cancer cell growth and protect cells from becoming cancerous.

We are conducting two multi-national, multi-site Phase 3 clinical trials of ADVEXIN therapy, both by itself and in combination with chemotherapy, in recurrent squamous cell cancer of the head and neck. Earlier multi-national, multi-site Phase 2 clinical trials of ADVEXIN therapy in 217 patients with recurrent squamous cell cancer of the head and neck treated previously with surgery, radiation or chemotherapy indicated that treatment with ADVEXIN therapy provided tumor growth control, including shrinkage and eradication of some tumors, and was well tolerated.

The design of our two Phase 3 clinical trials was agreed to by the Food and Drug Administration, or FDA, under its Special Protocol Assessment program, and we have received Fast Track designation for ADVEXIN therapy from the FDA. By designating ADVEXIN therapy as a Fast Track product, the FDA will take actions to expedite the evaluation and review of the ADVEXIN therapy marketing application. ADVEXIN therapy for head and neck cancer has also been designated as an Orphan Drug under the Orphan Drug Act, which may give us seven years of marketing exclusivity for ADVEXIN therapy for this indication if approved by the FDA.

We have also completed or are currently conducting numerous Phase 1 and Phase 2 clinical trials of ADVEXIN therapy by itself and in combination with chemotherapy or radiation therapy in a variety of cancers. These trials include a completed Phase 2 clinical trial of ADVEXIN administered as a complement with radiation therapy in non-small cell lung cancer; a Phase 2 clinical trial of ADVEXIN therapy combined

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with systemic chemotherapy for the treatment of breast cancer; a Phase 1/early Phase 2 clinical trial of ADVEXIN therapy for the treatment of advanced unresectable squamous cell esophageal cancer; a Phase 1 clinical trial of ADVEXIN therapy in prostate cancer; Phase 1 clinical trials of ADVEXIN therapy in bronchoalveolar cancer; and a Phase /early Phase 2 clinical trial in which ADVEXIN therapy is being administered to prevent precancerous oral lesions that have a high risk of developing into cancer.

To date, clinical investigators at sites in North America, Europe and Japan have treated over 500 patients with ADVEXIN therapy, establishing a large safety database. We hold the worldwide rights for pre-clinical and clinical development, manufacturing, marketing and commercialization of ADVEXIN therapy.

We are developing our second product candidate, INGN 241, for the treatment of solid tumors and in melanoma, a deadly form of skin cancer. INGN 241 combines the mda-7 gene with our adenoviral vector system to kill tumor cells, including metastatic tumor cells, through multiple mechanisms. A Phase 1/early Phase 2 trial indicated that in patients with various solid tumors, INGN 241 is well tolerated, displays minimal toxicity and is biologically active.

Our principal executive offices are located at 301 Congress Avenue, Suite 1850, Austin, Texas 78701 and our telephone number is (512) 708-9310. Our website is located at *www.introgen.com.* The information contained on our website is not a part of this Annual Report on Form 10-K.

Background

Gene Function and Genomics

A typical living cell in the body contains thousands of different proteins essential to cellular structure, growth and function. The cell produces proteins according to a set of genetic instructions encoded by DNA, which contains all the information necessary to control the cell s biological processes. DNA is organized into segments called genes, with each gene containing the information required to produce one or more specific proteins. The production of a protein that a particular gene encodes is known as gene expression or activity. Many of the proteins inside a cell participate in a series of receptor interactions and chemical reactions to form what are known as molecular pathways that enable a cell to perform its various metabolic functions. The improper expression of proteins by one or more genes can alter these pathways and affect a cell s normal function, frequently resulting in disease. The interaction of therapeutic agents with proteins in these pathways is known as targeted therapy. Targeted therapies are believed to be more precise in their action and have less potential for undesirable side effects.

In recent years, scientists have made significant progress toward understanding the nature of the complete set of human genes, which is referred to as the human genome, and evaluating the role that genes and the proteins they express play in both normal and disease states. Academic and governmental initiatives have sequenced a large number of the genes that comprise the human genome. As new genes are discovered and decoded within this sequence, scientists are identifying and understanding their functions and interactions within these pathways. These discoveries provide opportunities to develop targeted therapeutic applications for individual genes and the proteins they express, including treatment and prevention of disease.

Gene Therapy and Gene-Induced Protein Therapy Products

The common use of the term gene therapy relates to the application of genes to regulate cellular function or to correct cellular dysfunction. In this context, gene therapy processes involve the replacement or repair of genes to restore missing gene functions, correct aberrant gene functions, augment normal gene activity, neutralize the activity of defective genes or induce cell death. These applications generally contemplate a permanent or at least long lasting functioning of the administered gene, including a permanent integration into the patient s DNA.

Our gene-based products function differently from this model. Instead of replacing or repairing genes, our products use the proteins expressed by certain genes as therapeutic agents to selectively kill cancer cells while not harming normal cells. Under this approach, the genes expressing the therapeutic proteins do not integrate into the patient s DNA and are cleared from the body after administration. The result is pharmacologic

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intervention using the proteins produced by genes, such as p53 and mda-7, to create biopharmaceuticals with targeted, drug-like functionality. In some cases, the therapeutic protein expressed by the gene will simply act to replace a missing or dysfunctional protein or to augment the level of a protein that is otherwise inadequate to prevent disease or ameliorate an existing disease or dysfunction. In other cases, the therapeutic protein produced by the gene will act to eliminate the diseased cells through a process that scientists refer to as apoptosis. Apoptosis, or programmed cell death, is a normal process that the body uses to eliminate damaged cells and cells that are no longer necessary. In some circumstances, genes such as mda-7 send a signal for further proteins to be produced in cells beyond those in which the gene was initially expressed. This process is referred to as cytokine activity, which potentially results in an increased number of diseased tissue cells being addressed by gene-based therapy. The genes used to provide the protein for disease treatment are typically a normal human gene that is either being silenced in the disease tissue or is otherwise being expressed at too low a level to achieve the desired pharmacologic effect. Diseases like cancer come about by altering the function and expression of many genes which would otherwise act to protect the body.

In order to perform these processes, a gene for disease treatment, or therapeutic gene, is often combined with a delivery system, referred to as a vector, which enables the gene to enter the target cell and deliver the therapeutic protein it produces. The vector must be able to deliver a sufficient dose of the genes and the proteins they produce to cause a therapeutic effect. The most common delivery systems currently in use are modified versions of viruses such as adenoviruses. Scientists often use viruses as delivery systems because viruses have the ability to efficiently infect cells and carry their genetic material, or genome, into the cells. Scientists can modify these viruses by deleting pieces of the viral genome that are necessary for viral reproduction and replacing the deleted pieces with an additional gene which can cause the manufacture of a desired therapeutic protein. The resulting viral vector retains the ability of the virus to efficiently deliver the additional gene into cells, while losing the ability to reproduce itself and spread to other cells. While viruses are the most efficient means of introducing such genes into cells, scientists have also developed synthetic substances such as liposomes, which are structures made of fatty materials that have no viral pieces. The synthetic systems that lack any viral pieces, or non-viral systems, can also deliver genetic material to host cells. Scientists have developed these systems to mimic the characteristics of viral vector systems in order to expand the disease targets that can be treated with gene and their resulting proteins.

Many gene delivery systems in use today are based on adenoviral vectors. Scientists create adenoviral vectors using adenoviruses, which are among several common cold viruses. These vectors have been modified so that their ability to reproduce and spread will be inhibited in a human host. The DNA of adenoviral vectors rarely becomes incorporated into the cell genome. Instead, it remains as an independent genetic unit and eventually disintegrates. This feature protects normal cells that might have taken up the viral vector. For cancer treatment, where the goal is to rapidly kill or repair the cancer cells, the relatively short life of the adenoviral vector and its ability to carry sufficient genes for disease treatment makes its use particularly appropriate.

Cancer, a Genetic Disease

Cancer is the second leading cause of death in the United States, surpassed only by heart disease. In the United States, approximately 1.3 million people are newly diagnosed with cancer and over 557,000 people die from the disease each year. Although the prevalence of specific cancers varies among different populations, we believe that the overall incidence of cancer worldwide is similar to that experienced in the United States. The American Cancer Society estimates the annual direct cost of treating cancer patients in the United States is approximately $61.0 billion.

Cancer is a group of diseases in which the body s normal self-regulatory mechanisms no longer control the growth of some kinds of cells. Cells are frequently exposed to a variety of agents, from both external and internal sources, which damage DNA. Even minor DNA damage can have profound effects, causing certain genes to become overactive, to undergo partial or complete inactivation, or to function abnormally. Genes control a number of protective pathways in cells that prevent cells from becoming cancerous. For example, pathways that transmit signals for a cell to divide have on-off switches that control cell division. Cells also

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have mechanisms that allow them to determine if their DNA has been damaged, and they have pathways to repair that damage or eliminate the cell.

The failure of any of these protective pathways can lead to the development of cancer. Cancer is one of the more attractive initial applications for gene-induced protein therapies, because in contrast to more complex genetic disorders, which may require long-term function of the transferred gene, the treatment for cancer provides those functions that will lead to the destruction of the cancer cell. The introduction of normal tumor suppressor genes and the proteins they produce, such as p53 and mda-7, into cancer cells is a promising approach to treating cancer.

Tumor Suppressor Genes

Tumor suppressor genes and the proteins they produce are one class of genes that play a crucial role in preventing cancer and its spread. This class of genes includes the p53, mda-7, BAK and FUS-1 genes, among others.

The best known and most studied of the tumor suppressor genes is the p53 gene. The p53 gene is one of the most potent members of a group of naturally occurring tumor suppressor genes, which act to kill cancer cells, arrest cancer cell growth and protect cells from becoming cancerous. The p53 gene is involved in multiple cellular processes, including control of cell division, DNA repair, cell differentiation, genome integrity, apoptosis, and inhibition of blood vessel growth, or anti-angiogenesis. Angiogenesis refers to the process by which new blood vessels are formed, such as those that supply blood and nutrients to tumors to feed their growth. The p53 gene is capable of such wide-ranging effects because it orchestrates the activity of a host of other genes and proteins. If a cell suffers DNA damage, p53 responds to the damage by initiating a cascade of protective processes to either repair the DNA damage or to destroy the damaged cell through apoptosis. These p53-mediated processes prevent damaged cells from multiplying and progressing towards cancer.

Current Treatment of Cancer

Conventional therapeutic approaches, including surgery, chemotherapy and radiation therapy, are ineffective or only partially effective in treating many types of cancer. Surgery is inadequate for many patients because the cancer is inaccessible or impossible to remove completely. Surgery, although applicable to over half of all cancer cases, is also inadequate where the cancer has spread, or metastasized. For certain cancers such as head and neck cancer, surgery can be an effective treatment of the cancer, but may result in severe disfigurement of and disability to the patient. Radiation therapy and chemotherapy are, by their nature, toxic procedures that damage both normal and cancerous tissue. Physicians must carefully control administration of these therapies to avoid life-threatening side effects, and many patients are unable to withstand the most effective doses due to toxicity. These conventional therapies typically cause debilitating side effects such as bone marrow suppression, nausea, vomiting and hair loss, often requiring additional and costly medications to ameliorate such side effects. Further, the usefulness of certain chemotherapies may be limited in tumors that have developed mechanisms to evade the action of the drugs, a phenomenon known as multi-drug resistance.

Due to the various limitations of most cancer therapies currently utilized, the treatment of cancer remains complex. Physicians refer to the first treatment regimen for a newly-diagnosed cancer, usually surgery if possible, or radiation therapy, as primary treatment. If the primary treatment is not successful, the cancer will re-grow or continue to grow, which is referred to as recurrent disease. In most cases, recurrent cancer is not curable, with secondary treatment regimens, usually chemotherapy, only providing marginal benefits for a limited period of time. Physicians consider recurrent cancer that has proven resistant to a secondary treatment to be refractory. Most new cancer treatments are tested initially in patients with either recurrent or refractory disease because there are no standard therapies likely to provide them with clinical benefit.

Given that established cancer therapies often prove to be incomplete, ineffective or toxic to the patient, there is a need for additional new treatment modalities that either complement established therapies or replace them by offering better therapeutic outcomes. For example, in a limited number of cancers, immunotherapy, which seeks to stimulate a patient s own immune system to kill cancer cells, has rapidly become widely accepted by improving on the shortcomings of existing therapy. However, for a broad range of cancers,

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additional approaches, especially more specific ones that target specific dysfunctional pathways in the cancer cell, are needed to reduce the toxicity and improve upon marginal benefits common to current cancer treatments. Gene-induced protein therapy applications are designed to address the cellular dysfunction that causes cancer, compared with small molecule drugs or immunotherapeutic agents, which may act indirectly.

The Introgen Approach

Our primary approach for the treatment of cancers is to deliver genes that increase production of normal cancer-fighting proteins. Rather than acting to repair or replace aberrant or missing genes and thereby creating a long-term or permanent change to the patient s genome, our products work in a different manner by acting as templates for the transient in vivo production of proteins that have pharmacologic properties. The resultant proteins engage disease-related molecular targets or receptors to produce a specific therapeutic effect.

We believe that using genes that do not integrate into the patient s genome and are cleared from the body after administration in order to induce the production of biopharmaceutical proteins, is an emerging field that presents a new approach for treating many cancers without the toxic side effects common to traditional therapies. We have developed significant expertise in identifying therapeutic genes, which are genes that may be used to treat disease, and in using what we believe are safe and effective delivery systems to transport these genes to the cancer cells. We believe that we are able to treat a number of cancers in a way that kills cancer cells without harming normal cells.

Because most cancers are amenable to local treatment, we generally administer therapeutic proteins directly into a patient s cancerous tumor by hypodermic syringe. We have initially focused on advanced cancers that lack effective treatments and in which local tumor growth control, where the tumor stops growing or shrinks, is likely to lead to measurable benefit. We believe our clinical trials have shown that our gene-induced protein therapies can be used alone and in combination with conventional treatments such as surgery, radiation therapy and chemotherapy. To date, doctors at clinical sites in North America, Europe and Japan have treated hundreds of patients with our lead product candidate, ADVEXIN therapy, establishing a large safety database.

We have developed ADVEXIN therapy by combining the p53 gene with the adenoviral delivery system we have developed and extensively tested. Evidence from laboratory, pre-clinical and clinical trials suggests that proteins produced by the p53 tumor suppressor gene are sufficient to slow, stop or kill many cancer cell types without the gene being integrated into the patient s genome. We believe that ADVEXIN therapy holds promise as an effective anti-cancer therapeutic that kills cancer cells without harming normal cells, both in combination with conventional cancer treatment and as a stand-alone treatment for patients who are resistant to or unable to receive conventional therapies. In addition, data obtained from a Phase 1 clinical trial in patients with advanced cancer provide evidence that systemic, or intravenous, administration of ADVEXIN therapy is safe and well tolerated. We have also developed INGN 241 by inserting the mda-7 gene into the adenoviral delivery system we have developed and extensively tested, and believe it also holds promise as an effective anti-cancer therapeutic.

The Introgen Strategy

Our objective is to be the leader in the development of gene-induced protein therapies and other products for the treatment of cancer and other diseases that, like cancer, result from cellular dysfunction and uncontrolled cell growth. To accomplish this objective, we are pursuing the following strategies:

Develop and Commercialize ADVEXIN therapy and INGN 241 for Multiple Cancer Indications. We plan to continue developing ADVEXIN therapy using the p53 gene and our INGN 241 product using the mda-7 gene in multiple cancer indications.

Develop Our Portfolio of Gene-Induced Protein Therapy and Other Drug Products. Utilizing our significant research, clinical, and regulatory expertise, we are evaluating development of additional gene-induced protein therapies, such as FUS-1, and other drug products for various cancers. We have established an efficient process for evaluating new drug candidates and advancing them from pre-

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clinical to clinical development. We have identified and licensed multiple technologies, which we intend to combine with our adenoviral and non-viral vector systems and which we believe are attractive development targets for the treatment of various cancers. We are also evaluating the development of mebendazole (INGN 601), our first small molecule product candidate. We intend to evaluate additional opportunities to in-license or acquire new technologies.

Establish Targeted Sales and Marketing Capabilities. Because the oncology market is characterized by a concentration of specialists in relatively few major cancer centers, it can be effectively addressed by a small, focused sales force. We believe we can address this market by building a direct sales force as part of the ADVEXIN therapy commercialization process and by pursuing marketing and distribution agreements with corporate partners for ADVEXIN therapy as well as additional products.

Expand Our Market Focus to Non-Cancer Indications. We plan to leverage our scientific, research and process competencies in gene function and vector development to pursue gene-based protein therapies for a variety of other diseases and conditions. We believe these therapies could hold promise for diseases such as cardiovascular disease and rheumatoid arthritis, which, like cancer, result from cellular dysfunction or uncontrolled cell growth.

Product Development Programs

The following table summarizes the status of our product development programs.

Product (Gene)**	Cancer Indication	Development Status
ADVEXIN Therapy (p53)	Head and Neck	Phase 3
	Non-Small Cell Lung	Phase 2 completed
	Breast	Phase 2
	Perioperative (and surgery)	Phase 1-2
	Esophageal	Phase 1-2
	Prostate	Phase 1 completed*
	Intravenous Administration	Phase 1 completed*
	Ovarian	Phase 1 completed*
	Oral Cancer (mouthwash)	Phase 1-2*
	Bladder	Phase 1 completed*
	Bronchoalveolar	Phase 1 completed*
	Brain (glioblastoma)	Phase 1 completed*
	Rheumatoid Arthritis	Pre-clinical
INGN 225 (p53 vaccine)	Small Cell Lung	Phase 1-2
	Breast	Phase 1-2
INGN 241 (mda-7)	Various (solid tumors)	Phase 1-2
	Melanoma	Phase 1-2
	Pancreatic	Pre-clinical
	Breast	Pre-clinical
INGN 401 (FUS-1 program)	Lung	Phase 1
INGN 007 (Replication-competent viral therapy)	Various (solid tumors)	Pre-clinical

* Conducted in conjunction with the National Cancer Institute.

** We hold the worldwide commercial rights to the product candidates related to each of these programs.

Indications for ADVEXIN® Therapy (p53)

ADVEXIN therapy combines the p53 gene with an adenoviral vector for delivery in order to introduce the therapeutic protein or gene. The p53 gene works through multiple mechanisms of action including apoptosis, or programmed cell death, cancer cell growth arrest, and reducing the blood supply to tumors through a process known as anti-angiogenesis. Molecular pathways normally controlled by the p53 gene are abnormal in the vast majority of cancers. Patients may receive multiple doses of ADVEXIN therapy, and

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some patients have received ongoing ADVEXIN treatments for several years. Physicians typically inject ADVEXIN therapy directly into the tumor. The importance of the protein produced by the p53 gene in controlling tumor growth suggests that ADVEXIN therapy is applicable to multiple cancers. Our initial development strategy for ADVEXIN therapy is to obtain approval for cancer indications, such as head and neck and lung cancer, which have near-term clinical endpoints and where current treatment is inadequate.

Head and Neck Cancer

In the United States, the annual incidence of squamous cell cancer, a cancer of cells that line the oral cavity, pharynx and larynx, is approximately 40,000. The worldwide annual incidence of head and neck cancer, encompassing squamous cell cancer, as well as cancers of the tongue, mouth, vocal cords and tissues surrounding them, is approximately 400,000 new cases. Head and neck cancer is frequently fatal, with most patients dying from local and regional disease, rather than from metastasis to other organs. Primary treatments for head and neck cancer are generally surgery and radiation therapy. However, these treatments are debilitating and have permanent side effects, including loss of teeth, loss of voice or disfigurement. Moreover, a large number of patients with head and neck cancer experience recurrence. Patients with recurrent cancer do not typically respond well to further therapies, which may typically include chemotherapy, and extended patient survival is rare.

We are developing ADVEXIN therapy as a treatment for squamous cell cancer of the head and neck. Based on clinical results from our Phase 1 and Phase 2 clinical trials, we have commenced patient enrollment in two multi-national, multi-site Phase 3 clinical trials which we refer to as our 301 and 302 trials. The design of our two Phase 3 clinical trials was agreed to by the FDA under its Special Protocol Assessment program. If these trials are successful, we expect to use the resulting data, along with other data, to apply for regulatory approval.

Clinical trial 301 is a Phase 3 clinical trial that compares the efficacy of ADVEXIN therapy to a standard chemotherapy treatment in patients with recurrent squamous cell cancer of the head and neck in whom standard treatment of surgery and radiation therapy have not been effective. Clinical trial 301 is planned to enroll approximately 240 patients with recurrent disease. Patients in the control group receive weekly treatments of methotrexate, a standard chemotherapy treatment for this condition, while patients in the treatment group receive twice weekly intratumoral injections of ADVEXIN therapy. The clinical trial s primary endpoint is survival.

Clinicial trial 302 is a Phase 3 clinical trial that compares the efficacy of ADVEXIN therapy when it is used in combination with a standard chemotherapy treatment to that of standard chemotherapy treatment used alone in patients with recurrent disease. Clinical trial 302 is planned to enroll approximately 255 patients with recurrent squamous cell head and neck cancer. These patients will not have previously been treated with chemotherapy. Patients in the control group receive the chemotherapy drugs cisplatin and 5-fluorouracil, while the patients in the treatment group receive the same drugs plus intratumoral ADVEXIN therapy. Each treatment is repeated every four weeks, which is a standard interval for chemotherapy. The clinical trial s primary endpoint is time to progression of the treated lesions as measured by a patient s tumor growth beyond the patient s baseline, or tumor size at the beginning of the trial. Survival is the secondary endpoint. The 301 and 302 trials are designed to be complementary, with the primary endpoint in each serving as a secondary endpoint, or result that we will evaluate secondarily, in the other. Both of these studies are randomized, and are being conducted at numerous cancer centers in the United States, Canada and Europe.

