INTROGEN THERAPEUTICS INC
Form 10-K
March 31, 2003

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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, 2002

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 $21.3 million based upon the last sale price reported on the Nasdaq National Market for June 28, 2002. 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 24, 2003, the Registrant had 21,516,371 shares of common stock, $0.001 par value, issued and outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Certain information required by Items 10, 11, 12 and 13 of Form 10-K is incorporated by reference to the Registrant s proxy statement (2003 Proxy Statement) for the 2003 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, 2002.

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INTROGEN THERAPEUTICS, INC.

ANNUAL REPORT ON FORM 10-K

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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 Factors Affecting Future Operating Results 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 on June 17, 1993. We are a leading developer of gene therapy products for the treatment of cancer and other diseases. Our drug discovery and development programs have resulted in innovative approaches by which physicians may use genes to treat cancer and other diseases. Our lead product candidate, ADVEXIN® gene therapy, combines the p53 gene, one of the most potent members of a group of naturally occurring tumor suppressor genes, which act to protect cells from becoming cancerous, with an adenoviral gene delivery system that we have developed and extensively tested. We are conducting pivotal Phase 3 clinical trials of ADVEXIN gene therapy in head and neck cancer. Pivotal Phase 3 trials are typically the final trials required for FDA approval. We have completed a Phase 2 clinical trial of ADVEXIN gene therapy in non-small cell lung cancer, a category that includes approximately 80% of the various types of lung cancer, and are developing FDA registration plans. We are conducting a Phase 2 trial of ADVEXIN gene therapy in breast cancer. Phase 2 trials are efficacy trials. We are conducting Phase 1 clinical trials, or safety trials, of ADVEXIN gene therapy in other types of cancer. To date, doctors at clinical sites in North America, Europe and Japan have treated hundreds of patients with ADVEXIN gene therapy, establishing a large safety database. We hold the worldwide rights for pre-clinical and clinical development, manufacturing, marketing and commercialization of ADVEXIN gene therapy. ADVEXIN gene therapy is designated as an orphan drug under the Orphan Drug Act, which gives us seven years of marketing exclusivity for ADVEXIN gene therapy if approved by the FDA.

We are developing additional gene therapy product candidates that we believe may be effective in treating certain cancers, including those based on the mda-7 and PTEN genes, as well as associated vector technologies for delivering the gene-based products into target cells. Our INGN 241 product candidate, which combines the mda-7 gene with our gene delivery system, is undergoing safety testing in a clinical trial, with one of the objectives also being to determine if this technology displays anti-tumor activity.

We are investigating other vector technologies for delivering gene-based products into targeted cells. Through our strategic collaboration with VirRx, Inc., we are developing replication-competent viral therapies in which viruses bind directly to cancer cells, replicate in those cells, and cause those cancer cells to die. We

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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.

We believe our research and development expertise gained in gene therapy treatment 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 therapy product candidates in the treatment of cardiovascular disease and rheumatoid arthritis. In addition, we have developed a variety of technologies, which we refer to as enabling technologies, for administering gene therapy products to patients and enhancing the effects of these products. We also have specialized manufacturing expertise and a manufacturing facility to support our continued product development and commercialization efforts.

As a supplement to our gene therapy product programs, we are evaluating the development of mebendazole, our first small molecule candidate, which we refer to as INGN 601. 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 January 2003 edition of *Molecular Cancer Therapeutics.* We are working with The University of Texas M. D. Anderson Cancer Center to further evaluate this molecule as a cancer treatment.

We place substantial emphasis on developing and maintaining a strong intellectual property program. We own or exclusively control numerous patents and pending patent applications in the United States and elsewhere that cover ADVEXIN gene therapy in particular, adenoviral p53 in general, clinical applications of adenoviral and other forms of p53, and adenoviral production. Certain of our patents are licensed from The University of Texas System and from Aventis Pharmaceuticals, Inc. The patents directed to clinical applications of p53 broadly cover the use of p53 in combination with standard chemotherapy and clinical therapy with adenoviral p53 in general. Our adenoviral production patent position is of particular potential commercial importance in that it covers most methods currently in use by us and others for commercial scale adenoviral production and purification processes. We have recently been successful in having certain European patents held by our competitors revoked by the European patent office, subject to appeal by the patent holder, and we are pursuing similar proceedings with respect to an additional European patent. In addition to our p53 intellectual property position, we also own or have exclusively licensed rights in a number of other patents and applications directed to the clinical application of various other tumor suppressor genes.

We own and operate a manufacturing facility that we believe complies with the FDA s current Good Manufacturing Practices requirements, commonly known as CGMP requirements. We have produced ADVEXIN gene therapy in this facility for use in our Phase 1, 2 and 3 clinical trials. The designs of the facility and the processes operated therein have been reviewed with the FDA. Our work to validate our manufacturing processes in accordance with FDA regulations is ongoing. We plan to use this facility for our market launch of ADVEXIN gene therapy. We have produced over 20 batches of ADVEXIN gene 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 clinical trials.

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. Production of a protein that a particular gene encodes requires gene expression, or activity. Many of the proteins inside a cell interact to form pathways that enable a cell to perform its various functions. The

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improper expression of one or more genes can alter these pathways and affect a cell s normal function, frequently resulting in disease.

In recent years, scientists have made significant progress toward understanding the nature of the set of human genes, the human genome, and evaluating the role that genes play in both normal and disease states. Academic and governmental initiatives have sequenced all of the genes that comprise the human genome. As new genes are discovered and decoded, scientists are identifying and understanding their functions. These discoveries provide opportunities to develop therapeutic applications for individual genes, including treatment and prevention of disease.

Gene Therapy

Gene therapy uses genes to regulate cellular function or to correct cellular dysfunction. These processes involve the introduction of genes into cells to restore missing gene functions, correct aberrant gene functions, augment normal gene activity, neutralize the activity of defective genes or induce cell death. In order to perform these processes, a gene for disease treatment, or