ADVEXIN therapy was previously studied in three independent, multi-national, multi-site Phase 2 clinical trials of ADVEXIN therapy in 217 patients with recurrent squamous cell head and neck cancers. Starting in 2001 with the restructuring of our collaboration with Aventis, we began collecting and analyzing clinical data from three Phase 2 clinical trials conducted by Aventis. We and Aventis previously reported interim findings by Aventis from two of those Phase 2 clinical trials comprising approximately 112 patients. Additional Phase 2 clinical trial data from over 100 patients had not been previously included in a combined analysis of the ADVEXIN therapy Phase 2 clinicial trials for head and neck cancer. The case report forms and data from all three, independent, multi-institutional and multi-national studies were collected by us during the

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past several years and have provided us with the opportunity to closely examine the clinical trial information. We obtained independent confirmation of the Aventis Phase 2 clinicial trial response data. In addition, we have obtained and are continuing to obtain expert analysis from statistical, clinical, regulatory and oncology specialists.

All of the 217 patients in the Phase 2 head and neck cancer clinical trials had failed initial treatments with surgery, radiation or chemotherapy. Many patients had also been treated with subsequent additional chemotherapy. These patients typically do not respond well to further therapies. The 217 patients were treated with ADVEXIN therapy alone as monotherapy. After treatment with ADVEXIN therapy, many patients received subsequent chemotherapy.

In the combined analysis of the three multi-national, multi-site Phase 2 clinical trials, the overall tumor growth control rate was 59%. Tumor growth control rate represents the percentage of treated tumors where there was disappearance of the tumor, shrinkage of the tumor or the absence of additional tumor growth beyond 25% of pre-treatment measurements. In 10% of the treated lesions, there was either complete tumor regression or a reduction of tumor size greater than or equal to 50% of the pre-treatment size. These clinical findings are consistent with the results of earlier analysis of 112 patients and earlier clinical trials where tumor growth control was observed. These encouraging clinical findings are consistent with the results of multiple pre-clinical and clinical trials where tumor growth control was observed.

As in all of our previous clinical trials, ADVEXIN therapy was well tolerated without the significant side effects common to conventional cancer treatments. Side effects were consistent with those experienced in the Phase 1 clinical trial discussed below.

Previously, ADVEXIN therapy was tested in a Phase 1 safety clinical trial in patients with recurrent squamous cell head and neck cancer. In this trial, 33 patients received a total of 429 doses. We believe this trial demonstrates that physicians can safely inject ADVEXIN therapy into head and neck tumors repetitively over many months. Side effects were minimal, consisting of pain at the site of the injection and flu-like symptoms that could be readily treated without disrupting the administration of the drug. No patient had treatment stopped or reduced because of toxicity, even at the maximum dose. In 15 of these patients, we showed that surgery could be safely combined with ADVEXIN therapy without increasing the risk of wound infections or inhibiting healing.

Non-Small Cell Lung Cancer

Lung cancer is the most common cause of cancer-related death in the United States, with an estimated 172,000 new cases diagnosed annually. An estimated 157,000 people die from the disease annually. The five-year survival rate for patients diagnosed with lung cancer is 15%. Non-small cell, or NSC, lung cancer comprises approximately 80% of all lung cancer cases. Surgery can be an effective treatment in the early stages of disease, but only a minority of patients are eligible because early-stage diagnosis is uncommon. Up to 70% of NSC lung cancer patients have disease that is too far advanced for complete surgical resection. The remaining patients typically undergo a combination of surgery, radiation and chemotherapy. This combination treatment is only effective in a small percentage of cases. Clinical data has shown that of patients who have unresectable disease, approximately 80% will again have active cancer cells three months after completing a full course of radiation. Due to the ineffective treatment of NSC lung cancer in many patients, a significant, unmet need for better treatments exists, particularly if it can be combined with existing treatments without increasing the toxicity of those treatments.

We have completed a Phase 2 clinical trial of ADVEXIN therapy in combination with radiotherapy as the primary treatment for patients who had newly-diagnosed, inoperable NSC lung cancer and who could not tolerate chemotherapy. Radiotherapy is the standard treatment for patients in this condition. All patients in this trial received three ADVEXIN therapy injections into their tumors during a five-to-six week course of radiotherapy. These patients were evaluated for the efficacy, safety and side effects of the treatment to ascertain whether the combination of ADVEXIN therapy with radiation was tolerated. Other objectives of this trial were to determine if the addition of ADVEXIN therapy injected directly into the tumor and in

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combination with standard radiotherapy improved the response rate of the injected tumor in patients with inoperable NSC lung cancer, and to evaluate the tolerability of the combination treatment.

We conducted an analysis of 19 patients that the investigators treated and evaluated in the Phase 2 clinical trial of ADVEXIN therapy. This analysis included both radiographs to assess the size of the treated tumor mass supplemented by tumor biopsies to assess for living cancer cells within the tumor at the site of treatment. The patients were then followed without further treatment for clinical evidence of disease progression. The results of this analysis established an acceptable safety profile and showed evidence of local tumor growth control and reductions in tumor size. Twelve of the 19 patients that the investigators treated and evaluated, or 63%, had radiographic evidence of local tumor growth control, including 12 complete or partial responses of the tumor that the investigators injected. Furthermore, the preliminary analysis showed that nine of these 12 patients had no living tumor cells in the biopsy that the investigator took from the site of the injection. This study was published in the January 2003 issue of *Clinical Cancer Research.*

We conducted a Phase 1 safety clinical trial of ADVEXIN therapy in 53 patients with end-stage NSC lung cancer who had failed surgery, radiation and chemotherapy. In one arm of the trial, 29 patients received ADVEXIN therapy injected into a single tumor site. In the other arm, 24 patients received ADVEXIN therapy in combination with cisplatin, a commonly used chemotherapeutic agent. The patients in this trial tolerated the ADVEXIN therapy well, and the most severe side effects noted were consistent with those experienced with the use of cisplatin alone.

Breast Cancer

Physicians diagnose an estimated 213,000 new cases of breast cancer annually in the United States, and approximately 40,000 people are estimated to die from the disease each year. We are conducting a Phase 2 clinical trial using ADVEXIN therapy administered in combination with systematic chemotherapy in women who have newly diagnosed, locally advanced breast cancers. Interim results of this trial were published in June 2003 at the annual meeting of the American Society of Clinical Oncology. Data from this clinical trial indicated that objective clinical responses (complete tumor regression or greater than 50% reduction in tumor size) were documented in 83% of the patients that received ADVEXIN therapy combined with systematic chemotherapy. The resectability rate was 100% at mastectomy. This clinical trial is part of our ADVEXIN therapy development plan, which is to administer ADVEXIN therapy in the setting of primary, multi-modality local therapy of cancer in conjunction with surgery, chemotherapy and radiation therapy. In addition, the NCI has concluded a Phase 1 clinical trial using ADVEXIN therapy in patients with locally recurrent breast cancer involving the chest wall.

Prostate Cancer

Prostate cancer is one of the most common forms of cancer. Approximately 221,000 new cases occur annually in the United States and approximately 29,000 people are estimated to die from the disease each year. Most prostate cancer patients are treated with either surgery or radiation therapy. Because newer and simpler methods of diagnosis that detect the disease at an earlier stage exist today, a significant number of patients who are diagnosed with prostate cancer before it has metastasized may benefit from local treatment therapies such as ADVEXIN therapy.

We have completed enrollment and treatment in a Phase 1 clinical trial of 30 patients with prostate cancer where investigators injected ADVEXIN therapy into the prostate gland with a subsequent surgical resection of the gland. The patients tolerated the ADVEXIN therapy well. In a preliminary analysis, 27% of the patients showed measurable evidence of tumor shrinkage following ADVEXIN therapy injections.

Other Cancers

There are several other cancer indications for which ADVEXIN therapy is in earlier stages of clinical development. To evaluate the possible use of ADVEXIN therapy in these indications, we collaborate with the NCI under a Cooperative Research and Development Agreement, or CRADA. Under this program the NCI has conducted and is conducting clinical trials with ADVEXIN therapy at leading cancer centers using

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clinical protocols that we have developed with the NCI. These protocols are designed to demonstrate the safety of ADVEXIN therapy in these indications and by various routes of administration.

Ovarian Cancer. There are an estimated 25,000 new cases of ovarian cancer and 14,000 deaths attributed to ovarian cancer in the United States each year. Approximately 80% of patients with advanced disease can be treated with simple intraperitoneal administration, that is, administration of gene therapeutic agents into the abdominal cavity. The NCI has conducted a Phase 1 clinical trial of ADVEXIN therapy in this population.

Bladder Cancer. There are an estimated 57,000 new cases of bladder cancer each year in the United States. The annual number of deaths from this indication in the United States is estimated to be 12,000. The anatomy of the bladder allows delivery of gene therapeutic agents via catheter. The NCI has conducted a Phase 1 clinical trial using ADVEXIN therapy in this indication.

Brain Cancer (Glioblastoma). An estimated 13,000 people die from cancers of the brain and central nervous system in the United States each year. Glioblastoma multiforme, or GBM, is a particularly deadly form of primary brain cancer and represents approximately 30% of all brain cancer cases in the United States. GBM is not effectively treated with conventional therapies because the lesions are deep within the brain, are often large and grow rapidly. The NCI has conducted a Phase 1 clinical trial using ADVEXIN therapy in recurrent GBM.

Bronchoalveolar Cancer. We estimate that 10,000 new cases of bronchoalveolar cancer in the United States each year. Bronchoalveolar cancer is a form of non-small cell lung cancer that typically spreads throughout the airspaces in the lungs, but does not spread elsewhere in the body. Current treatments are not effective for this condition. The NCI is conducting a Phase 1 clinical trial in bronchoalveolar cancer with ADVEXIN therapy administered by directly bathing the airway leading to the diseased lung segments. Data from this study was published in the June 2003 *Proceedings of the American Society for Clinical Oncology* demonstrating that the therapy was well-tolerated in all 26 patients treated, that there was an improved ability to breathe in 20% of the patients who were able to be evaluated and that the disease stabilized and did not continue to grow in some of these patients.

Premalignant Oral Lesions. Through a Clinical Trials Agreement we and the NCI are conducting a Phase 1/early Phase 2 clinical trial in which ADVEXIN therapy is administered in the form of an oral rinse or mouthwash. This trial is the first to investigate the effect of ADVEXIN therapy on non-malignant, oral lesions that are at high risk for developing into cancer. Currently, there are no such cancer prevention treatments approved by the FDA for head and neck malignancies.

Esophageal Cancer. Esophageal cancer is a major health problem in Japan. We are conducting a Phase 1/early Phase 2 study of ADVEXIN therapy for the treatment of advanced unresectable squamous cell esophageal cancer. The study protocol was developed and is sponsored by investigators at Chiba University in Japan. The purpose of the study is to determine the safety and biological and therapeutic activity of ADVEXIN therapy in esophageal cancer. Preliminary results demonstrating safety and positive biological effect resulting from the expression of the p53 protein were published in June 2003 at the meeting of the American Society of Clinical Oncology. Of the first eight patients evaluated to date, one patient was observed to have minor tumor regression following ADVEXIN therapy injection.

Indications for INGN 241 (mda-7)

Our second product candidate, INGN 241, uses the mda-7 gene, a promising tumor suppressor gene that we believe, like p53, has broad potential to induce apoptosis or cell deaths in many types of cancer. We have combined the mda-7 gene product with our adenoviral gene delivery system to form INGN 241. Our pre-clinical trials have shown that the protein produced by INGN 241 suppresses the growth of many cancer cells, including those of the breast, lung, ovaries, colon, prostate and the central nervous system, while not affecting growth of normal cells. Because INGN 241 kills cancer cells, even if other tumor suppressor genes, including p53 or p16, are not functioning properly, it appears that mda-7 functions via a novel mechanism of tumor suppression.

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We have conducted pre-clinical work indicating that in addition to its known activity as a tumor suppressor gene, the protein produced by the mda-7 gene may also stimulate the body s immune system to kill metastatic tumor cells and to protect the body against cancer, thereby offering the potential of providing an added advantage in treating various cancers because it may attack cancer using two different mechanisms. Because the mda-7 gene product may act as a cytokine, or immune system modulator, it is also known as interleukin-24, or IL-24. The mda-7 gene and the protein it produces may also work as a radiation sensitizer to make several types of human cancer cells more susceptible to radiation therapy, and we have seen evidence of this effect in our pre-clinical work. We have also published the results of a pre-clinical trial indicating INGN 241 may suppress the growth in vivo of non-small cell lung cancer through apoptosis in combination with anti-angiogenesis.

We have completed enrollment of a Phase 1/early Phase 2 clinical trial using INGN 241 to evaluate safety, mechanism of action and efficacy in approximately 25 patients with solid tumors. This trial has indicated that in patients with solid tumors, INGN 241 was well tolerated, was biologically active and displayed minimal toxicity associated with its use. We are planning to initiate a Phase 1/early Phase 2 clinical trial using INGN 241 in melanoma.

Also, pre-clinical studies in INGN 241 in breast cancer cell lines have shown that treatment with a combination of INGN 241 plus Herceptin induces cell death in Her-2/neu positive breast cancer cells at a rate above that seen with either agent alone. In these studies, it was also noted that while Herceptin exhibited no activity on Her-2/neu negative cells, INGN 241 did induce cell death in these cells.

We have an exclusive license to the mda-7 gene for our therapeutic applications from Corixa Corporation. Our pre-clinical program with INGN 241 has included research at The University of Texas M. D. Anderson Cancer Center, Columbia University and Corixa Corporation.

Indications for INGN 225 (p53 vaccine)

As a supplement to our gene-induced therapeutic protein programs, we are developing INGN 225 using ADVEXIN therapy to create a highly specific therapeutic cancer vaccine that stimulates a particular type of immune system cell known as a dendritic cell. Recently published research in *Current Opinion in Drug Discovery & Development* concluded that ADVEXIN therapy can be used with a patient s isolated dendritic cells as an antigen delivery and immune enhancing therapeutic strategy. Pre-clinical testing has shown that the immune system can recognize and kill tumors after treatment with dendritic cells stimulated by ADVEXIN therapy, which suggests a vaccine consisting of ADVEXIN therapy stimulated dendritic cells (INGN 225) could have broad utility as a treatment for progression of solid tumors. We are conducting a Phase 1/early Phase 2 trial, performed in collaboration with the University of South Florida and the Moffitt Cancer Center, in patients with small-cell lung cancer and are initiating a Phase 1/early Phase 2 trial in patients with breast cancer both using INGN 225 after treatment with standard chemotherapy.

Indications for INGN 401 (FUS-1)

Pre-clinical studies have shown that gene delivery of FUS-1, which we exclusively license from The University of Texas M. D. Anderson Cancer Center, significantly inhibits the growth of tumors and greatly reduces the metastatic spread of lung cancer in animals when delivered to tumor cells via either an adenoviral or a non-viral delivery system. A Phase 1 trial is ongoing at The University of Texas M. D. Anderson Cancer Center testing INGN 401 in patients with advanced non-small cell lung cancer who have previously been treated with chemotherapy.

Research and Development Programs

In addition to our ongoing clinical programs, we are conducting a number of pre-clinical and research programs involving a variety of therapeutic genes for the treatment of cancer. These programs involve genes that act through diverse mechanisms to inhibit the growth of or kill cancer cells.

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We are conducting research on additional genes, including BAK, which hold promise as therapeutic candidates. BAK is a pro-apoptotic gene that kills cancer cells. We are working with our collaborators at M. D. Anderson Cancer Center to identify and develop both viral and non-viral vectors containing this gene. We had exclusive rights to use the BAK gene under a license with LXR Biotechnology, Inc., the rights of which were subsequently sold to Tanox, Inc. We have licensed the adenoviral vector containing the p16 gene, a widely known tumor suppressor gene, from M. D. Anderson Cancer Center and have demonstrated that the gene inhibits tumor growth in animal models.

We license from M. D. Anderson Cancer Center a group of genes known as the 3p21.3 family of genes. Pre-clinical research performed on these genes by collaborators at The University of Texas Southwestern Medical Center and M. D. Anderson Cancer Center suggests that the 3p21.3 genes play a critical role in the suppression of tumor growth in lung and other cancers. This family of genes includes the FUS-1 gene that we are testing as INGN 401 in a Phase 1 study. We are working with M. D. Anderson Cancer Center to further evaluate other 3p21.3 genes as clinically relevant therapeutics.

As a supplement to our gene-induced protein therapy product programs, we are evaluating the development of mebendazole, our first small molecule candidate, which we refer to as INGN 601, for treatment of cancer and other hyperproliferative diseases. The use of the mebendazole compound is approved by the FDA for the oral treatment of parasitic diseases. Pre-clinical trials suggest that mebendazole may also be an effective treatment of cancer. The results of pre-clinical trials involving mebendazole and lung cancer are published in the October 2002 edition of *Clinical Cancer Research* and the January 2003 edition of *Molecular Cancer Therapeutics.* We are working with M. D. Anderson Cancer Center to further evaluate this molecule as a cancer treatment.

We are investigating vector technologies for delivering gene-based products into targeted cells. Through our strategic collaboration with VirRx, Inc., we are developing INGN 007, a replication-competent viral therapy that over-expresses an adenoviral gene and thereby causes rapid disruption of tumor cells in which the adenovirus replicates. Pre-clinical testing indicates that INGN 007 can eradicate human tumors in animal models. We anticipate pursuing clinical confirmation of this therapeutic candidate. We are also evaluating whether this replicating viral construct could form the basis of a self-amplifying delivery system, which could complement our existing replication-disabled, adenoviral gene delivery system in selected therapeutic scenarios.

We believe our research and development expertise gained from our gene-induced protein therapies for cancer is also applicable to other diseases that, like cancer, result from cellular dysfunction and uncontrolled cell growth. As a result, we are conducting research in collaboration with medical institutions to understand the safety and effectiveness of our gene-induced protein therapy product candidates in the treatment of other diseases.

Introgen Enabling Technologies

We have a portfolio of technologies, referred to as enabling technologies, for administering gene-based products to patients and for enhancing the effects of these products, which we plan to exploit to develop additional gene-based products to treat cancer and other diseases which, like cancer, result from cellular dysfunction and uncontrolled cell growth.

Viral Delivery Systems

Adenoviral Systems. We have demonstrated that ADVEXIN therapy and INGN 241, which use our adenoviral vector system, enter tumor cells and express their proteins despite the body s natural immune response to the adenoviral vector. While the adenoviral vector system used appears to be appropriate for the treatment of cancer by local administration, we have developed a number of additional systems that utilize modified adenoviral vectors for gene delivery. These systems also may be applicable to indications where activity of the gene for disease treatment is required for longer periods of time or where systemic administration may be necessary.

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Replication-Competent Systems. Through our strategic collaboration with VirRx, Inc., we are developing INGN 007, a replication-competent viral therapy in which viruses bind directly to cancer cells, replicate in those cells, and cause those cancer cells to die. Pre-clinical testing indicates that INGN 007 over-expresses a gene that allows the vector to saturate the entire tumor and to suppress tumor growth in animal models. We anticipate pursuing clinical confirmation as to whether this self-amplifying delivery system can complement our existing adenoviral gene delivery system, which is replication disabled, in selected therapeutic scenarios.

Non-Viral Delivery Systems

We have in-licensed and are developing a non-viral delivery platform as a potential alternative to viral delivery for certain types of cancers, or clinical indications, particularly those that require systemic administration. We are currently using this technology to deliver the FUS-1 gene in a Phase 1 clinical study in collaboration with The University of Texas M. D. Anderson Cancer Center.

Additional Enabling Technologies

Our research activities include a number of additional technologies that expand our capabilities. These activities include the following:

Multi-Gene Vector System. This technology is designed to combine multiple genes with a vector. This has the potential to be used with both viral and non-viral delivery systems to allow the activity of more than one gene for disease treatment at a time.

Pro-Apoptotic Gene Delivery System. This technology is designed to allow the activity of pro-apoptotic, or apoptosis-inducing, genes during treatment only, while temporarily suppressing the ability of the gene for disease treatment to kill producer cells during production. This will facilitate higher volume production of pro-apoptotic agents.

Tissue-Specific Targeting Systems. This technology is designed to limit the activity of the gene for disease treatment to particular cell types. It is intended to be applied to both viral and non-viral vectors.

Manufacturing and Process Development

Commercialization of a gene-based product requires process methodologies, formulations and quality release assays in order to produce high quality materials at a large scale. We believe that the expertise we have developed in the areas of manufacturing and process development represents a competitive advantage. We have developed scale-up methodologies for both upstream and downstream production processes, formulations that are safe and stable, and product release assays that support product quality control.

We own and operate a state-of-the-art, validated manufacturing facility that we believe complies with the FDA s current Good Manufacturing Practices requirements, commonly known as CGMP requirements. We produce ADVEXIN therapy in this facility for use in our Phase 1, 2 and 3 clinical trials. The design and processes of this facility have been reviewed with the FDA. The validation of our manufacturing processes is ongoing. We plan to use this facility for our market launch of ADVEXIN therapy. To date, we have produced over 20 batches of ADVEXIN therapy clinical material, including all clinical material used in the Phase 2 and Phase 3 clinical trials for this product candidate. In addition, we have entered into agreements with third parties under which we have provided process development and manufacturing services related to products they are developing. We also have produced in a separate facility INGN 241 for use in our Phase 1/early Phase 2 clinical trial.

Business and Collaborative Arrangements

VirRx, Inc.

We are working with VirRx, Inc. (VirRx) to investigate other vector technologies, specifically replication-competent viral therapies, for delivering gene-based products into targeted cells. We have an agreement with VirRx, which began in 2002, to purchase shares of VirRx s Series A Preferred Stock. We purchased

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$1,125,000 of this stock for cash through December 31, 2003, which we have recorded as research and development expense. We have agreed to purchase an additional $150,000 of this stock for cash on the first day of each quarter through January 1, 2006. VirRx is required to use the proceeds from these stock sales in accordance with the terms of a collaboration and license agreement between us and VirRx for the development of VirRx s technologies. We may unilaterally terminate this collaboration and license agreement with 90 days prior notice, which would also terminate the requirement for us to make any additional stock purchases. Provided the collaboration and license agreement remains in place, we are required to make additional milestone stock purchases, either for cash or through the issuance of our common stock, upon the completion of Phase 1, Phase 2 and Phase 3 clinical trials involving technologies licensed under this agreement and we are required to make a $5.0 million cash milestone payment to VirRx, for which we receive no VirRx stock, upon approval by the FDA of a Biologics License Application for the first collaboration product based on these technologies. To the extent we have already made cash milestone payments, we may receive a credit of 50% of the Phase 2 clinical trial milestone payments and 25% of the Phase 3 clinical trial milestone payments against this $5.0 million cash milestone payment. The additional milestone stock purchases and cash payment are not anticipated to be required in the near future. We have an option to purchase all outstanding shares of VirRx at any time until March 2007.

Aventis Pharma AG

In October 1994, we entered into two collaboration agreements with Rhône-Poulenc Rorer Pharmaceuticals Inc., which ultimately became part of Aventis Pharma, or Aventis, a global pharmaceutical company. In June 2001, we restructured this collaborative relationship and assumed responsibility for the worldwide development of all p53 and K-ras products, and acquired all marketing and commercialization rights with respect to those products. We also assumed the control and performance of ongoing clinical trials for p53-and K-ras-based products and full responsibility for all pre-clinical research and development and clinical trials for new products involving these genes. In connection with this restructuring and pursuant to a stock purchase agreement executed on June 30, 2001, Aventis purchased $25.0 million of non-voting preferred stock from us. During the quarter ended September 30, 2001, we made a one-time payment of $2.0 million to Aventis in consideration for internal costs it incurred in facilitating the transition of control and performance of these clinical trials from Aventis to us. We are also obligated to reimburse Aventis for amounts paid by Aventis to non-affiliate third parties or government entities pursuant to those third party agreements extant at the time of the restructured agreement, including royalties, license fees, milestone or other payments.

Under the restructured p53 and K-ras collaboration agreement, we have the exclusive, worldwide right to market and manufacture the products developed under each of the prior collaboration agreements, as well as any new p53- or K-ras-based products. Aventis licensed or transferred to us all of its patents covering the manufacture, sale, offering for sale, importation or use of ADVEXIN therapy and other K-ras patents, delivery patents and targeting technologies, as well as all trademarks and goodwill associated with ADVEXIN therapy. Aventis also agreed, for a period of seven years, not to conduct any activities directed to the development or commercialization of any gene-based products using the p53 or K-ras genes. We are not pursuing any research and development programs with respect to the K-ras genes at this time.

Prior to the restructuring of the collaboration agreements, Aventis provided us with approximately $57.2 million in the form of funding for early-stage development programs and purchases of ADVEXIN therapy product for later-stage clinical development and purchased over $39.4 million of preferred stock from us. These purchases of preferred stock were made upon the achievement of the milestones contemplated in our stock purchase agreement with Aventis.

Academic and Other Collaborations

Academic collaboration agreements have been a cost-effective way of expanding our intellectual property portfolio, generating data necessary for regulatory submissions, accessing industry expertise and finding new technology in-license candidates, all without building a large internal scientific and administrative infrastructure.

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The University of Texas M. D. Anderson Cancer Center

Many of our core technologies were developed by scientists at The University of Texas M. D. Anderson Cancer Center in Houston, Texas, one of the largest academic cancer centers in the world. We sponsor research conducted at M. D. Anderson Cancer Center to further the development of technologies that have potential commercial viability. Through these sponsored research agreements, we have access to M. D. Anderson Cancer Center s resources and expertise for the development of our technology. In addition, we have the right to include certain patentable inventions arising from these sponsored research agreements under our exclusive license with M. D. Anderson Cancer Center.

We entered into this license agreement with The Board of Regents of the University of Texas System and M. D. Anderson Cancer Center in 1994. It terminates on July 20, 2009 (if no patent rights are applicable) or upon the last to expire of the relevant patents. The agreement is also terminable upon our insolvency, either party s breach or upon our notice on a patent-by-patent basis. The technologies we have licensed from M. D. Anderson Cancer Center, under the exclusive license agreement, relate to p53 and the 3p21.3 family of genes. Under the agreement, we have agreed to pay M. D. Anderson Cancer Center royalties on sales of products utilizing these technologies. We are obligated to reimburse any of M. D. Anderson Cancer Center s costs that may be incurred in connection with obtaining patents related to the licensed technologies. Our strategy for product development is designed to take advantage of the significant multidisciplinary resources available at M. D. Anderson Cancer Center. These efforts have resulted in our becoming a significant corporate sponsor of activities at M. D. Anderson Cancer Center in recent years and have yielded to us exclusive patent and licensing rights to numerous technologies.

National Cancer Institute

We have a cooperative research and development agreement, or CRADA, with the NCI. The CRADA has a flexible duration, but is terminable upon the mutual consent of the parties or upon 30 days notice of either party. Under the CRADA, NCI agreed to sponsor and conduct pre-clinical and human clinical trials to evaluate the effectiveness and potential superiority to other treatments of ADVEXIN therapy against a range of designated cancers, including breast cancer, ovarian cancer, bladder cancer and brain cancer. To date, NCI has conducted or is conducting numerous Phase 1 clinical trials for ADVEXIN therapy. NCI provided most of the funding for these activities. We supplied NCI with ADVEXIN therapy product to be administered in these trials. We have exclusive rights to all pre-clinical and clinical data accumulated under the CRADA.

Corixa Corporation

We have a research and license agreement with Corixa Corporation pursuant to which we acquired an exclusive, worldwide license to the mda-7 gene for the therapeutic applications we are pursuing. The agreement is effective until the last to expire of the subject patents. It is terminable upon the breach or insolvency of either party, or upon our notice on a patent-by-patent or product-by-product basis. Under the agreement, we paid Corixa an initial license fee and have agreed to make additional payments upon the achievement of development milestones, as well as royalty payments on product sales. We also made research payments to Corixa in connection with research it performed involving the mda-7 gene. Corixa originally licensed the mda-7 gene from Columbia University.

Marketing and Sales

We currently have no sales or marketing infrastructure. We are focusing our current product development and commercialization efforts on the oncology market. This market is characterized by its concentration of specialists in relatively few major cancer centers, which we believe can be effectively addressed by a small, focused sales force. We will likely address this market by building a direct sales force as part of the ADVEXIN therapy commercialization process and by pursuing marketing and distribution arrangements with corporate partners for ADVEXIN therapy as well as additional products.

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Patents and Intellectual Property

Our Portfolio

Our success will depend in part on our ability to develop and maintain proprietary aspects of our technology. To this end, we have an intellectual property program directed at developing proprietary rights in technology that we believe may be important to our success. We also rely on a licensing program to ensure continued strong technology development and technology transfer from companies and research institutions with whom we work. We have entered into a number of exclusive license agreements or options with companies and institutions, including M. D. Anderson Cancer Center, Sidney Kimmel Cancer Center, Corixa, Aventis, Columbia University, VirRx, Inc. and LXR Biotechnology, Inc., with the LXR rights being subsequently sold to Tanox, Inc. In addition to patents, we rely on trade secrets and proprietary know-how, which we seek to protect, in part, through confidentiality and proprietary information agreements.

We currently own or have an exclusive license to a large number of issued and pending United States and foreign patents and patent applications. If we do not seek a patent term extension, the currently issued United States patents that we own or have exclusively licensed will expire between the years 2010 and 2017. The exclusive licenses that give us rights on the patents, and applications that such licenses cover, will expire no earlier than the life of any patent covered under the license.

Adenoviral p53 Compositions and Therapies

In developing our patent portfolio, we have focused our efforts in part on seeking protection for our potential products and how they will be used in the clinical trials. Arising out of our work with M. D. Anderson Cancer Center, we currently have an exclusive license to a number of United States and corresponding international patent applications directed to adenoviruses that contain the p53 gene, referred to as adenoviral p53, adenoviral p53 pharmaceutical compositions and the use of adenoviral p53 compositions in various cancer therapies and protocols. One of these applications, directed to the clinical use of adenoviral p53 to treat cancer, has issued as a United States patent. Additionally, two other United States patents have issued to which we have licensed exclusive rights, which are directed to adenoviral p53 compositions in general, as well as a patent covering the DNA core of adenoviral p53. We have also exclusively licensed from Aventis a patent application directed to adenoviral p53 and its clinical applications. We also have an exclusive license to a United States patent application and corresponding international applications directed to the use of the p53 gene in the treatment of cancer patients whose tumors express a normal p53 protein.

Combination Therapy with the p53 Gene

We have also focused our portfolio development on seeking protection for clinical therapeutic strategies that combine the use of the p53 gene with traditional cancer therapies. In this regard, also arising out of our work with M. D. Anderson Cancer Center, we have an exclusive license to two issued United States patents, with corresponding international applications, directed to cancer therapy using the p53 gene in combination with DNA-damaging agents such as conventional chemotherapy or radiotherapy. This patent and corresponding international applications concern the therapeutic application of the p53 gene before, during or after chemotherapy or radiotherapy. We have also exclusively licensed from Aventis a United States patent and corresponding international applications directed to therapy using the p53 gene together with taxanes such as Taxol® or Taxotere®. Furthermore, we have exclusively licensed a United States patent application, and corresponding international applications, directed to the use of the p53 gene in combination with surgical intervention in cancer therapy.

Adenovirus Production, Purification and Formulation

Another focus of our research has involved the development of procedures for the commercial scale production of our potential adenoviral-based products, including that of ADVEXIN therapy. In this regard, we own an issued United States patent as well as a number of pending United States applications, and corresponding international applications, directed to commercial scale processes for producing adenoviral gene-based compositions having a high level of purity, as well as to storage-stable formulations. These

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applications include procedures for preparing commercial quantities of recombinant adenoviruses for gene-based products and include procedures applicable to the p53 gene, as well as any of the other of our potential gene-based products. We have also licensed from Aventis a United States application and corresponding international applications directed to processes for the production of purified adenoviruses, which are useful for gene-based applications. With respect to formulations, we were recently issued a United States patent directed to compositions and methods concerning improved, storage-stable adenovirus formulations. This patent is not limited to our ADVEXIN product candidate and may eventually replace formulations currently in use.

Other Tumor Suppressor Genes

We either own or have exclusively licensed rights in a number of other patents and applications directed to the clinical application of various tumor suppressor genes other than the p53 gene, including the p16, mda-7, BAK, the 3p21.3 gene family (FUS-1) and anti-sense K-ras genes. We have exclusively licensed or optioned rights in two issued United States patents covering the use of the BAK and mda-7 genes, a United States patent relating to the PTEN gene and a United States patent directed to the use of the adenoviral p16 in cancer therapy.

Other Therapeutic, Composition and Process Technologies

We also own or have exclusively licensed a number of United States and international patent applications on a range of additional technologies. These include various applications relating to the p53 gene, combination therapy with 2-methoxyestradiol, anti-proliferative factor technologies, retroviral delivery systems, stimulation of anti-p53, screening and product assurance technologies, as well as second-generation p53 gene molecules. We have exclusively licensed a number of United States and international applications directed to various improved vectors for use in gene-based protocols, gene-based applications employing more than one gene for disease treatment, as well as applications directed to the delivery of genes for disease treatment without the use of a vector, or non-viral therapy. For example, a United States patent, exclusively licensed to Introgen, was recently issued that is directed to adenoviruses that exhibit tissue specific replication. We also have exclusive rights in an issued United States patent and corresponding international applications directed to a low toxicity analogue of IL-2, also called F42K.

Benzimidazole Small Molecule Cancer Therapy Program

We also have exclusively licensed a United States and a corresponding international patent application directed to the use of a family of known anti-helminthic benzimidazole molecules, most notably mebendazole, in the treatment of cancer. These applications are directed generally to the use of small molecules of the benzimidazole family to induce apoptosis in cancers, as well as to treat cancer patients, particularly those having p53-related cancers. Both of these therapeutic actions are based on the discovery by our scientists and their collaborators that members of the benzimidazole family will actively induce apoptosis in cancer cells, particularly in conjunction with the action of endogenous or exogenously added p53.

Trade Secrets

We rely on trade secrets law to protect technology where we believe patent protection is not appropriate or obtainable. However, trade secrets are difficult to protect. In addition, we generally require employees, academic collaborators and consultants to enter into confidentiality agreements. Despite these measures, we may not be able to adequately protect our trade secrets or other proprietary information. We are a party to various license agreements that give us rights to use specified technologies in our research and development processes. If we are not able to continue to license this technology on commercially reasonable terms, our product development and research may be delayed. In addition, in the case of technologies that we have licensed, we do not have the ability to make the final decisions on how the patent application process is managed, and accordingly are unable to exercise the same degree of control over this intellectual property as we exercise over our internally developed technology. Our research collaborators and scientific advisors have rights to publish data and information in which we have rights. If we cannot maintain the confidentiality of our

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technology and other confidential information in connection with our collaborations, then our ability to receive patent protection or protect our proprietary information will be diminished.

Government Regulation

The Drug Approval Process

Prescription pharmaceutical products and biologics are subject to extensive pre and post marketing regulation by the FDA, including regulations that govern the testing, manufacturing, safety, efficacy, labeling, storage, recordkeeping, advertising and promotion of the products under the Federal Food, Drug, and Cosmetics Act, and the Public Health Services Act, and by comparable agencies in most foreign countries. The process required by the FDA before a new drug, or biologic may be marketed in the United States generally involves the following; completion of preclinical laboratory and animal testing; submission of an investigational new drug application, or IND, which must become effective before clinical trials may begin; performance of adequate and well controlled human clinical trials to establish the safety and efficacy of the proposed drug or biologic s intended use; and in the case of a new drug, approval by the FDA of a New Drug Application (NDA) or of a Biologic s License Application (BLA) for a biologic. Our products will be regulated as biologics.

Facilities used to manufacture drugs and biologics are subject to periodic inspection by the FDA and other authorities where applicable, and must comply with FDA s Good Manufacturing Practice (GMP) regulations. Manufacturers of biologics also must comply with FDA s general biological product standard. Failure to comply with the statutory and regulatory requirements subjects the manufacturer to possible legal or regulatory action, such as suspension of manufacturing, seizure of product or voluntary recall of a product.

Pre-Clinical Testing

Pre-clinical testing includes laboratory evaluation of product chemistry and formulation as well as animal trials to assess the potential safety and effectiveness of the product. Compounds must be adequately manufactured and pre-clinical safety tests must be conducted in compliance with FDA Good Laboratory Practices regulations. The results of the pre-clinical tests are submitted to the FDA as part of an IND application to be reviewed by the FDA prior to the commencement of human clinical trials. Submission of an IND application may not result in FDA authorization to commence clinical trials, but the IND becomes effective if not rejected by the FDA within 30 days. The IND application must indicate: the results of previous testing; how, where and by whom the clinical trials will be conducted; the chemical structure of the compound; the method by which it is believed to work in the human body; any toxic effects of the compound found in the animal trials; and how the compound is manufactured.

Clinical Trials

Clinical trials involve the administration of the drug or biologic to healthy volunteers or to patients, under the supervision of qualified principal investigators. All clinical trials must be conducted in accordance with Good Clinical Practices regulations, under protocols that detail the objectives of the trial, the parameters to be used to monitor safety and the effectiveness criteria to be evaluated. Each protocol must be submitted to the FDA for review as part of the IND application prior to commencing the trial. Further, each clinical trial must be conducted under the auspices of an independent review panel termed the Institutional Review Board, or IRB, at the institution at which the trial will be conducted. The IRB will consider, among other things, ethical factors, the safety of human subjects, informed consent and the possible liability of the institution. Progress reports detailing the status of on-going clinical trials must be submitted at least annually to the FDA.

Clinical trials are typically conducted in three sequential phases, but the phases often overlap. In Phase 1, the initial introduction of the drug into healthy volunteers or patients, the drug is tested for safety or adverse effects, dosage tolerance, absorption, distribution, metabolism, excretion and clinical pharmacology. Phases 2 and 3 involve clinical trials in patient populations to determine the effectiveness of the drug for specific, targeted indications, determine dosage tolerance and optimal dosage. Phase 3 clinical trials typically contain

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control groups and are undertaken to further evaluate clinical effectiveness, to further test for safety within an expanded patient population at geographically dispersed clinical trial sites and may be utilized to seek marketing approval by the FDA.

National Institutes of Health

The National Institutes of Health, or NIH, publishes guidelines concerning gene-based and gene therapy products. The NIH guidelines require that human gene-based and gene therapy protocols subject to the guidelines, and involving a novel product, disease indication, route of administration or other component, be discussed at the quarterly meetings of the NIH Recombinant DNA Advisory Committee. Companies involved in clinical trials as sponsors generally are expected to report all serious adverse events to the NIH.

We report to the FDA and the NIH serious adverse events and deaths, whether treatment-related or not, that occur in our clinical trials. Clinical trials we conduct include cancer patients who have failed all conventional treatments available to them, and who therefore have short life expectancies and who sometimes die before completion of their full course of treatment in our clinical trials.

Marketing Applications

If the clinical data indicate that the drug is safe and effective, a BLA or an NDA is filed with the FDA for approval of the marketing and commercial shipment of the drug. This marketing application must contain all of the information on the drug gathered to that date, including data from the clinical trials. It is often over 100,000 pages in length.

The FDA reviews all marketing applications submitted to it before it accepts them for filing and may request additional information, rather than accepting the application for filing. In such event, the application must be re-submitted with the additional information and the application is again subject to review before filing. Once the submission is accepted for filing, the FDA begins an in-depth review of the BLA or NDA. Under the FDC Act, the FDA has 180 days in which to review it and respond to the applicant. The review process is often significantly extended by FDA requests for additional information or clarification of information already provided in the submission. The FDA may refer the application to an appropriate advisory committee, typically a panel of clinicians, for review, evaluation and a recommendation as to whether the application should be approved. However, the FDA is not bound by the recommendation of an advisory committee. If the FDA evaluations of the marketing application and the manufacturing facilities are favorable, the FDA may issue either an approval letter or an approvable letter. An approvable letter usually contains a number of conditions that must be met in order to secure final approval of the application. When, and if, those conditions have been met to the FDA s satisfaction, the FDA will issue an approval letter, authorizing commercial marketing of the drug for certain indications. Approvals may be withdrawn if compliance with regulatory standards is not maintained or if problems occur following initial marketing. If the FDA s evaluation of the submission or manufacturing facilities is not favorable, the FDA may refuse to approve the BLA or NDA or issue a not-approvable letter.

If the FDA approves the BLA or NDA, the drug becomes available for physicians to prescribe. Periodic reports must be submitted to the FDA, including descriptions of any adverse reactions reported. The FDA may request additional trials, referred to as Phase 4 clinical trials, to evaluate long-term effects. Phase 4 clinical trials and post-marketing trials may also be conducted to explore new indications and to broaden the application and use of the drug and its acceptance in the medical community.

Satisfaction of FDA premarket approval requirements for new drugs and biologics typically takes several years and the actual time required may vary substantially based upon the type, complexity and novelties of the product or disease. Government regulation may delay or present marketing of potential products for a considerable period of time and impose costly procedures upon our activities. Success in early stage clinical trials and on prior versions of the products does not assure success in later stage clinical trials. Data obtained from clinical activities is not always conclusive and may be susceptible to varying interpretations that could delay, limit or prevent regulatory approval.

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Orphan Drug Act

We have received Orphan Drug designation for ADVEXIN therapy for the treatment of head and neck cancer under the Orphan Drug Act. This act provides incentives to manufacturers to develop and market drugs for rare diseases and conditions affecting fewer than 200,000 people in the United States. The first developer to receive FDA marketing approval for an Orphan Drug is entitled to a seven-year exclusive marketing period in the United States following FDA approval of that product. However, the FDA will allow the sale of a drug clinically superior to or different from another approved Orphan Drug, although for the same indication, during the seven-year exclusive marketing period.

We may pursue Orphan Drug designation for other products we are developing. We cannot be sure that any of those potential products will ultimately receive Orphan Drug designation, or that the benefits currently provided by such a designation will not subsequently be amended or eliminated. The Orphan Drug Act has been controversial, and legislative proposals have from time to time been introduced in Congress to modify various aspects of the Orphan Drug Act, particularly the market exclusivity provisions. New legislation may be introduced in the future that could adversely affect the availability or attractiveness of Orphan Drug status for our potential products. Orphan Drug designation does not convey any advantage in, or shorten the duration of, the regulatory review and approval process.

Off-Label Use

Physicians may prescribe drugs for uses that are not described in the product s labeling that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties and may constitute the best treatment for many patients in various circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturers communications on the subject of off-label use. Companies cannot actively promote FDA-approved drugs for off-label uses. However, new regulations, if followed, provide a safe harbor from FDA enforcement action that would allow us to disseminate to physicians articles published in peer-reviewed journals, like the *New England Journal of Medicine,* that discuss off-label uses of approved products. We cannot disseminate articles concerning drugs that have not been approved for any indication.

Fast Track Products

Fast track designation. FDA s fast track program is intended to facilitate the development and expedite the review of drugs that are intended for the treatment of a serious or life-threatening condition for which there is no effective treatment and that demonstrates the potential to address unmet medical needs for their condition. Under the fast track program, the sponsor of a new drug may request the FDA to designate the drug for a specific indication as a fast track product at any time during the clinical development of the product. The FDA must determine if the product qualifies for fast track designation within 60 days of receipt of the sponsor s request.

If fast track designation is obtained, the FDA may initiate review of sections of an NDA or BLA before the applicant is complete. This rolling review is available if the applicant provides a schedule for the submission of the remaining information and pays applicable user fees. However, the time period specified in the Prescription Drug User Fees Act, which governs the time period goals the FDA has committed to reviewing an application, does not begin until the complete application is submitted. Additionally, the fast track designation may be withdrawn by the FDA if the FDA believes that the designation is no longer supported by data emerging in the clinical trial process.

In some cases, a fast track designated product may also qualify for one or more of the following programs:

Priority review. Under FDA policies, a product is eligible for priority review, or review within a six-month time frame from the time an NDA or BLA is accepted for filing, if the product provides a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease. A fast-track designated product would ordinarily meet the FDA s criteria for priority review.

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We cannot guarantee any of our products will receive a priority review designation, or if a priority designation is received, that review or approval will be faster than conventional FDA procedures.

Accelerated approval. Under the FDA s accelerated approval regulations, the FDA is authorized to approve products that have been studied for their safety and effectiveness in treating serious or life-threatening illnesses and that provide meaningful therapeutic benefit to patients over existing treatments based upon either a surrogate endpoint that is reasonably likely to predict clinical benefit or on the basis of an effect on a clinical endpoint other than patient survival. In clinical trials, surrogate endpoints are alternative measurements of the symptoms of a disease or condition that are substituted for measurements of observable clinical symptoms. Accelerated approval of an application will be subject to Phase 4 or post-approval studies to validate the surrogate endpoint or confirm the effect on the clinical endpoint. Failure to validate a surrogate endpoint or confirm a clinical benefit during post-marketing studies will allow the product to be withdrawn from the market by the FDA on an expedited basis. All promotional materials for drugs approved under accelerated regulations are subject to prior review by the FDA.

Although we have obtained a fast track designation for ADVEXIN therapy from the FDA, we cannot guarantee a faster development process, review process or approval compared to conventional FDA procedures. We also may elect not to seek or we may be prevented from seeking approval under the accelerated approval process for any of our products.

When appropriate, we also intend to seek fast track designation for our other products. We cannot predict the ultimate impact, if any, of the fast track process on the timing or likelihood of FDA approval of any of our other potential products.

ADVEXIN therapy is designated as a Fast Track product by the FDA for its effect on prolonging survival and the time to loco-regional disease progression in patients with recurrent, unresectable squamous cell carcinoma of the head and neck. By designating ADVEXIN therapy as a Fast Track Drug Product, the FDA will take actions to expedite the evaluation and review of the application for approval of ADVEXIN therapy.

We will continue to seek fast track designation to secure expedited review of additional appropriate products. It is uncertain whether we will obtain fast track designation. We cannot predict the ultimate effect, if any, of the new fast track process on the timing or likelihood of FDA approval of any of our potential products.

International

Steps similar to those in the United States must be undertaken in virtually every other country comprising the market for our products before any such product can be commercialized in those countries. The approval procedure and the time required for approval vary from country to country and may involve additional testing. We cannot be sure that approvals will be granted on a timely basis, or at all. In addition, regulatory approval of prices is required in most countries, other than the United States. There can be no assurance that the resulting prices would be sufficient to generate an acceptable return to us.

Competition

The biotechnology and pharmaceutical industries are subject to rapid and intense technological change. We face, and will continue to face, competition in the development and marketing of our product candidates from academic institutions, government agencies, research institutions and biotechnology and pharmaceutical companies. Competition may arise from other drug development technologies, methods of preventing or reducing the incidence of disease, including vaccines, and new small molecule or other classes of therapeutic agents. Developments by others may render our product candidates or technologies obsolete or non-competitive.

We compete with pharmaceutical and biotechnology companies, including Canji, Inc. and Genvec, Inc., which are pursuing forms of treatment for the diseases ADVEXIN therapy and our other product candidates target. We are aware that Canji, with its parent Schering-Plough Corporation, has in the past been involved in research and/or development of adenoviral p53 products and owns or controls patents and patent applications

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directed to adenoviral p53 therapy. We understand that Schering-Plough has stopped its adenoviral p53 clinical trials, and it is unknown whether these parties are continuing their adenoviral p53 research and/or development efforts. We are also aware that a Chinese pharmaceutical company, SiBioNo GeneTech, Inc., has recently announced that it has received regulatory approval from the Chinese drug regulatory agency to market an adenoviral p53 product only in China. There are many other companies, both publicly and privately held, including well-known pharmaceutical companies, engaged in developing products for human therapeutic applications. We also compete with universities and other research institutions in the development of products, technologies and processes. In many instances, we compete with other commercial entities in acquiring products or technologies from universities and other research institutions.

We expect that competition among products approved for sale will be based, among other things, on product efficacy, safety, reliability, availability, price, patent position and sales, marketing and distribution capabilities. Our competitive position also depends upon our ability to attract and retain qualified personnel, obtain patent protection or otherwise develop proprietary products or processes, and secure sufficient capital resources for the often substantial period between technological conception and commercial sales.

Human Resources

As of March 1, 2004, we had approximately 72 employees and contracted personnel engaged in research and development, regulatory affairs, clinical affairs, manufacturing and quality, finance and corporate development activities. Our employees include eight holders of a Ph.D. or M.D. degree. Many of our employees have extensive experience in pharmaceutical and biotechnology industries.

Scientific Advisory Board

We receive guidance on a broad range of scientific, clinical and technical issues from our Scientific Advisory Board. Members of our Scientific Advisory Board are recognized experts in their respective fields of research and clinical medicine related to molecular oncology. The members of the Scientific Advisory Board are:

Jack A. Roth, M.D., Chairman of the Scientific Advisory Board, is Chairman of the Department of Thoracic and Cardiovascular Surgery at M. D. Anderson Cancer Center. Dr. Roth was one of our founders and is our Chief Medical Advisor. Dr. Roth is a widely-recognized pioneer in the application of genes to the treatment of cancer. He is the primary inventor of the technology supporting our gene-based products. He received his M.D. from The Johns Hopkins University School of Medicine.

Carol L. Prives, Ph.D., is a professor of biology at Columbia University. She is the Chair of the NIH Experimental Virology Trial Section, a member of the NCI Intramural Scientific Advisory Board, and a member of the Advisory Board of the Dana-Farber Cancer Center in Boston. Dr. Prives is an editor of the Journal of Virology and serves on the editorial boards of three other prominent journals. She received her Ph.D. in biochemistry from McGill University.

Daniel D. Von Hoff, M.D., is the Director of the Arizona Cancer Center in Tucson, Arizona, and a professor of medicine in the Department of Medicine of the University of Arizona. Dr. Von Hoff is a past President of the American Association for Cancer Research. Dr. Von Hoff is certified in medical oncology by the American Board of Internal Medicine. He received his M.D. from The Columbia College of Physicians and Surgeons.

Elizabeth Grimm, Ph.D., is a professor of tumor biology at M. D. Anderson Cancer Center. Dr. Grimm has served as Cancer Expert, Surgical Branch of the NCI. She received her Ph.D. in microbiology from the University of California, Los Angeles School of Medicine.

Michael J. Imperiale, Ph.D., is the Director of Cancer Biology Training Programs at the University of Michigan Cancer Center and holds a concurrent position in the Department of Microbiology and Immunology at the University of Michigan. Dr. Imperiale earned his Ph.D. degree in biological sciences from Columbia University and received postdoctoral training at the Rockefeller University Laboratory of Molecular Cell Biology, where he studied the regulation of early adenovirus gene expression.

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Item 2. ***Properties***

We lease from TMX Realty Corporation, our wholly-owned subsidiary, facilities in Houston, Texas, totaling approximately 42,000 square feet in two buildings. These buildings consist of a 12,000 square foot CGMP production facility designed to support an ADVEXIN therapy product launch, as well as support multiple vector manufacturing, and a 30,000 square foot building which contains our research and development laboratories and administrative offices. We sublease to M. D. Anderson Cancer Center approximately 10,000 square feet of space in our Houston research and development facility at prevailing market rates under a lease with an initial term expiring in 2009. Our corporate offices are located in Austin, Texas. We expect our current facilities to satisfy our requirements for the foreseeable future.

TMX Realty Corporation leases the land for these facilities from a third party. The buildings are financed under mortgage notes, and such buildings are pledged as collateral for the notes. Certain equipment in the buildings is financed under leases, and such equipment is pledged as collateral for the leases. See the discussion under Liquidity and Capital Resources in this Report for a summary of our obligations under these mortgage notes and leases.

Item 3. ***Legal Proceedings***

We are involved from time to time in legal proceedings relating to claims arising out of our operation in the ordinary course of business, including actions relating to intellectual property rights.

We do not believe that the outcome of any present, or all litigation in the aggregate, other than our opposition of three European patents controlled by Canji discussed under Risk Factors will have a material effect on our business. You can read the discussion of our opposition of the patents under Risk Factors.

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

No matter was submitted to a vote of security holders during the fourth quarter of the fiscal year covered by this Report.

PART II

Item 5. ***Market for Registrant s Common Equity and Related Stockholder Matters***
Market and Equityholder Information

Our common stock has been quoted on the Nasdaq National Market under the symbol INGN since our initial public offering in October 2000. Prior to October 2000, there was no established public trading market for our common stock. The following table sets forth, for the periods indicated, the high and low sale prices reported on the Nasdaq National Market.

	High	Low
Fiscal Year Ended December 31, 2002:		
First Fiscal Quarter	$ 5.59	$3.56
Second Fiscal Quarter	4.97	1.80
Third Fiscal Quarter	2.80	1.35
Fourth Fiscal Quarter	2.58	1.48
Fiscal Year Ended December 31, 2003:		
First Fiscal Quarter	$ 3.36	$1.97
Second Fiscal Quarter	10.16	2.00
Third Fiscal Quarter	11.24	5.26
Fourth Fiscal Quarter	10.20	6.95

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At December 31, 2003, there were 26,539,529 shares of our common stock issued and outstanding held by 154 stockholders of record. We estimate we have approximately 4,049 beneficial stockholders.

Dividend Policy

We have never declared or paid any dividends on our capital stock. We currently expect to retain all of our future earnings, if any, to support the development of our business and do not anticipate paying any cash dividends in the foreseeable future.

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Item 6. ***Selected Consolidated Financial Data***

The selected consolidated statement of operations data for the years ended December 31, 2003 and 2002, the six months ended December 31, 2001 and the year ended June 30, 2001 and the consolidated balance sheet data as of December 31, 2003 and 2002 are derived from the audited consolidated financial statements of Introgen Therapeutics, Inc. and our subsidiaries, which appear in Part IV of this Report. The selected consolidated statement of operations data for the year ended June 30, 2000 and the consolidated balance sheet data as of December 31, 2001, June 30, 2001 and 2000 are derived from the audited consolidated financial statements of Introgen Therapeutics, Inc. not included in this Report. The selected consolidated statement of operations data for the year ended December 31, 2001 and the six months ended December 31, 2000 are derived from the unaudited consolidated financial statements of Introgen Therapeutics, Inc. The selected consolidated financial data set forth below is qualified in its entirety by, and should be read in conjunction with, the Consolidated Financial Statements and Notes thereto and Management s Discussion and Analysis of Financial Condition and Results of Operations included elsewhere in this Report.

	Year Ended June 30,		Six Months Ended December 31,		Year Ended December 31,		
	2000	2001	2000	2001	2001	2002	2003
			(Unaudited)		(Unaudited)		
			(In thousands except per share amounts)				
Statement of Operations Data:							
Contract services, grants and other revenue	$ 97	$ 684	$ 391	$ 298	$ 591	$ 1,173	$ 304
Collaborative research and development revenues from affiliate	6,204	3,016	3,016				
Product sales to Affiliate	2,087	1,500	1,500				
Cost of product Sales	1,476	2,488	2,488				
Gross margin on product Sales	611	(988)	(988)				
Operating costs and expenses:							
Research and development	10,075	15,014	5,153	10,063	19,923	21,512	14,973
General and administrative	4,701	4,875	2,040	3,526	6,361	6,722	6,102
Total operating costs and expenses	14,776	19,889	7,193	13,589	26,284	28,234	21,075
Loss from operations	(7,864)	(17,177)	(4,774)	(13,291)	(25,693)	(27,061)	(20,771)
Interest income (expense), net	140	381	403	(445)	423	(207)	393
Other income		354		518	871	1,140	1,052
Net loss	$ (7,724)	$ (16,442)	$ (4,371)	$ (12,328)	$ (24,399)	$ (26,128)	$ (19,326)
Net loss per share, basic and diluted	$ (1.89)	$ (1.02)	$ (0.39)	$ (0.58)	$ (1.14)	$ (1.22)	$ (0.84)
Shares used in computing basic and diluted net loss per share	4,096	16,163	11,121	21,440	21,440	21,471	22,902

	June 30,	December 31,

	2000	2001	2001	2002	2003
			(In thousands)		
Balance Sheet Data:					
Cash, cash equivalents, and short-term investments	$ 11,765	$ 34,977	$ 48,825	$ 23,467	$ 36,397
Working capital	10,263	54,296	43,175	18,852	31,091
Total assets	24,855	72,347	60,424	33,316	44,483
Long-term debt and capital lease obligations, net of current portion	8,021	9,798	9,037	7,435	6,714
Accumulated deficit	(18,744)	(35,186)	(47,515)	(73,643)	(92,969)
Stockholders equity	13,592	56,069	44,566	19,835	31,285

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

The following discussion and analysis should be read in conjunction with our condensed consolidated financial statements and the related notes thereto included in this Report on Form 10-K. The discussion and analysis contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. These statements include the statements below under Risk Factors. These forward-looking statements are based on our current expectations and entail various risks and uncertainties. Our actual results could differ materially from those projected in the forward-looking statements as a result of various factors, including those set forth below under Risk Factors.

Overview

Introgen Therapeutics, Inc. was incorporated in Delaware in 1993. We are a biopharmaceutical company focused on the discovery, development and commercialization of targeted therapies for the treatment of cancer and other diseases. We are developing product candidates to treat a wide range of cancers using non-integrating gene agents. These agents are designed to increase production of normal cancer-fighting proteins that act to overpower cancerous cells. Our lead product candidate, ADVEXIN therapy, combines the p53 gene with a non-replicating, non-integrating adenoviral gene delivery system that we have developed and extensively tested. The p53 gene is one of the most potent members of a group of naturally occurring tumor suppressor genes, which act to kill cancer cells, arrest cancer cell growth and protect cells from becoming cancerous.

In order to commercialize our product candidates, we must obtain certain regulatory approvals. Satisfaction of regulatory requirements typically takes many years, and involves compliance with requirements covering research and development, testing, manufacturing, quality control, labeling and promotion of drugs for human use. To obtain regulatory approvals, we must, among other requirements, complete clinical trials demonstrating that our product candidates are safe and effective for a particular cancer type or other disease.

Since our inception in 1993, we have used our resources primarily to conduct research and development activities for ADVEXIN therapy and, to a lesser extent, for other product candidates. At December 31, 2003, we had an accumulated deficit of $93.0 million. We anticipate that we will incur losses in the future that may be greater than losses incurred in prior periods. At December 31, 2003, we had cash and cash equivalents of $36.4 million. During the year ended December 31, 2003, we used $14.9 million of cash for operating activities. We expect to incur substantial additional operating expenses and losses over the next several years as our research, development, pre-clinical testing and clinical trial activities increase, and as we expand our operations and develop systems to support commercialization of our product candidates, these losses, among other things, have caused and may cause our stockholders equity and working capital to decrease. Currently, we earn revenue or income from federal research grants, contract services and process development activities, the lease of a portion of our facilities to M. D. Anderson Cancer Center and interest income on cash placed in short-term, investment grade securities. In order to fund our operating losses, we will need to raise additional funds through public or private equity offerings, debt financings or additional corporate collaboration and licensing arrangements. We do not know whether such additional financing will be available when needed, or on terms favorable to us or our stockholders.

In October 1994, we entered into two collaboration agreements with Rhône-Poulenc Rorer Pharmaceuticals Inc., which ultimately became part of Aventis Pharma, or Aventis, for technology relating to p53 and K-ras pathway inhibition. Aventis funded the clinical trials under these programs. In June 2001, we and Aventis restructured our relationship whereby we assumed responsibility for the worldwide development of all p53 and K-ras products, including funding, control and performance of ongoing clinical trials.

In June 2003, we sold 2.0 million shares of our common stock for an aggregate purchase price of $11.5 million to selected institutional investors through a private placement pursuant to Regulation D promulgated under the Securities Act of 1933, as amended. Our net proceeds from this transaction, after related fees and expenses, were $10.8 million. In connection with this sale, we issued warrants to purchase 400,000 shares of our common stock at $7.89 per share. These warrants are exercisable at any time by the warrant holders through June 2008. Beginning in June 2005, we may force the exercise of these warrants if the

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average closing market price of our common stock during any 20 consecutive trading days is greater than $15.78 per share. The shares of common stock issued and issuable upon the exercise of the warrants issued in this transaction were registered on a registration statement on Form S-3, effective August 7, 2003 (Commission File No. 333-107028).

In December 2003, we sold approximately 2.9 million shares of our common stock in a direct equity offering pursuant to a shelf registration for an aggregate purchase price of approximately $20.0 million. Our net proceeds from this transaction, after related fees and expenses, were approximately $18.5 million. The shares of common stock issued in this transaction were registered pursuant to a registration statement on Form S-3, effective August 25, 2003 (Commission File No. 333-107799) registering shares of our common stock with an aggregate offering price of $100.0 million. We may sell additional shares of our common stock pursuant to this registration statement in the future.

Summary of Significant Accounting Policies

Use of Estimates. The preparation of financial statements in conformity with generally accepted accounting principles 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.

Cash and Cash Equivalents. Our cash and cash equivalents include investments in short-term, investment grade securities, which currently consist primarily of United States federal government obligations. These investments are classified as held-to-maturity and are carried at amortized cost. At any point in time, amortized costs may be greater or less than fair value. If investments are sold prior to maturity, we could incur a realized gain or loss based on the fair market value of the investments at the date of sale. We could incur future losses on investments if the investment issuer becomes impaired or the investment is downgraded.

Research and Development Costs. In conducting our clinical trials of ADVEXIN therapy and other product candidates, we procure services from numerous third-party vendors. The cost of these services constitutes a significant portion of the cost of these trials and of our research and development expenses in general. These vendors do not necessarily provide us billings for their services on a regular basis and, accordingly, are often not a timely source of information to determine the costs we have incurred relative to their services for any given accounting period. As a result, we make significant accounting estimates as to the amount of costs we have incurred relative to these vendors in each accounting period. These estimates are based on numerous factors, including, among others, costs set forth in our contracts with these vendors, the period of time over which the vendor will render the services and the rate of enrollment of patients in our clinical trials. Using these estimates, we record expenses and accrued liabilities in each accounting period that we believe fairly represent our obligations to these vendors. Actual results could differ from these estimates, resulting in increases or decreases in the amount of expense recorded and the related accrual. Our experience has been that our estimates have reasonably reflected the expenses we actually incur.

Results of Operations

Comparison of Years Ended December 31, 2003 and 2002

Revenues

Contract Services, Grant and Other Revenue. We earn contract services revenues from third parties under agreements to provide manufacturing process development services and to produce products for them. We earned contract research services revenue from Aventis Pharmaceuticals Products, Inc., one of our stockholders, under an agreement through which Aventis provided funding for the conduct of a Phase 2 clinical trial of ADVEXIN therapy in breast cancer. We earn grant revenue under research grants from U.S. Government agencies. Total contract services, grant and other revenue was $304,000 in 2003 and $1.2 million in 2002, a decrease of 75%. This decrease was primarily due to (1) a decline in the level of our contract manufacturing activity due to the completion of work under services agreements with certain third

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parties during 2003, which was not replaced with new contract manufacturing work due to our focus during 2003 on the preparation of regulatory filings for ADVEXIN therapy and development of our other product candidates, and (2) a decrease in contract services revenue earned from Aventis as the initial portion of the Phase 2 clinical trial of ADVEXIN therapy in breast cancer approached completion.

Costs and Expenses

Research and Development. Research and development expenses were $15.0 million in 2003, compared to $21.5 million in 2002. This expense included compensation related to the issuance of stock options of $242,000 in 2003 and $399,000 in 2002. This 30% decrease in research and development expense was primarily due to cost control programs implemented during 2003 that reduced the rate at which we used cash for operations.

General and Administrative. General and administrative expenses were $6.1 million in 2003 and were $6.7 million in 2002. This expense included compensation related to the issuance of stock options of $1.1 million in 2003 and $978,000 in 2002. This 9% decrease in general and administrative expense was primarily due to cost control programs implemented during 2003 that reduced the rate at which we used cash for operations.

Compensation Related to the Issuance of Stock Options. Compensation related to the issuance of stock options was $1.4 million in 2003 and $1.4 million in 2002. Even though compensation expense related to certain stock options granted in previous periods declined due to deferred compensation related to those stock options becoming fully amortized during 2003, total stock option compensation expense was relatively unchanged between years due to stock options granted in 2003 to (1) certain members of our Board of Directors for which some of the options have exercise prices below the market value of our common stock at the date of grant and were fully vested upon issuance, and (2) our corporate secretary, who is not a director or employee and for whom options grants are subject to fair value accounting. The amount of compensation expense related to stock options to be recorded in future periods may increase if additional options are issued at a price below the market price of common stock at the date of grant or are issued to individuals or entities other than employees or directors and may decrease if unvested options for which deferred compensation has been recorded are subsequently forfeited or as previously recorded deferred compensation becomes fully amortized.

Interest Income, Interest Expense and Other Income

Interest income was $1.0 million in 2003 compared to $596,000 in 2002, an increase of 68%. Included in the 2003 amount is $775,000 we received from the settlement of litigation related to a decline in the market value of certain commercial paper we held as an investment in 2000 and 2001. Excluding the amount from this settlement, interest income for 2003 was $225,000, which decreased 62% compared to interest income for 2002, due to our lower average cash and cash equivalents balances during 2003 and declining interest rates.

Interest expense was $624,000 in 2003 compared to $803,000 in 2002, a decrease of 22%. This decrease was a result of lower principal amounts upon which interest was incurred in 2003 compared to 2002 as a result of continuing debt service payments on notes payable and capital lease obligations.

Other income was $1.1 million in both 2003 and 2002. This income consists primarily of rental income related to our sublease of research laboratories in our facilities to M. D. Anderson Cancer Center, which is activity that was relatively unchanged between years.

Comparison of Years Ended December 31, 2002 and 2001 (Unaudited)

Revenues

Contract Services, Grant and Other Revenue. This revenue was $1.2 million in 2002 and $591,000 in 2001. This 103% increase was due to a higher level of manufacturing and process development contract services activity for third parties in 2002 compared to 2001 and funding received from Aventis in 2002 to support a Phase 2 clinical trial of ADVEXIN therapy in breast cancer.

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Costs and Expenses

Research and Development. Research and development expenses were $21.5 million in 2002 and $19.9 million in 2001. This expense included amortization of deferred stock compensation of $399,000 in 2002 and $462,000 in 2001. This 8% increase in research and development expense was primarily due to our assumption in the third quarter of 2001 and thereafter of responsibility for conducting, managing and funding the Phase 2 and Phase 3 clinical trials activities for ADVEXIN therapy under the terms of the restructuring of our collaboration with Aventis. In 2002, we incurred $525,000 of research and development expenses in conjunction with our collaboration and license agreement with VirRx.

General and Administrative. General and administrative expenses were $6.7 million in 2002 and $6.4 million in 2001. This expense included amortization of deferred stock compensation of $978,000 in 2002 and $1.2 million in 2001. This 5% increase in general and administrative expense was due primarily to the additional cost of providing administrative support for our conduct and management of the Phase 2 and Phase 3 clinical trials activities for ADVEXIN therapy, the responsibility for which we assumed in the third quarter of 2001 under the terms of the restructuring of our collaboration with Aventis.

Amortization of Deferred Compensation. Amortization of deferred stock compensation was $1.4 million in 2002 and $1.7 million in 2001. This 18% decrease was due primarily to deferred compensation for certain options becoming fully amortized during 2002.

Interest Income and Interest Expense. Interest income was $596,000 in 2002 and $1.4 million in 2001. This 57% decrease was due to lower average cash balances and interest rates during 2002 compared to 2001. Interest expense was $803,000 in 2002 and $936,000 in 2001. This 14% decrease was due primarily to lower average principal balances outstanding under mortgage notes payable and capital leases as principal was amortized through normal debt service and lease payments.

Other Income. Other income was $1.1 million in 2002 compared to $871,000 in 2001. This 26% increase was due to 2002 being the first full year in which we earned rental income related to our sublease of research laboratories in our facilities to M. D. Anderson Cancer Center.

Comparison of Six-Month Periods Ended December 31, 2001 and 2000 (Unaudited)

Revenues

Revenue from Collaborations. Collaborative research and development revenues from Aventis were zero for the six-month period ended December 31, 2001 and $3.0 million for the six-month period ended December 31, 2000. This decrease was due to the restructuring of our collaboration with Aventis, which resulted in our not receiving payments from Aventis subsequent to December 31, 2000 for early-stage research and development related to p53-based gene therapy products. Prior to this restructuring, we earned revenue for the early-stage research and development we performed under our collaboration agreements with Aventis.

Revenue from Product Sales to Affiliate. Revenues from product sales to Aventis were zero for the six-month period ended December 31, 2001 and $1.5 million for the six-month period ended December 31, 2000. This decrease was due to the restructuring of our collaboration with Aventis, which resulted in no product sales subsequent to December 31, 2000. The restructuring eliminated our product sales to Aventis since we are using the product internally for the future development of ADVEXIN therapy.

Other Revenue. Other revenue was $298,000 for the six-month period ended December 31, 2001 and $391,000 for the six-month period ended December 31, 2000. This decrease was due to a decline in amounts earned under research grants from U.S. Government agencies and contract manufacturing work for third parties.

Costs and Expenses

Cost of Product Sales. Cost of product sales was zero for the six-month period ended December 31, 2001 and $2.5 million for the six-month period ended December 31, 2000. This decrease was due to the

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restructuring of our collaboration with Aventis, which resulted in no product sales subsequent to December 31, 2000, thereby eliminating our cost of product sales.

Research and Development. Research and development expenses were $10.1 million for the six-month period ended December 31, 2001, and $5.1 million for the six-month period ended December 31, 2000. This expense included amortization of deferred stock compensation of $229,000 for the six-month period ended December 31, 2001 and $209,000 for the six-month period ended December 31, 2000. The 98% increase in research and development expense in 2001 compared to 2000 was primarily due to our assumption of responsibility for conducting, managing and funding the Phase 2 and Phase 3 clinical trials activities for ADVEXIN therapy under the terms of the restructuring of our collaboration with Aventis.

General and Administrative. General and administrative expenses were $3.5 million in 2001 and $2.0 million in 2000. This expense included amortization of deferred stock compensation of $570,000 for the six-month period ended December 31, 2001 and $537,000 for the six-month period ended December 31, 2000. The 75% increase in general and administrative expense in 2001 was due primarily to the additional, ongoing costs associated with operating as a public company, subsequent to our initial public offering in October 2000, and the cost of providing administrative support for our conduct and management of the Phase 2 and Phase 3 clinical trials activities for ADVEXIN therapy, the responsibility for which we assumed under the terms of the restructuring of our collaboration with Aventis.

Amortization of Deferred Compensation. Amortization of deferred stock compensation was $799,000 for the six-month period ended December 31, 2001 and $746,000 for the six-month period ended December 31, 2000. The 7% increase in 2001 was due primarily to deferred compensation arising from the issuance to an officer in April 2001 of an option to purchase shares of our common stock.

Interest Income and Interest Expense. Interest income was $912,000 for the six-month period ended December 31, 2001 and $783,000 for the six-month period ended December 31, 2000. The 16% increase was primarily due to higher average cash and investment balances in 2001 on which interest was earned as a result of our initial public offering in October 2000. Interest expense was $467,000 for the six-month period ended December 31, 2001 and $380,000 for the six-month period ended December 31, 2000. The 23% increase in 2001 was primarily due to higher balances under notes payable in 2001 compared to 2000 as a result of borrowings to finance tenant improvements to our facility related to our sublease of space to M. D. Anderson Cancer Center.

Other Income. Other income was $518,000 for the six-month period ended December 31, 2001 compared to zero for the six-month period ended December 31, 2000 due to 2001 being the first year in which we earned rental income related to our sublease of research laboratories in our facilities to M. D. Anderson Cancer Center.

Liquidity and Capital Resources

We have incurred annual operating losses since our inception, and at December 31, 2003, we had an accumulated deficit of $93.0 million. From inception through December 31, 2003, we have financed our operations using $49.7 million of collaborative research and development payments from Aventis, $32.2 million of net proceeds from our initial public offering in October 2000, $39.4 million of private equity sales to Aventis, $26.0 million of private equity sales, net of offering costs, to others (including $10.8 million from the private sale of our common stock in June 2003), $18.5 million of equity sales in a registered direct offering under a shelf registration in December 2003, $7.5 million of sales of ADVEXIN therapy product to Aventis for use in later-stage clinical trials, $9.2 million in mortgage financing from banks for our facilities, $4.5 million in leases from commercial leasing companies to acquire equipment pledged as collateral for those leases and $12.2 million from contract services, grants, interest and other income.

At December 31, 2003, we had cash and cash equivalents of $36.4 million, compared with $23.5 million at December 31, 2002. This increase was primarily a result of the use of $14.9 million of cash to fund our operations offset by the sale of 4.9 million shares of our common stock in June and December 2003 for net proceeds of $29.3 million. For at least the next two years, we expect to focus our activities primarily on

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conducting Phase 3 and other clinical trials, conducting data analysis, preparing regulatory documentation submissions to the FDA and conducting pre-marketing activities for ADVEXIN therapy. We also expect to continue our research and development of various other gene-based technologies. The majority of our expenditures over this two-year period will most likely relate to the clinical trials of ADVEXIN therapy and the preparation of regulatory filings for ADVEXIN therapy. These activities may increase the rate at which we use cash in the future as compared to the cash we used for operating activities during 2003. We believe our existing working capital can fund our operations for the next 18 to 24 months, although unforeseen events could shorten that time period. Our existing resources may not be sufficient to support the commercial introduction of any of our product candidates. In order to fund our operating losses, we will need to raise additional funds through public or private equity offerings, debt financings or additional corporate collaboration and licensing arrangements. We do not know whether such additional financing will be available when needed, or on terms favorable to us or our stockholders.

Net cash used in operating activities was $14.9 million in 2003 compared to $23.6 million in 2002. In general, this decrease was primarily due to cost control programs implemented during 2003 that reduced the rate at which we used cash for operations. Specifically, the decrease in cash used was primarily the result of a lower net loss in 2003 compared to 2002, after considering adjustments for depreciation and compensation related to the issuance of stock options, further affected by (1) a larger decrease in other assets in 2003 compared to 2002 primarily due to an increased use of previously prepaid expenses to fund operations, (2) a smaller increase in accounts payable in 2003 compared to 2002 and a decrease in accrued liabilities in 2003 compared to an increase in accrued liabilities in 2002, both as a result of cost control programs implemented in 2003 resulting in a lower level of obligations to vendors and services providers, and (3) a smaller increase in deferred revenue in 2003 compared to 2002 due to funding received in 2002 for contract manufacturing process development and contract research that was subsequently earned and not replaced by additional funding for similar services.

Net cash used in investing activities was $233,000 in 2003 compared to net cash provided by investing activities of $11.3 million in 2002. The absence of activity related to short-term investments in 2003 as compared to 2002 was due to our not having any short-term investments in 2003. Our purchases of property and equipment in 2003 compared to 2002 was relatively unchanged as our need for additional property and equipment did not vary significantly between the periods. While we have no obligations at this time to purchase significant amounts of additional property or equipment, our needs may change. It may be necessary for us to purchase larger amounts of property and equipment to support our clinical programs and other research, development and manufacturing activities. We may need to obtain debt or lease financing to facilitate such purchases. If that financing is not available, we may need to use our existing resources to fund those purchases, which could result in a reduction in the cash and cash equivalents available to fund operating activities.

Net cash provided by financing activities was $28.1 million in 2003 compared to net cash used in financing activities of $1.6 million in 2002. The 2003 amount includes $10.8 million of net proceeds from the sale of 2.0 million shares of our common stock in June 2003 and $18.5 million of net proceeds from the sale of 2.9 million shares of our common stock in December 2003. Excluding the proceeds from those sales of common stock, the remaining use of $1.2 million for financing activities in 2003 is lower than the comparable amount for 2002 due to the receipt of proceeds under a lease line of credit during 2003 for which there was no similar activity in 2002, offset by higher principal payments on notes payable and capital leases as those obligations continue to amortize.

We have an agreement with VirRx, Inc. (VirRx) that began in 2002 to purchase $150,000 of VirRx Series A Preferred Stock on the first day of each quarter through January 1, 2006. We purchased $600,000 and $525,000 of this stock for cash in 2003 and 2002, respectively. We record these purchases as research and development expense. VirRx is required to use the proceeds from these stock sales in accordance with the terms of a collaboration and license agreement between VirRx and us for the development of VirRx s technologies. We may unilaterally terminate this collaboration and license agreement with 90 days prior notice, which would also terminate our requirement to make any additional stock purchases. Provided the collaboration and license agreement remains in place, we are required to make additional milestone stock

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purchases, either for cash or through the issuance of our common stock, upon the completion of Phase 1, Phase 2 and Phase 3 clinical trials involving technologies licensed under this agreement and we are required to make a $5.0 million cash milestone payment to VirRx, for which we receive no VirRx stock, upon FDA approval of a biologics license application involving these technologies. To the extent we have already made cash milestone payments, we may receive a credit of 50% of the Phase 2 clinical trial milestone payments and 25% of the Phase 3 clinical trial milestone payments against this $5.0 million cash milestone payment. The additional milestone stock purchases and cash payment are not anticipated to be required in the near future. We have an option to purchase all outstanding shares of VirRx at any time until March 2007.

We have fixed debt service and lease payment obligations under notes payable and capital leases for which the liability is reflected on our balance sheet. We used the proceeds from these notes payable and leases to finance facilities and equipment. Aggregate payments due under these obligations are as follows (in thousands):

Total debt service and lease payments due during the year ending December 31:	
2004	$ 1,516
2005	1,388
2006	911
2007	537
2008	537
Thereafter	8,597
Total debt service and lease payments	13,486
Less portion representing interest	(5,769)
Total principal balance at December 31, 2003	$ 7,717
Principal balance presented on the December 31, 2003 balance sheet as liabilities in these categories:	
Current portion of obligations under capital leases and notes payable	$ 1,003
Capital lease obligations, net of current portion	172
Notes payable, net of current portion	6,542
Total principal balance at December 31, 2003	$ 7,717

We have a fixed rent obligation under a ground lease for the land on which we built our facilities. Since this is an operating lease, there is no liability reflected on our balance sheet for this item, which is in accordance with generally accepted accounting principles. We make total annual rent payments of $144,000 under this lease which will continue until the expiration of the initial term of this lease in September 2026. We have other operating leases expiring in 2003 with significantly smaller rent payments that we also account for as operating leases. Future annual rental payments due under all operating leases are as follows (in thousands):

Year ending December 31, 2004	$ 325
2005	206
2006	144
2007	144
2008	144
Thereafter	2,563
Total minimum lease payments under operating leases	$3,526

In the normal course of business, we enter into various long-term agreements with vendors to provide services to us. Some of these agreements require up-front payment prior to services being rendered, some require periodic monthly payments and some provide for the vendor

to bill us for their services as they are

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rendered. In substantially all cases, we may cancel these agreements at any time with minimal or no penalty and pay the vendor only for services actually rendered. Regardless of the timing of the payments under these agreements, we record the expenses incurred in the periods in which the services are rendered.

Pursuant to a consulting agreement, we pay consulting fees of approximately $175,000 per annum to EJ Financial Enterprises, Inc., a company owned by the Chairman of our Board of Directors and that formerly employed one of our directors. EJ Financial Enterprises, Inc. provides us guidance on strategic product development, business development and marketing activities. We are obligated to continue paying this fee until we terminate the services of that company at our option.

We have a consulting agreement with Jack A. Roth, M.D., Chairman of the Department of Thoracic Surgery and Director of the Keck Center for Gene Therapy at The University of Texas M. D. Anderson Cancer Center. Dr. Roth is the primary inventor of the technology upon which our ADVEXIN therapy is based and numerous other technologies we utilize. We licensed Dr. Roth s inventions from M. D. Anderson Cancer Center. Dr. Roth is our Chief Medical Advisor and chairman of our scientific advisory board. His duties involve the regular interaction and consultation with our scientists and others on our behalf. As compensation for his services and responsibilities, this consulting agreement provides for payments to Dr. Roth of $200,000 per annum through the end of its term on September 30, 2009, with such future payments subject to adjustment for inflation. We may terminate this agreement at our option upon one year s advance notice. If we had terminated this agreement as of December 31, 2003, we would have been obligated to make final payments totaling $200,000. Dr. Roth is one of our stockholders.

We sublease a portion of our facilities to M.D. Anderson Cancer Center under a lease with a non-cancelable term that expires in 2009. M.D. Anderson Cancer Center is obligated to pay us rent of approximately $76,000 per month until February 2006 and $13,053 per month thereafter.

Comparison of Years Ended December 31, 2002 and 2001 (Unaudited)

At December 31, 2002, we had cash and short-term investments of $23.5 million, compared with $48.8 million at December 31, 2001. This decrease was primarily a result of the use of cash to fund our operations.

Net cash used in operating activities was $23.6 million for the year ended December 31, 2002, compared with $17.4 million for the year ended December 31, 2001. In general, this increase in cash used was due to our having responsibility for conducting the Phase 2 and Phase 3 clinical trials for ADVEXIN therapy throughout 2002 whereas we did not have this responsibility in 2001 until June of that year. Specifically, the increase in cash used was primarily the result of a higher net loss in 2002 compared to 2001, after considering adjustments for depreciation and compensation related to the issuance of stock options, offset primarily by (1) a decrease in receivables and inventory that was smaller in 2002 than in 2001 due to the primary activity in these accounts in 2001 being related to the restructuring of the Aventis collaboration in 2001, (2) a decrease in accounts payable and accrued liabilities in 2002 compared to an increase in these accounts in 2001 because the 2001 increase included $2.0 million related to expenses we agreed to pay Aventis in connection with the restructuring of the Aventis collaboration in 2001, and (3) an increase in deferred revenue in 2002 compared to a decrease in this amount in 2001 due to (a) the deferral of the recognition of income under the lease of space to M. D. Anderson Cancer Center, which was in effect for the entire 2002 period but for only a portion of the 2001 period and (b) a decrease in deferred revenue in 2001 relating to the earning of revenue on sales of inventory to Aventis, an activity that no longer exists due to the restructuring of the Aventis collaboration in June 2001.

Net cash provided by investing activities was $11.3 million for the year ended December 31, 2002, compared to net cash provided by investing activities of $45.6 million for the year ended December 31, 2001. The change in the amounts of purchases and maturities of short-term investments 2002 compared to 2001 was due to a significant portion of our investment activity in the 2001 period being in short-term investments, followed by a period subsequent to September 11, 2001, during which we concentrated our investments in cash and cash equivalents, which was then followed in the 2002 period by more investments in short-term securities. The costs associated with purchases of property and equipment declined in 2002 compared to 2001

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because 2001 included costs related to the completion of tenant improvements to the space leased to M. D. Anderson Cancer Center, for which there were no similar costs in 2002.

Net cash used in financing activities was $1.6 million for the year ended December 31, 2002, and net cash provided by financing activities was $25.3 million for the year ended December 31, 2001. This change between periods is due to the 2001 period including the receipt of proceeds from (1) the purchase of preferred stock by Aventis in connection with the restructuring of our collaboration agreement with them and (2) a note payable used to finance tenant improvements for the lease of space to M. D. Anderson Cancer Center, whereas there were no similar events in 2002. Offsetting these items were higher principal payments under notes payable and capital lease obligations in 2002 compared to 2001 due to debt service payments on the note payable for tenant improvements being made for all of 2002, but for only a portion of 2001, and a larger portion of debt service payments on all mortgage notes and capital lease obligations applying to principal as the principal balances under these obligations continue to be amortized.

Comparison of Six-Month Periods Ended December 31, 2001 and 2000 (Unaudited)

At December 31, 2001, we had cash and short-term investments of approximately $48.8 million, compared with $36.4 million at December 31, 2000. Net cash used by operating activities was $10.4 million and $1.7 million for the six-month period ended December 31, 2001 and the six-month period ended December 31, 2000, respectively. This increase in cash used by operating activities was primarily due to a higher net loss from operations and payment of accrued liabilities, offset partially by a smaller increase in accounts receivable and the absence of a decrease in inventory during 2001 as compared to 2000. The payment of accrued liabilities was higher due to the increased level of activity associates with our Phase 3 clinical trials of ADVEXIN therapy. The smaller increase in accounts receivable and the absence of the decrease in inventory was due to the elimination of sales of ADVEXIN therapy to Aventis as a result of the restructuring of our collaboration with them.

Net cash provided by investing activities was $9.2 million for the six-month period ended December 31, 2001, and net cash used in investing activities was $30.0 million for the six-month period ended December 31, 2000. During the six-month period ended December 31, 2000, we invested a portion of our cash in short-term investments with maturities in excess of 90 days. During the six-month period ended December 31, 2001, we modified our investment policy and concentrated our investing activities in instruments with maturities shorter than 90 days. This change in policy resulted in a decrease in cash used by investing activities. We also purchased less property and equipment in the 2001 period compared to the 2000 period since the 2000 period included our activities related to the finish-out of a portion of our facilities for lease to M. D. Anderson Cancer Center.

Net cash provided by financing activities was $24.3 million for the six-month period ended December 31, 2001 and $34.6 million for the six-month period ended December 31, 2000. This decline was primarily due to the proceeds from our initial public offering of common stock in October 2000 being greater than the proceeds from our sale of preferred stock to Aventis in July 2001, and a decline in the amount of new notes payable in 2001 compared to 2000 due to the leasehold improvements related to our sublease of space to M. D. Anderson Cancer Center being completed and all financing related thereto in place in early 2001. At December 31, 2001, we had $8.8 million outstanding under notes payable for our facilities and $1.8 million outstanding under capital leases to finance the purchase of equipment.

Quarterly Results of Operations

The following table sets forth certain unaudited quarterly financial data for the years ended December 31, 2002 and 2003. This information has been prepared on the same basis as the Consolidated Financial Statements and all necessary adjustments have been included in the amounts stated below to present fairly the

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selected quarterly information when read in conjunction with the Consolidated Financial Statements and Notes thereto. Historical quarterly financial results and trends may not be indicative of future results.

	Three Months Ended							
	March 31, 2002	June 30, 2002	September 30, 2002	December 31, 2002	March 31, 2003	June 30, 2003	September 30, 2003	December 31, 2003
	(Unaudited) In thousands, except per share amounts							
Statement of Operations Data:								
Contract services, grant and other revenue	229	322	453	170	150	143	9	2
Operating expenses:								
Research and development	6,699	5,805	4,633	4,375	4,342	2,957	3,572	4,102
General and administrative	1,755	1,679	1,729	1,559	1,387	1,808	1,404	1,503
Loss from operations	(8,225)	(7,162)	(5,909)	(5,764)	(5,579)	(4,622)	(4,976)	(5,603)
Interest income (expense), net	(28)	(38)	(45)	(96)	(108)	314	249	(62)
Other income	316	333	261	229	248	254	292	258
Net loss	$ (7,937)	$ (6,867)	$ (5,693)	$ (5,631)	$ (5,439)	$ (4,054)	$ (4,426)	$ (5,407)
Basic and diluted net Loss per share	$ (0.37)	$ (0.32)	$ (0.27)	$ (0.26)	$ (0.25)	$ (0.19)	$ (0.19)	$ (0.21)
Shares used in computing basic and diluted net loss per share	21,450	21,463	21,465	21,471	21,525	21,851	23,650	21,562

Contractual Obligations

The following table summarizes our contractual obligations as of December 31, 2003:

	Total	One Year or Less	Two to Three Years	Four to Five Years	More Than Five Years
			(In thousands)		
Long-Term Debt	$13,046	$1,268	$2,109	$1,074	$ 8,595
Capital Lease Obligations	439	248	191		
Operating Leases	3,526	325	350	288	2,563
Employment Agreements	1,230	476	754		
Consulting Agreements	1,150	200	400	400	150
Total	$19,391	$2,517	$3,804	$1,762	$11,308

Risk Factors

If we are unable to commercialize ADVEXIN therapy in various markets for multiple indications, particularly for the treatment of head and neck cancer, our business will be harmed.

Our ability to achieve and sustain operating profitability depends in large part on our ability to commence, execute and complete clinical programs and obtain regulatory approvals for ADVEXIN therapy and other drug candidates. In particular, our ability to achieve and sustain profitability will depend in large part on our ability to commercialize ADVEXIN for the treatment of head and neck cancer in the United States. We cannot assure you that we will receive approval for ADVEXIN for the treatment of head and neck cancer or other types of cancer or indications in the United States or in other countries or if approved that we will achieve significant level of sales. If we are unable to do so, our business will be harmed.

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If we fail to comply with FDA requirements or encounter delays or difficulties in clinical trials for our product candidates, we may not obtain regulatory approval of some or all of our product candidates on a timely basis, if at all.

In order to commercialize our product candidates, we must obtain certain regulatory approvals. Satisfaction of regulatory requirements typically takes many years, and involves compliance with requirements covering research and development, testing, manufacturing, quality control, labeling and promotion of drugs for human use. To obtain regulatory approvals, we must, among other requirements, complete clinical trials demonstrating that our product candidates are safe and effective for a particular cancer type or other disease. Regulatory approval of a new drug is never guaranteed. The FDA has substantial discretion in the approval process. Despite the time and experience exerted, failure can occur at any stage, and we could encounter problems that could cause us to abandon clinical trials.

We have completed three Phase 2 clinical trials and are conducting two Phase 3 clinical trials of our lead product candidate, ADVEXIN therapy, for the treatment of head and neck cancer. In addition, we have completed a Phase 2 clinical trial of ADVEXIN therapy for the treatment of non-small cell lung cancer and are conducting a Phase 2 clinical trial of ADVEXIN therapy for the treatment of breast cancer. We also are conducting or have conducted several Phase 1 and Phase 2 clinical trials of ADVEXIN therapy for other types of cancer. Current or future clinical trials may demonstrate that ADVEXIN therapy is neither safe nor effective.

While we have completed enrollment in a Phase 1/early Phase 2 clinical trial of INGN 241, a product candidate based on the mda-7 gene, our most significant clinical trial activity and experience has been with ADVEXIN therapy. We will need to continue conducting significant research and animal testing, referred to as pre-clinical testing, to support performing clinical trials for our other product candidates. It will take us many years to complete pre-clinical testing and clinical trials, and failure could occur at any stage of testing. Current or future clinical trials may demonstrate that INGN 241 or our other product candidates are neither safe nor effective.

Any delays or difficulties we encounter in our pre-clinical research and clinical trials, in particular the Phase 3 clinical trials of ADVEXIN therapy for the treatment of head and neck cancer, may delay or preclude regulatory approval. Our product development costs will increase if we experience delays in testing or regulatory approvals or if we need to perform more or larger clinical trials than planned. Any delay or preclusion could also delay or preclude the commercialization of ADVEXIN therapy or any other product candidates. In addition, we or the FDA might delay or halt any of our clinical trials of a product candidate at any time for various reasons, including:

the product candidate is less effective and/or more toxic than current therapies;

the presence of unforeseen adverse side effects of a product candidate, including its delivery system;

a longer than expected time required to determine whether or not a product candidate is effective;

the death of patients during a clinical trial, even if the product candidate did not cause those deaths;

the failure to enroll a sufficient number of patients in our clinical trials;

the inability to produce sufficient quantities of a product candidate to complete the trials; or

the inability to commit the necessary resources to fund the clinical trials.

We cannot be certain that the results we observed in our pre-clinical testing will be confirmed in clinical trials or that the results of any of our clinical trials will support FDA approval. Pre-clinical and clinical data can be interpreted in many different ways, and FDA officials could interpret data that we consider promising differently, which could halt or delay our clinical trials or prevent regulatory approval.

Despite the FDA s designation of ADVEXIN therapy as a Fast Track product, we may encounter delays in the regulatory approval process due to additional information requirements from the FDA, unintentional omissions in our Biologics License Application for ADVEXIN therapy, or other delays in the FDA s review

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process. We may encounter delays or rejections in the regulatory approval process because of additional government regulation from future legislation or administrative action or changes in FDA policy during the period of product development, clinical trials and FDA regulatory review.

Even if our products are approved by regulatory authorities, if we fail to comply with on-going regulatory requirements, or if we experience unanticipated problems with our products, these products could be subject to restrictions or withdrawal from the market.

Any product for which we obtain marketing approval, along with the manufacturing processes, post-approval clinical data and promotional activities for such product, will be subject to continual review and periodic inspections by FDA and other regulatory bodies. Even if regulatory approval of a product is granted, the approval may be subject to limitations on the indicated uses for which the product may be marketed or certain requirements for costly post-marketing testing and surveillance to monitor the safety or efficacy of the product. Later discovery of previously unknown problems with our products, including unanticipated adverse events of unanticipated severity or frequency, manufacturer or manufacturing processes or failure to comply with regulatory requirements, may result in restrictions on such products or manufacturing processes, withdrawal of the products from the market, voluntary or mandatory recall, fines, suspension of regulatory approvals, product seizures or detention, injunctions or the imposition of civil or criminal penalties.

Failure to comply with foreign regulatory requirements governing human clinical trials and marketing approval for drugs could prevent us from selling our products in foreign markets, which may adversely affect our operating results and financial conditions.

For marketing drugs and biologics outside the United States, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from country to country and may require additional testing. The time required to obtain approvals outside the United States may differ from that required to obtain FDA approval. We may not obtain foreign regulatory approval on a timely basis, if at all. Approval by the FDA does not ensure approval by regulatory authorities in other countries, and approval by one foreign regulatory authority does not ensure approval by regulatory authorities in other countries or by the FDA. Failure to comply with these regulatory requirements or to obtain required approvals could impair our ability to develop these markets and could have a material adverse effect on our results of operations and financial condition.

We have a history of operating losses, expect to incur significant additional operating losses and may never become profitable.

We have generated operating losses since we began operations in June 1993. As of December 31, 2003, we had an accumulated deficit of approximately $93.0 million. We expect to incur substantial additional operating expenses and losses over the next several years as our research, development, pre-clinical testing and clinical trial activities increase. As we expand our operations and develop systems to support commercialization of our product candidates, these losses, among other things, have had, and are expected to continue to have, an adverse impact on our total assets, stockholders equity and working capital.

We have no products that have generated any commercial revenue. Presently, we earn minimal revenue from contract services activities, grants, interest income and rent from the lease of a portion of our facilities to The University of Texas M. D. Anderson Cancer Center. We do not expect to generate revenues from the commercial sale of products in the near future, and we may never generate revenues from the commercial sale of products.

If we continue to incur operating losses for a period longer than we anticipate and fail to obtain the capital necessary to fund our operations, we will be unable to advance our development program and complete our clinical trials.

Developing a new drug and conducting clinical trials is expensive. Our product development efforts may not lead to commercial products, either because our product candidates fail to be found safe or effective in

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clinical trials or because we lack the necessary financial or other resources or relationships to pursue our programs through commercialization. Our capital and future revenues may not be sufficient to support the expenses of our operations, the development of commercial infrastructure and the conduct of our clinical trials and pre-clinical research.

We expect that we will fund our operations over approximately the next 18 to 24 months with our current working capital, which we accumulated primarily from sale of equity securities, income from contract services and research grants, debt financing of equipment acquisitions, the lease of a portion of our facilities to M. D. Anderson Cancer Center and interest on invested funds. We may need to raise additional capital sooner, however, under various circumstances, including if we experience:

an acceleration of the number, size or complexity of our clinical trials;

slower than expected progress in developing ADVEXIN therapy, INGN 241 or other product candidates;

higher than expected costs to obtain regulatory approvals;

higher than expected costs to pursue our intellectual property strategy;

higher than expected costs to further develop and scale up our manufacturing capability;

higher than expected costs to develop our sales and marketing capability;

the rate of progress and cost of our research and development and clinical trial activities;

the amount and timing of milestone payments we receive from collaborators;

the costs of preparing an application for FDA approval of ADVEXIN therapy;

the costs of developing the processes and systems to support FDA approval of ADVEXIN therapy;

our timetable and costs for the development of marketing operations and other activities related to the commercialization of ADVEXIN therapy and our other product candidates;

our degree of success in our Phase 3 clinical trial of ADVEXIN therapy and in the clinical trials of our other products;

the emergence of competing technologies and other adverse market developments; and

changes in or terminations of our existing collaboration and licensing arrangements.

We do not know whether additional financing will be available when needed, or on terms favorable to us or our stockholders. We may need to raise any necessary funds through public or private equity offerings, debt financings or additional corporate collaboration and licensing arrangements. To the extent we raise additional capital by issuing equity securities, our stockholders will experience dilution. If we raise funds through debt financings, we may become subject to restrictive covenants. To the extent that we raise additional funds through collaboration and licensing arrangements, we may be required to relinquish some rights to our technologies or product candidates, or grant licenses on terms that are not favorable to us. If we are not able to raise additional funds, we may have to delay, reduce or eliminate our clinical trials and our development programs.

If we cannot maintain our existing corporate and academic arrangements and enter into new arrangements, we may be unable to develop products effectively, or at all.

Our strategy for the research, development and commercialization of our product candidates may result in our entering into contractual arrangements with corporate collaborators, academic institutions and others. We have entered into sponsored research, license and/or collaborative arrangements with several entities, including M. D. Anderson Cancer Center, the National Cancer Institute, Chiba University in Japan, VirRx and Corixa Corporation, as well as numerous other institutions that conduct clinical trials work for us. Our success depends upon our collaborative partners performing their responsibilities under these arrangements

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and complying with the regulations and requirements governing clinical trials. We cannot control the amount and timing of resources our collaborative partners devote to our research and testing programs or product candidates, or their compliance with regulatory requirements which can vary because of factors unrelated to such programs or product candidates. These relationships may in some cases be terminated at the discretion of our collaborative partners with only limited notice to us. We may not be able to maintain our existing arrangements, enter into new arrangements or negotiate current or new arrangements on acceptable terms, if at all. Some of our collaborative partners may also be researching competing technologies independently from us to treat the diseases targeted by our collaborative programs.

If we are not able to create effective collaborative marketing relationships, we may be unable to market ADVEXIN therapy successfully or in a cost-effective manner.

To effectively market our products, we will need to develop sales, marketing and distribution capabilities. In order to develop or otherwise obtain these capabilities, we may have to enter into marketing, distribution or other similar arrangements with third parties in order to sell, market and distribute our products successfully. To the extent that we enter into any such arrangements with third parties, our product revenues are likely to be lower than if we directly marketed and sold our products, and any revenues we receive will depend upon the efforts of such third parties. We have no experience in marketing or selling pharmaceutical products and we currently have no sales, marketing or distribution capability. We may be unable to develop sufficient sales, marketing and distribution capabilities to commercialize our products successfully.

Serious and unexpected side effects attributable to gene therapy may result in governmental authorities imposing additional regulatory requirements or a negative public perception of our products.

ADVEXIN therapy and our other product candidates under development could be broadly described as gene therapies. A number of clinical trials are being conducted by other pharmaceutical companies involving gene therapy, including compounds similar to, or competitive with, our product candidates. The announcement of adverse results from these clinical trials, such as serious unwanted and unexpected side effects attributable to treatment, any response by the FDA to such clinical trials, may impede the timing of our clinical trials, delay or prevent us from obtaining regulatory approval or negatively influence public perception of our product candidates, which could harm our business and results of operations and depress the value of our stock.

For example, in 2002, the FDA placed a clinical hold on gene therapy clinical trials using retroviral vectors to transduce hematopoietic stem cells after two participants in such a trial for the X-linked form of severe combined immune deficiency disease (X-SCID), being conducted in Europe, developed what appeared to be a leukemia-like illness. This clinical hold requires a case-by-case review of the use of retroviral vectors in these European trials before consideration of the removal of this clinical hold for these trials. We do not use retroviral vectors in our ongoing clinical trials and are not developing products using the production process used in those clinical trials. We have received no communications from the FDA to indicate this clinical hold will affect our clinical trials, and we anticipate no future negative effects on our clinical trials from this event but we cannot assure you that the FDA or any other regulatory authority will not issue a clinical hold with respect to any of our clinical trials in the future. In accordance with our pharmacovigilance procedures and regulatory procedures, we monitor every patient in our clinical trials for safety and report all side effects to the FDA and the National Institutes of Health, or NIH.

The United States Senate has held hearings concerning the adequacy of regulatory oversight of gene therapy clinical trials, as well as the adequacy of research subject education and protection in clinical research in general, and to determine whether additional legislation is required to protect healthy volunteers and patients who participate in such clinical trials. The Recombinant DNA Advisory Committee, or RAC, which acts as an advisory body to the NIH has expanded its public role in evaluating important public and ethical issues in gene therapy clinical trials. Implementation of any additional review and reporting procedures or other additional regulatory measures could increase the costs of or prolong our product development efforts or clinical trials.

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We report to the FDA and other regulatory agencies serious adverse events, including those that we believe may be reasonably related to the treatments administered in our clinical trials. Such serious adverse events, whether treatment-related or not, could result in negative public perception of our treatments and require additional regulatory review or measures, which could increase the cost of or prolong our clinical trials.

To date the FDA has not approved any gene therapy product or gene-induced product for sale in the United States. The commercial success of our products will depend in part on public acceptance of the use of gene therapy products or gene-induced products, which are a new type of disease treatment for the prevention or treatment of human diseases. Public attitudes may be influenced by claims that gene therapy products or gene-induced products are unsafe, and these treatment methodologies may not gain the acceptance of the public or the medical community. Negative public reaction to gene therapy products or gene-induced products could also result in greater government regulation and stricter clinical trial oversight.

We cannot predict the safety profile of the use of ADVEXIN therapy when used in combination with other therapeutics.

Many of our trials involve the use of ADVEXIN therapy in combination with other drugs or therapies. While the data we have evaluated to date suggest that ADVEXIN therapy does not increase the adverse effects of other therapies, we cannot predict if this will continue to be true or whether possible adverse side effects not directly attributable to the other drugs will compromise the safety profile of ADVEXIN therapy when used in certain combination therapies.

If we fail to adequately protect our intellectual property rights, our competitors may be able to take advantage of our research and development efforts to develop competing drugs.

Our commercial success will depend in part on obtaining patent protection for our products and other technologies and successfully defending these patents against third-party challenges. Our patent position, like that of other biotechnology and pharmaceutical companies, is highly uncertain. One uncertainty is that the United States Patent and Trademark Office, or PTO, or the courts, may deny or significantly narrow claims made under patents issued to us or patent applications we file. This is particularly true for patent applications or patents that concern biotechnology and pharmaceutical technologies, such as ours, since the PTO and the courts often consider these technologies to involve unpredictable sciences. Another uncertainty is that any patents that may be issued or licensed to us may not provide any competitive advantage to us because they may not effectively preclude others from developing and marketing products like ours. Also, our patents may be successfully challenged, invalidated or circumvented in the future. In addition, our competitors, many of which have substantial resources and have made significant investments in competing technologies, may seek to apply for and obtain patents that will prevent, limit or interfere with our ability to make, use and sell our potential products either in the United States or in international markets.

Our ability to develop and protect a competitive position based on our biotechnological innovations, innovations involving genes, gene-induced therapeutic protein agents, viruses for delivering the genes to cells, formulations, gene therapy delivery systems that do not involve viruses, and the like, is particularly uncertain. Due to the unpredictability of the biotechnological sciences, the PTO, as well as patent offices in other jurisdictions, has often required that patent applications concerning biotechnology-related inventions be limited or narrowed substantially to cover only the specific innovations exemplified in the patent application, thereby limiting their scope of protection against competitive challenges. Similarly, courts have invalidated or significantly narrowed many key patents in the biotechnology industry. Thus, even if we are able to obtain patents that cover commercially significant innovations, our patents may not be upheld or our patents may be substantially narrowed.

Through our exclusive license from The University of Texas System for technology developed at M. D. Anderson Cancer Center, we have obtained and are currently seeking further patent protection for adenoviral p53, including ADVEXIN therapy, and its use in cancer therapy. Further, the PTO issued us a United States patent for our adenovirus production technology. We also control, through licensing arrangements, four issued United States patents for combination therapy involving the p53 gene and conventional chemotherapy or

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radiation, one issued United States patent covering the use of adenoviral p53 in cancer therapy, one issued United States patent covering adenoviral p53 as a product and an issued United States patent covering the core DNA of adenoviral p53. We have recently been notified by the PTO that additional applications relating to our adenoviral p53, purified adenoviral composition and mda-7 technology have been allowed. We cannot assure you these allowed applications will actually issue as United States patents. Our competitors may challenge the validity of one or more of our patents in the courts or through an administrative procedure known as an interference, in which the PTO determines the priority of invention where two or more parties are claiming the same invention. The courts or the PTO may not uphold the validity of our patents, we may not prevail in such interference proceedings regarding our patents and none of our patents may give us a competitive advantage. In this regard, we have recently been notified by the PTO that an unidentified third party is attempting to provoke an interference with one of our patents directed to adenoviral p53 therapy. We do not at present know the identity of this party, and cannot assess the likelihood that an interference will actually be declared. Should that party prevail in an interference proceeding, a patent may issue to that party that is infringed by, and therefore potentially preclude our commercialization of, products like ADVEXIN therapy that are used for adenoviral p53 therapy.

Schering-Plough has filed with the European Patent Office, or EPO, an opposition against our European patent directed to combination therapy with p53 and conventional chemotherapy and/or radiation. An opposition is an administrative proceeding instituted by a third party and conducted by the EPO to determine whether a patent should be maintained or revoked in part or in whole, based on evidence brought forth by the party opposing the patent. The EPO held an initial oral proceeding on October 20, 2003 and determined that our patent should be maintained as amended. Schering-Plough can appeal this decision. Resolution of such an appeal, if taken, will require that we expend time, effort and money. If Schering-Plough ultimately prevails in having our European patent revoked on appeal, then the scope of our protection for our product in Europe will be reduced. We would not expect, however, such a result to have a significant impact on our commercialization efforts in Europe.

Third-party claims of infringement of intellectual property could require us to spend time and money to address the claims and could limit our intellectual property rights.

The biotechnology and pharmaceutical industry has been characterized by extensive litigation regarding patents and other intellectual property rights, and companies have employed intellectual property litigation to gain a competitive advantage. We are aware of a number of issued patents and patent applications that relate to gene therapy, the treatment of cancer and the use of the p53 and other tumor suppressor genes. Schering-Plough Corporation, including its subsidiary Canji, Inc., controls various United States patent applications and a European patent and applications, some of which are directed to therapy using the p53 gene, and others to adenoviruses that contain the p53 gene, or adenoviral p53, and to methods for carrying out therapy using adenoviral p53. Adenoviral p53 technology underlies our ADVEXIN therapy product candidate. In addition, Canji controls an issued United States patent and its international counterparts, including a European patent, involving a method of treating mammalian cancer cells lacking normal p53 protein by introducing a p53 gene into the cancer cell. Furthermore, we are aware of a United States patent directed to replication-deficient recombinant adenoviral vectors apparently controlled by Transgene SA. While we believe that the claims of the Canji p53 patents or the Transgene adenoviral vector patent are invalid or not infringed by our products, Transgene, Canji or Schering-Plough could assert a claim against us.

One of the foregoing patent applications directed to p53 therapy, which we understand is owned by The Johns Hopkins University and controlled by Schering-Plough, is involved in a PTO interference proceeding with a patent owned by Canji. We further understand that this Johns Hopkins application is the United States counterpart to the European patent that was recently revoked in its entirety by the EPO (see below). We have now learned that priority of invention in this interference has been awarded by the PTO to the Johns Hopkins application, and the Canji patent has been found unpatentable. We cannot at present assess whether any patent might ultimately issue on the Johns Hopkins application or the potential impact, if any, of this PTO ruling on our business. If this application issues as a patent, Schering-Plough or Johns Hopkins may assert that our ADVEXIN therapy, which uses p53 therapy, infringes the claims of such patent. While we believe

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that we would have an invalidity defense against such an assertion, in the United States an issued patent enjoys a presumption of validity, which can be overcome only through clear and convincing evidence. We cannot assure you that such a defense would prevail.

We may also become subject to infringement claims or litigation arising out of other patents and pending applications of our competitors, if they issue, or additional interference proceedings declared by the PTO to determine the priority of inventions. The defense and prosecution of intellectual property suits, PTO interference proceedings and related legal and administrative proceedings are costly and time-consuming to pursue, and their outcome is uncertain. Litigation may be necessary to enforce our issued patents, to protect our trade secrets and know-how or to determine the enforceability, scope and validity of the proprietary rights of others. An adverse determination in litigation or interference proceedings to which we may become a party could subject us to significant liabilities, require us to obtain licenses from third parties, or restrict or prevent us from selling our products in certain markets. Although patent and intellectual property disputes are often settled through licensing or similar arrangements, costs associated with such arrangements may be substantial and could include ongoing royalties. Furthermore, the necessary licenses may not be available to us on satisfactory terms, if at all. In particular, if we were found to infringe a valid claim of the Transgene adenoviral vector United States patent, Canji p53 issued United States patent or a claim that may issue from a currently pending application, such as the Johns Hopkins application discussed above or other patents that might issue with similar claims, our business could be materially harmed.

We are currently involved in opposing three European patents in proceedings before the EPO, in which we are seeking to have the EPO revoke three different European patents owned or controlled by Canji/ Schering-Plough. These European patents relate to the use of a p53 gene, or the use of tumor suppressor genes, in the preparation of therapeutic products. In one opposition involving a European patent directed to the use of a tumor suppressor gene, the EPO revoked the European patent in its entirety. Canji has appealed this revocation. A hearing to determine the outcome of this appeal is scheduled for late April 2004. In the second opposition, involving a patent that is directed to therapeutic and other applications of the p53 gene and that is owned by Johns Hopkins and, we understand, controlled by Schering-Plough, the EPO recently revoked the patent in its entirety. The patent owner has appealed this decision. In a third case involving the use of a p53 gene, the European patent at issue was upheld following an initial hearing. A second hearing to determine whether this patent should be revoked will be held in late April 2004. If we do not ultimately prevail in one or more of these oppositions, our competitors could seek to assert by means of litigation any patent surviving opposition against European commercial activities involving our potential products. If our competitors are successful in any such litigation, it could have a significant detrimental effect on our ability to commercialize our potential commercial products in Europe.

We may be subject to litigation and infringement claims that may be costly, divert management s attention, and materially harm our business.

Extensive litigation regarding patents and other intellectual property rights has been common in the biopharmaceutical industry. Litigation may be necessary to assert infringement claims, enforce patent rights, protect trade secrets or know-how and determine the enforceability, scope and validity of certain proprietary rights. The defense and prosecution of intellectual property lawsuits, PTO interference proceedings, and related legal and administrative proceedings in the United States and internationally involve complex legal and factual questions. As a result, such proceedings are costly and time-consuming to pursue and their outcome is uncertain.

Regardless of merit or outcome, our involvement in any litigation, interference or other administrative proceedings could cause us to incur substantial expense and could significantly divert the efforts of our technical and management personnel. An adverse determination may subject us to the loss of our proprietary position or to significant liabilities, or require us to seek licenses that may include substantial cost and ongoing royalties. Licenses may not be available from third parties, or may not be obtainable on satisfactory terms. An adverse determination or a failure to obtain necessary licenses may restrict or prevent us from manufacturing and selling our products, if any. These outcomes could materially harm our business, financial condition and results of operations.

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If we fail to meet our obligations under license agreements, we may lose our rights to key technologies on which our business depends.

Our business depends in part on patents licensed from third parties. Those third-party license agreements impose obligations on us, such as payment obligations and obligations to diligently pursue development of commercial products under the licensed patents. If a licensor believes that we have failed to meet our obligations under a license agreement, the licensor could seek to limit or terminate our license rights, which could lead to costly and time-consuming litigation and, potentially, a loss of the licensed rights. During the period of any such litigation, our ability to carry out the development and commercialization of products candidates could be significantly and negatively affected. If our license rights were restricted or ultimately lost, our ability to continue our business based on the affected technology platform would be severely adversely affected.

Competition and technological change may make our product candidates and technologies less attractive or obsolete.

We compete with pharmaceutical and biotechnology companies, including Canji, Inc. and Genvec, Inc., which are pursuing forms of treatment similar to ours for the diseases ADVEXIN therapy and our other product candidates target. We are aware that Canji, with its parent Schering-Plough Corporation, has in the past been involved in research and/or development of adenoviral p53 products and has numerous patents and patent applications relating to adenoviral p53 therapy. We understand that Schering-Plough has stopped its adenoviral p53 clinical trials, and it is unknown whether these parties are continuing their adenoviral p53 research and/or development efforts. We are also aware that a Chinese pharmaceutical company, SiBioNo GeneTech, Inc., has recently announced that it has received regulatory approval from the Chinese drug regulatory agency to market an adenoviral p53 product in China. We control an issued Chinese patent covering adenoviral p53, and a number of pending Chinese applications directed to p53 therapy and adenoviral production. We do not at present know whether SiBioNo s adenoviral p53 product is covered by patent protection or whether it infringes our Chinese patent or pending applications. We understand that enforcement of patents in China is unpredictable and we do not know if monetary damages could be recovered from SiBioNo GeneTech if its product infringes our patent or patent applications. Patent enforcement and respect of international patent standards, rules and laws have not historically been a key characteristic of the Chinese government and patent system. Further, geopolitical developments, including trade and tariff disputes that are currently ongoing between the government of China and the United States Department of Commerce could add additional uncertainty to any effort to enforce patents, recover damages, if any, or engage in the sales and marketing of patented products in China. We also may face competition from companies that may develop internally or acquire competing technology from universities and other research institutions. As these companies develop their technologies, they may develop competitive positions that may prevent or limit our product commercialization efforts.

Some of our competitors are established companies with greater financial and other resources than ours. Other companies may succeed in developing products earlier than we do, obtaining FDA approval for products more rapidly than we do or developing products that are more effective than our product candidates. While we will seek to expand our technological capabilities to remain competitive, research and development by others may render our technology or product candidates obsolete or non-competitive or result in treatments or cures superior to any therapy developed by us.

Even if we receive regulatory approval to market ADVEXIN therapy, INGN 241, INGN 225 or other product candidates, we may not be able to commercialize them profitably.

Our profitability will depend on the market s acceptance of ADVEXIN therapy, INGN 241, INGN 225, if approved, and our other product candidates. The commercial success of our product candidates will depend on whether:

they are more effective than alternative treatments;

their side effects are acceptable to patients and doctors;

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insurers and other third-party healthcare payers will provide adequate reimbursement for them;

we produce and sell them at a profit; and

we market ADVEXIN therapy, INGN 241, INGN 225 and other product candidates effectively.

Because the target patient populations for the primary indication of ADVEXIN therapy, our lead product candidate, are small, we must achieve significant market share and obtain high per-patient prices for our products to achieve profitability.

ADVEXIN therapy, our lead product candidate for the treatment of recurrent squamous cell cancer of the head and neck, targets diseases with small patient populations. As a result, our per-patient prices must be relatively high in order to recover our development costs and achieve profitability. We estimate that the annual incidence for squamous cell cancer of the head and neck is 40,000 patients in the United States. We believe that we will need to market worldwide to achieve significant market penetration. In addition, we are developing other drug candidates to treat cancers with small patient populations. Due to the expected costs of treatment for ADVEXIN therapy, we may be unable to obtain sufficient market share for our drug products at a price high enough to justify our product development efforts.

If we are unable to manufacture our products in sufficient quantities or obtain regulatory approvals for our manufacturing facility, or if our manufacturing process is found to infringe a valid patented process of another company, then we may be unable to meet demand for our products and lose potential revenues.

To complete our clinical trials and commercialize our product candidates, if approved, we will need access to, or development of, facilities to manufacture a sufficient supply of our product candidates. We have used a manufacturing facility in Houston, Texas, which we constructed and own, to manufacture ADVEXIN therapy, INGN 241 and other product candidates for currently planned clinical trials. We anticipate that this facility is suitable for the initial commercial launch of ADVEXIN therapy. We have no experience manufacturing ADVEXIN therapy, INGN 241 or any other product candidates in the volumes that would be necessary to support commercial sales. If we are unable to manufacture our product candidates in clinical or, when necessary, commercial quantities, then we will need to rely on third-party manufacturers to produce our products for clinical and commercial purposes. These third-party manufacturers must receive FDA approval before they can produce clinical material or commercial product. Our products may be in competition with other products for access to these facilities and may be subject to delays in manufacture if third parties give other products greater priority than ours. In addition, we may not be able to enter into any necessary third-party manufacturing arrangements on acceptable terms. There are very limited contract manufacturers who currently have the capability to produce ADVEXIN therapy, INGN 241 or our other product candidates, and the inability of any of these contract manufacturers to deliver our required quantities of product candidates timely and at commercially reasonable prices would negatively affect our operations.

Before we can begin commercially manufacturing ADVEXIN therapy, INGN 241 or any other product candidate, we must obtain regulatory approval of our manufacturing facility and process. Manufacturing of our product candidates for clinical and commercial purposes must comply with the FDA s current Good Manufacturing Practices requirements, commonly known as CGMP requirements, and foreign regulatory requirements. The CGMP requirements govern quality control and documentation policies and procedures. In complying with CGMP and foreign regulatory requirements, we will be obligated to expend time, money and effort in production, record keeping and quality control to assure that the product meets applicable specifications and other requirements. We must also pass a pre-approval inspection prior to FDA approval.

Our current manufacturing facilities have not yet been subject to an FDA or other regulatory dossier-related inspection. Failure to pass a pre-approval inspection may significantly delay FDA approval of our products. If we fail to comply with these requirements, we would be subject to possible regulatory action and may be limited in the jurisdictions in which we are permitted to sell our products. Further, the FDA and foreign regulatory authorities have the authority to perform unannounced periodic inspections of our manufacturing facilities to ensure compliance with CGMP and foreign regulatory requirements. Our facility in Houston, Texas is our only manufacturing facility. If this facility were to incur significant damage or

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destruction, then our ability to manufacture ADVEXIN therapy, INGN 241 or any other product candidates would be significantly hampered, and our pre-clinical testing, clinical trials and commercialization efforts would be delayed.

In order to produce our products in the quantities that we believe will be required to meet anticipated market demand, if our products are approved, we will need to increase, or scale-up, our production process. If we are unable to do so, or if the cost of this scale-up is not economically viable to us, we may not be able to produce our products in a sufficient quantity to meet the requirements of future demand.

Canji controls a United States patent and the corresponding international applications, including a European counterpart, relating to the purification of viral or adenoviral compositions. While we believe that our manufacturing process does not infringe this patent, Canji could still assert a claim against us. We may also become subject to infringement claims or litigation if our manufacturing process infringes upon other patents. The defense and prosecution of intellectual property suits and related legal and administrative proceedings are costly and time-consuming to pursue, and their outcome is uncertain.

We rely on only one supplier for some of our manufacturing materials. Any problems experienced by any such supplier could negatively affect our operations.

We rely on third-party suppliers for most of the equipment, materials and supplies used in the manufacturing of ADVEXIN therapy, INGN 241 and our other product candidates. Some items critical to the manufacture of these product candidates are available from only one supplier or vendor. We do not have supply agreements with these key suppliers. To mitigate the related supply risk, we maintain inventories of these items. Any significant problem that one of our sole source suppliers experiences could result in a delay or interruption in the supply of materials to us until that supplier cures the problem or until we locate an alternative source of supply. Such problems would likely lead to a delay or interruption in our manufacturing operations or could require a significant modification to our manufacturing process, which could impair our ability to manufacture our product candidates in a timely manner and negatively affect our operations.

If product liability lawsuits are successfully brought against us, we may incur substantial damages and demand for our product candidates may be reduced.

The testing and marketing of medical products is subject to an inherent risk of product liability claims. Regardless of their merit or eventual outcome, product liability claims may result in:

decreased demand for our product candidates;

injury to our reputation and significant media attention;

withdrawal of clinical trial volunteers;

substantial delay in FDA approval;

costs of litigation; and

substantial monetary awards to plaintiffs.

We currently maintain product liability insurance with coverage of $5.0 million per occurrence with a $15.0 million annual aggregate limit. This coverage may not be sufficient to protect us fully against product liability claims. We intend to expand our product liability insurance coverage beyond clinical trials to include the sale of commercial products if we obtain marketing approval for any of our product candidates. Our inability to obtain sufficient product liability insurance at an acceptable cost to protect against product liability claims could prevent or limit the commercialization of our products.

We use hazardous materials in our business, and any claims relating to improper handling, storage or disposal of these materials could harm our business.

Our business involves the use of a broad range of hazardous chemicals and materials. Environmental laws impose stringent civil and criminal penalties for improper handling, disposal and storage of these materials. In

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addition, in the event of an improper or unauthorized release of, or exposure of individuals to, hazardous materials, we could be subject to civil damages due to personal injury or property damage caused by the release or exposure. A failure to comply with environmental laws could result in fines and the revocation of environmental permits, which could prevent us from conducting our business.

Our stock price may fluctuate substantially.

The market price for our common stock will be affected by a number of factors, including:

progress and results of our pre-clinical and clinical trials;

announcement of technological innovations by us or our competitors;

developments concerning proprietary rights, including patent and litigation matters;

publicity regarding actual or potential results with respect to products under development by us or by our competitors;

regulatory developments;

the announcement of new products by us or our competitors;

quarterly variations in our or our competitors results of operations;

failure to achieve operating results projected by securities analysts;

changes in earnings estimates or recommendations by securities analysts;

developments in our industry; and

general market conditions and other factors.

In addition, stock prices for many companies in the technology and emerging growth sectors have experienced wide fluctuations that have often been unrelated to the operating performance of such companies.

Any acquisition we might make may be costly and difficult to integrate, may divert management resources or dilute stockholder value.

As part of our business strategy, we may acquire assets or businesses principally relating to or complementary to our current operations, and we have in the past evaluated and discussed such opportunities with interested parties. Any acquisitions that we undertake will be accompanied by the risks commonly encountered in business acquisitions. These risks include, among other things:

potential exposure to unknown liabilities of acquired companies;

the difficulty and expense of assimilating the operations and personnel of acquired businesses;

diversion of management time and attention and other resources;

loss of key employees and customers as a result of changes in management;

the incurrence of amortization expenses; and

possible dilution to our stockholders.

In addition, geographic distances may make the integration of businesses more difficult. We may not be successful in overcoming these risks or any other problems encountered in connection with any acquisitions.

If we do not progress in our programs as anticipated, our stock price could decrease.

For planning purposes, we estimate the timing of a variety of clinical, regulatory and other milestones, such as when a certain product candidate will enter clinical development, when a clinical trial will be completed or when an application for regulatory approval will be filed. Some of our estimates are included in this prospectus supplement. Our estimates are based on present facts and a variety of assumptions. Many of

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the underlying assumptions are outside of our control. If milestones are not achieved when we expect them to be, investors could be disappointed, and our stock price may decrease.

If we lose key personnel or are unable to attract and retain additional, highly skilled personnel required to develop our products or obtain new collaborations, our business will suffer.

We depend, to a significant extent, on the efforts of our key employees, including senior management and senior scientific, clinical, regulatory and other personnel. The development of new therapeutic products requires expertise from a number of different disciplines, some of which are not widely available. We depend upon our scientific staff to discover new product candidates and to develop and conduct pre-clinical studies of those new potential products. Our clinical and regulatory staff is responsible for the design and execution of clinical trials in accordance with FDA requirements and for the advancement of our product candidates toward FDA approval. The quality and reputation of our scientific, clinical and regulatory staff, especially the senior staff, and their success in performing their responsibilities, are a basis on which we attract potential funding sources and collaborators. In addition, our Chief Executive Officer and other executive officers are involved in a broad range of critical activities, including providing strategic and operational guidance. The loss of these individuals, or our inability to retain or recruit other key management and scientific, clinical, regulatory and other personnel, may delay or prevent us from achieving our business objectives. We face intense competition for personnel from other companies, universities, public and private research institutions, government entities and other organizations.

Some of our insiders are parties to transactions with us that may cause conflicting obligations.

Dr. John N. Kapoor, the Chairman of our Board of Directors, is also associated with EJ Financial Enterprises, Inc., a health care investment firm which is wholly owned by him, and therefore may have conflicts of interest in allocating his time among us and his other business activities, and he may have legal obligations to multiple entities. We have entered into a consulting agreement with EJ Financial. The consulting agreement provides that we will pay EJ Financial $175,000 per year for certain management consulting services, which is based on anticipated time spent by EJ Financial personnel on the Company s affairs. EJ Financial is also involved in the management of health care companies in various fields, and Dr. Kapoor is involved in various capacities with the management and operation of these companies. In addition, EJ Financial is involved with other companies in the cancer field. Although these companies are pursuing different therapeutic approaches for the treatment of cancer, discoveries made by one or more of these companies could render our products less competitive or obsolete.

David Parker, Ph.D., J.D., our Vice President, Intellectual Property, is a partner with the law firm Fulbright & Jaworski LLP, which provides legal services to us as our primary outside counsel for intellectual property matters.

We are in negotiations with Dr. Robert Sobol, our Senior Vice President, Medical and Scientific Affairs, to acquire a company of which he is the sole shareholder. The terms of the proposed transaction have not been determined, but the purchase price is likely to be between $1 million and $2 million and to be paid in shares of our common stock. We believe the technology which is owned by Dr. Sobol s company will be a valuable addition to our intellectual property portfolio. We have endeavored to conduct the negotiations at arms length, and any transaction would be subject to the approval of the independent members of our Board of Directors.

In addition, we have relationships with Jack A. Roth, M.D., and The University of Texas M.D. Anderson Cancer Center, both of whom are affiliated with The Board of Regents of the University of Texas System, one of our stockholders. For more information concerning these relationships, see the notes to our consolidated financial statements.

We believe the foregoing transactions with insiders were and are in our best interests; however, the transactions may cause conflicts of interest with respect to those insiders.

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

Our exposure to market risk for changes in interest rates relates primarily to our fixed rate long-term debt and short-term investments in investment grade securities, which consist primarily of federal and state government obligations, commercial paper and corporate bonds. Investments are classified as held-to-maturity and are carried at amortized costs. We do not hedge interest rate exposure or invest in derivative securities. A hypothetical 100-basis point decrease in the interest rates of our investments at the investment balances as of December 31, 2003 would decrease our interest income by approximately $364,000.

At December 31, 2003, the fair value of our fixed-rate debt approximated its carrying value based upon discounted future cash flows using current market prices.

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

The information required by this Item is set forth in our Financial Statements and Notes thereto beginning at page F-3 of this Report.

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

On March 6, 2002, we dismissed Arthur Andersen LLP as our independent public accountants, effective upon completion of Arthur Andersen LLP s services in connection with the filing of our Transition Report on Form 10-KT for the six-month transition period ended December 31, 2001.

Arthur Andersen LLP s reports on our financial statements for each of the years ended June 30, 2000 and 2001 and for the six-month transition period ended December 31, 2001 did not contain an adverse opinion or a disclaimer of opinion, and were not qualified or modified as to uncertainty, audit scope or accounting principles.

The decision to change independent public accountants was recommended by the Audit Committee of our Board of Directors and was approved by our Board of Directors.

During each of the two years ended June 30, 2000 and 2001 and for the six-month transition period ended December 31, 2001, and through March 20, 2002, there were no disagreements with Arthur Andersen LLP on any matter of accounting principles or practices, financial statement disclosure, or auditing scope or procedures, which disagreements, if not resolved to the satisfaction of Arthur Andersen LLP, would have caused it to make reference to the subject matter of the disagreement in connection with its report.

During each of the two years ended June 30, 2000 and 2001 and for the six-month transition period ended December 31, 2001, and through March 20, 2002, Arthur Andersen LLP did not advise us of any reportable events as described in Item 304(a)(1)(v) of Regulation S-K under the Securities Act of 1933, as amended.

On March 6, 2002, we engaged Ernst & Young LLP as our principal accountants to audit our financial statements.

During each of the two years ended June 30, 2000 and 2001 and for the six-month transition period ended December 31, 2001, and through March 6, 2002, we did not consult Ernst & Young LLP on any matters described in Items 304(a)(2)(i) or 304(a)(2)(ii) of Regulation S-K.

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

Evaluation of disclosure controls and procedures. Our management evaluated, with the participation of our Chief Executive Officer and our Chief Financial Officer, the effectiveness of our disclosure controls and procedures as of the end of the period covered by this Annual Report on Form 10-K. Based on this evaluation, our Chief Executive Officer and our Chief Financial Officer have concluded that our disclosure controls and procedures are effective to ensure that information we are required to disclose in reports that we file or submit under the Securities Exchange Act of 1934 is recorded, processed, summarized and reported within the time periods specified in Securities and Exchange Commission rules and forms.

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Changes in internal control over financial reporting. There was no change in our internal control over financial reporting that occurred during the last fiscal quarter covered by this Annual Report on Form 10-K that has materially affected, or is reasonably likely to materially affect, our internal control over financial reporting.

PART III

Item 10. ***Directors and Executive Officers of the Registrant***

The information required by this item is incorporated by reference to the information under the sections captioned Election of Directors, Executive Officers, Section 16(a) Beneficial Ownership Reporting Compliance and Code of Ethics contained in the 2004 Proxy Statement.

Item 11. ***Executive Compensation***

The information required by this item is incorporated by reference to the information under the section captioned Executive Compensation contained in the 2004 Proxy Statement.

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

The information required by this item related to security ownership of certain beneficial owners and management is incorporated by reference to the information under the sections captioned Security Ownership contained in the 2004 Proxy Statement.

Equity Compensation Plan Information

Plan Category	(a) Number of Securities to be Issued Upon Exercise of Outstanding Options, Warrants and Rights	(b) Weighted-Average Exercise Price of Outstanding Options, Warrants and Rights	(c) Number of Securities Remaining Available for Future Issuance Under Equity Compensation Plans (Excluding Securities Reflected in Column (a))
	(In thousands)		(In thousands)
Equity compensation plans approved by security holders	5,156	$3.30	1,484
Equity compensation plans not approved by security holders			
Total	5,156	$3.30	1,484

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

The information required by this item is incorporated by reference to the information under the sections captioned Certain Relationships and Related Transactions and Compensation Committee Interlocks and Insider Participation contained in the 2004 Proxy Statement.

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

The information required by this Item related to principal accountant fees and services as well as related pre-approval policies is incorporated by reference to the information under the sections captioned Fees Paid to Ernst & Young LLP and Audit Committee Pre-Approval

of Audit and Permissible Non-Audit Services of Independent Auditors contained in the 2004 Proxy Statement.

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PART IV

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

1. Consolidated Financial Statements

The following financial statements are filed as part of this Report:

2. Financial Statement Schedules

All financial statement schedules are omitted because they are not applicable or not required, or because the required information is included in the consolidated financial statements or notes thereto.

3. Exhibits

(a) *Exhibits*

Exhibit Number	Description of Document
3.1(a)(6)	Certificate of Incorporation as currently in effect
3.1(b)(6)	Amendment to Certificate of Incorporation, effective as of December 21, 2001
3.2(4)	Bylaws of Introgen as currently in effect
4.1(2)	Specimen Common Stock Certificate
4.2(5)	Certificate of Designations of Series A Non-Voting Convertible Preferred Stock
4.3(9)	Form of Stock Purchase Warrant
10.1(1)	Form of Indemnification Agreement between Introgen and each of its directors and officers
10.2(1)	1995 Stock Plan and form of stock option agreement Thereunder
10.3(3)	2000 Stock Option Plan and forms of stock option agreements thereunder
10.4(3)	2000 Employee Stock Purchase Plan and forms of agreements thereunder
10.5(1)	Form of Series C Preferred Stock Purchase Agreement among Introgen and certain investors 10.6(1)
10.7(a)(1)	Assignment of Leases, dated November 23, 1998, by TMX Realty Corporation and Riverway Bank, and other related agreements
10.7(b)(1)	Lease Agreement, dated June 7, 1996, by and between Introgen and Plaza del Oro Business Center
10.7(c)(2)	Amendment No. 1 to Lease Agreement, effective as of May 9, 1997
10.7(d)(2)	Amendment No. 2 to Lease Agreement, effective as of July 31, 1998
10.7(e)(2)	Amendment No. 3 to Lease Agreement, effective as of June 29, 2000
10.8(a) (1)	Patent and Technology License Agreement, effective as of July 20, 1994, by and between the Board of Regents of The University of Texas System, M. D. Anderson Cancer Center and Introgen
10.8(b) (1)	Amendment No. 1 to Patent License Agreement, effective as of September 1, 1996
10.9 (3)	

Sponsored Research Agreement for Clinical Trial, No. CS 93-27, dated February 11, 1993, between Introgen and M. D. Anderson, as amended

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Exhibit Number	Description of Document
10.10	Reserved
10.11 (3)	Sponsored Research Agreement No. SR 93-04, dated February 11, 1993 between M. D. Anderson and Introgen, as amended
10.12	Reserved
10.13 (3)	Sponsored Research Agreement No. SR 96-004 between Introgen and M. D. Anderson, dated January 17, 1996
10.14	Reserved
10.15 (3)	License Agreement, dated March 29, 1996 between Introgen and SKCC
10.16(1)	Consulting Agreement between Introgen and Jack A. Roth, M. D., effective as of October 1, 1994
10.17(1)	Consulting Agreement between EJ Financial Enterprises, Inc. and Introgen, effective as of July 1, 1994
10.18(a)(1)	Employment Agreement dated as of August 1, 1996 between Introgen and David G. Nance
10.18(b)(1)	Amendment No. 1 to Employment Agreement, effective as of August 1, 1998
10.18(c)(1)	Amendment No. 2 to Employment Agreement, effective as of February 15, 2000
10.19(1)	Service Agreement, effective as of July 1, 1994, between Introgen and Domecq Technologies, Inc.
10.20(a) (1)	Collaboration Agreement (p53 Products), effective as of October 7, 1994, between Introgen and RPR, as amended
10.20(b) (3)	Addendum No. 1 to Collaboration Agreement (p53 Products), dated January 23, 1996, between Introgen and RPR
10.20(c) (1)	1997 Agreement Memorandum, effective as of July 22, 1997, between Introgen and RPR
10.20(d) (3)	Letter Agreement, dated April 19, 1999, from Introgen to RPR regarding manufacturing process for ADVEXIN therapy
10.21(a) (1)	Collaboration Agreement (K-ras Products), effective as of October 7, 1994, between Introgen and RPR, as amended
10.21(b)(1)	Amendment No. 1 to Collaboration Agreement (K-ras Products), effective as of September 27, 1995, between Introgen and RPR
10.22 (3)	Collaborative Research and Development Agreement dated October 30, 1998 between Introgen, RPR and NCI
10.23 (1)	Non-Exclusive License Agreement, effective as of April 16, 1997, by Introgen and Iowa Research Foundation
10.24 (3)	Option Agreement, effective as of June 1, 1998, by Introgen and Imperial Cancer Research Technology Limited (ICRT)
10.25 (3)	Option Agreement, effective as of January 1, 1999, by Introgen and ICRT
10.26 (3)	Exclusive License Agreement, effective as of July 19, 1999, by Introgen and Corixa Corporation
10.27(a)	Reserved
10.27(b)(1)	Letter dated January 28, 2000, from Introgen to LXR Biotechnology (LXR), notifying LXR of its exercise of its option
10.27(c) (2)	Exclusive License Agreement, effective as of May 16, 2000, by and between Introgen and LXR
10.28 (3)	Administrative Services and Management Agreement, effective as of January 1, 1999, by and between Introgen and Gendux, Inc.
10.29 (3)	Research and Development Agreement, effective as of January 1, 1999, by and between Introgen and Gendux, Inc.
10.30 (3)	Delivery Technology License Agreement, effective as of January 1, 1999, by and between Introgen and Gendux, Inc.

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Exhibit Number	Description of Document
10.31 (3)	Target Gene License Agreement, effective as of January 1, 1999, by and between Introgen and Gendux, Inc.
10.32 (1)	Non-Exclusive License Agreement, effective as of August 17, 1998, by and between Introgen and National Institutes of Health
10.33	Reserved
10.34(2)	Master Lease Agreement, effective as of August 4, 1999, by and between Introgen and Finova Capital Corporation
10.35(2)	Construction Loan Agreement, effective as of July 24, 2000, by and between Introgen and Compass Bank
10.36 (5)	Restated p53 and K-ras Agreement, effective as of June 30, 2001, by and among Introgen, Aventis Pharmaceuticals Inc. (API) and Aventis Pharma S.A. (Aventis)
10.37(5)	p53 Assignment Agreement, effective as of June 30, 2001, by and among Introgen, API and Aventis
10.38(5)	K-ras Assignment Agreement, effective as of June 30, 2001, by and among Introgen, API and Aventis
10.39(5)	Registration Rights Agreement, effective as of June 30, 2001, by and among Introgen, API and RPR
10.40(5)	Voting Agreement, effective as of June 30, 2001, by and among Introgen, API and RPR
10.41(7)	Master Services Agreement, effective as of July 9, 2001, by and between Introgen and PPD Development, LLC
10.42(8)	Series A Preferred Stock Purchase Agreement, effective as of March 7, 2002, by and between Introgen and VirRx, Inc.
10.43(8)	Collaboration and License Agreement, effective as of March 7, 2002, by and between Introgen and VirRx, Inc.
10.44(9)	Securities Purchase Agreement, effective as of June 18, 2003, by and among Introgen and the Investors named therein.
10.45(10)	Placement Agent Agreement, effective as of November 26, 2003, by and among Introgen, SG Cowen Securities Corporation and First Albany Capital Inc.
21.1(1)	List of subsidiaries of Introgen
23.1	Consent of Ernst & Young LLP, independent auditors
23.2	Information Regarding Consent of Arthur Andersen LLP
23.3(11)	Consent of Ernst & Young LLP, independent auditors
24.1	Power of Attorney (See page 55)
31.1	Certification of Chief Executive Officer and Chief Financial Officer pursuant to Rule 13a-14(a) and Rule 15d-14(a) of the Securities Exchange Act, as amended
32.1	Certification of Chief Executive Officer and Chief Financial Officer Pursuant to 18 U.S.C. 1350, as Adopted Pursuant to Section 906 of the Sarbanes-Oxley Act of 2002

(1) Incorporated by reference to the same-numbered exhibit filed with Introgen s Registration Statement on Form S-1 (No. 333-30582) filed with the Securities and Exchange Commission on February 17, 2000.

(2) Incorporated by reference to the same-numbered exhibit filed with Amendment No. 2 to Introgen s Registration Statement on Form S-1 (No. 333-30582) filed with the Securities and Exchange Commission on September 8, 2000.

(3) Incorporated by reference to the same-numbered exhibit filed with Amendment No. 3 to Introgen s Registration Statement on Form S-1 (No. 333-30582) filed with the Securities and Exchange Commission on October 4, 2000.

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(4) Incorporated by reference to the same-numbered exhibit filed with Introgen s Quarterly Report on Form 10-Q, for the quarter ended December 31, 2000, (File No. 000-21291), filed with the Securities and Exchange Commission on February 14, 2001.

(5) Incorporated by reference to the same-numbered exhibit filed with Introgen s Annual Report on Form 10-K for the fiscal year ended June 30, 2001 (File No. 000-21291), filed with the Securities and Exchange Commission on September 19, 2001.

(6) Incorporated by reference to the same-numbered exhibit filed with Introgen s Transition Report on Form 10-KT for the six-month transition period ended December 31, 2001 (File No. 000-21291), filed with the Securities and Exchange Commission on March 20, 2002.

(7) Incorporated by reference to the same-numbered exhibit filed with Amendment No. 1 to Introgen s Transition Report on Form 10-KT for the six-month transition period ended December 31, 2001 (File No. 000-21291), filed with the Securities and Exchange Commission on March 26, 2002.

(8) Incorporated by reference to the same-numbered exhibit filed with Introgen s Quarterly Report on Form 10-Q, for the quarter ended March 31, 2002 (File No. 000-21291), filed with the Securities and Exchange Commission on May 15, 2002.

(9) Incorporated by reference to the same-numbered exhibit filed with Introgen s Current Report on Form 8-K, filed with the Securities and Exchange Commission on June 18, 2003.

(10) Incorporated by reference to the same-numbered exhibit filed with Introgen s Current Report on Form 8-K, filed with the Securities and Exchange Commission on November 26, 2003.

(11) Incorporated by reference to the same-numbered exhibit filed with Introgen s Annual Report on Form 10-K for the fiscal year ended December 31, 2002 (File No. 000-21291), filed with the Securities and Exchange Commission on March 31, 2003.

Confidential treatment has been granted for portions of this exhibit.

Confidential treatment has been requested for portions of this exhibit.

(b) *Reports on Form 8-K*

Current Report on Form 8-K announcing Introgen s third quarter 2003 financial results and furnishing certain financial statements, filed with the Securities and Exchange Commission on November 13, 2003.

Current Report on Form 8-K announcing the Placement Agent Agreement entered into by and among Introgen, SG Cowen Securities Corporation and First Albany Capital Inc. and filing the Placement Agent Agreement as an exhibit thereto, filed with the Securities and Exchange Commission on November 26, 2003.

(c) *Exhibits*

See Item 15(3) above.

(d) *Financial Statement Schedules*

See Item 15(2) above.

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SIGNATURES

Pursuant to the requirements of Section 13 or 15(d) of the Securities Exchange Act of 1934 the Registrant has duly caused this Annual Report on Form 10-K to be signed on its behalf by the undersigned thereunto duly authorized in the City of Austin, Texas, this March 5, 2004.

INTROGEN THERAPEUTICS, INC.

By: /s/ DAVID G. NANCE

David G. Nance
President, Chief Executive Officer and Director
(Principal Executive Officer)

By: /s/ JAMES W. ALBRECHT, JR.

James W. Albrecht, Jr.
Chief Financial Officer
(Principal Financial and Accounting Officer)

POWER OF ATTORNEY

KNOW ALL PERSONS BY THESE PRESENTS, that each person whose signature appears below hereby constitutes and appoints David G. Nance and James W. Albrecht, Jr. and each of them acting individually, as his or her attorney-in-fact, each with full power of substitution, for him or her in any and all capacities, to sign any and all amendments to this Report on Form 10-K, and to file the same, with all exhibits thereto and other documents in connection therewith, with the Securities and Exchange Commission.

Pursuant to the requirements of the Securities Exchange Act of 1934, as amended, this Report on Form 10-K has been signed on behalf of the Registrant by the following persons in the capacities and on the dates indicated:

Signature	Title	Date
/s/ DAVID G. NANCE (David G. Nance)	President, Chief Executive Officer, and Director (Principal Executive Officer)	March 5, 2004
/s/ JAMES W. ALBRECHT, JR. (James W. Albrecht, Jr.)	Chief Financial Officer (Principal Financial and Accounting Officer)	March 5, 2004
/s/ JOHN N. KAPOOR, PH.D. (John N. Kapoor, Ph.D.)	Chairman of the Board and Director	March 5, 2004
/s/ WILLIAM H. CUNNINGHAM, PH.D. (William H. Cunningham, Ph.D.)	Director	March 5, 2004
/s/ MALCOLM GILLIS, PH.D. (Malcolm Gillis, Ph.D.)	Director	March 5, 2004

/s/ CHARLES E. LONG (Charles E. Long)	Director	March 5, 2004
/s/ MAHENDRA G. SHAH, PH.D. (Mahendra G. Shah, Ph.D.)	Director	March 5, 2004

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REPORT OF INDEPENDENT AUDITORS

To the Board of Directors and Stockholders of

Introgen Therapeutics, Inc. and Subsidiaries:

We have audited the accompanying consolidated balance sheets of Introgen Therapeutics, Inc. and subsidiaries as of December 31, 2003 and 2002, and the related consolidated statements of operations, stockholders equity, and cash flows for the years then ended. These financial statements are the responsibility of Introgen Therapeutics, Inc. s management. Our responsibility is to express an opinion on these financial statements based on our audit. The financial statements of Introgen Therapeutics, Inc. and subsidiaries for the six months ended December 31, 2001 and for the year ended June 30, 2001, were audited by other auditors whose report dated January 18, 2002, expressed an unqualified opinion on those statements.

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 consolidated financial position of Introgen Therapeutics, Inc. and subsidiaries as of December 31, 2003 and 2002, and the consolidated results of their operations and their cash flows for the years then ended in conformity with accounting principles generally accepted in the United States.

/s/ ERNST & YOUNG LLP

Austin, Texas

January 16, 2004

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REPORT OF INDEPENDENT AUDITORS

To the Board of Directors of

Introgen Therapeutics, Inc.:

We have audited the accompanying consolidated balance sheets of Introgen Therapeutics, Inc. (a Delaware corporation), and subsidiaries as of June 30, 2000 and 2001 and December 31, 2001, and the related consolidated statements of operations, stockholders equity and cash flows for each of the three years in the period ended June 30, 2001 and for the six months ended December 31, 2001. These financial statements are the responsibility of Introgen Therapeutics, 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 Introgen Therapeutics, Inc., and subsidiaries as of June 30, 2000 and 2001 and December 31, 2001, and the results of their operations and their cash flows for each of the three years in the period ended June 30, 2001 and the six months ended December 31, 2001, in conformity with accounting principles generally accepted in the United States.

/s/ ARTHUR ANDERSEN LLP

Austin, Texas

January 18, 2002

THIS IS A COPY OF THE AUDIT REPORT PREVIOUSLY ISSUED BY ARTHUR ANDERSEN LLP IN CONNECTION WITH INTROGEN THERAPEUTICS, INC. S FILING ON FORM 10-K FOR THE AS OF AND FOR THE SIX MONTH PERIOD ENDED DECEMBER 31, 2001. THIS AUDIT REPORT HAS NOT BEEN REISSUED BY ARTHUR ANDERSEN LLP IN CONNECTION WITH THIS FILING ON FORM 10-K. SEE EXHIBIT 23.2 FOR FURTHER DISCUSSION.

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INTROGEN THERAPEUTICS, INC. AND SUBSIDIARIES

CONSOLIDATED BALANCE SHEETS

(Amounts in thousands)

	December 31,	
	2002	2003
ASSETS		
Current Assets:		
Cash and cash equivalents	$ 23,467	$ 36,397
Prepaid expenses and other current assets	812	302
Total current assets	24,279	36,699
Property and equipment, net of accumulated depreciation of $8,228 and $9,661, respectively	8,742	7,502
Other assets	295	282
Total assets	$ 33,316	$ 44,483
LIABILITIES AND STOCKHOLDERS EQUITY		
Current Liabilities:		
Accounts payable	$ 1,774	$ 2,054
Accrued liabilities	1,997	2,535
Deferred revenues from affiliate	69	16
Current portion of notes payable	789	777
Current portion of capital lease obligations	798	225
Total current liabilities	5,427	5,608
Capital lease obligations, net of current portion	125	172
Notes payable, net of current portion	7,310	6,542
Deferred revenue, long-term	619	876
Commitments and Contingencies		
Stockholders Equity:		
Series A non-voting convertible preferred stock, $.001 par value; 100 shares authorized, issued and outstanding	1	1
Common stock, $.001 par value; 50,000 shares authorized; 21,487 and 26,539 shares issued and outstanding in 2002 and 2003, respectively	21	27
Additional paid-in capital	94,430	124,270
Deferred compensation	(974)	(44)
Accumulated deficit	(73,643)	(92,969)
Total stockholders equity	19,835	31,285
Total liabilities and stockholders equity	$ 33,316	$ 44,483

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

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INTROGEN THERAPEUTICS, INC. AND SUBSIDIARIES

CONSOLIDATED STATEMENTS OF OPERATIONS

(Amounts in thousands, except per share amounts)

	Year Ended June 30, 2001	Six Months Ended December 31,		Year Ended December 31,	
		2000	2001	2002	2003
		(Unaudited)			
Contract services, grant and other Revenue	$684	$391	$298	$1,173	$304
Collaborative research					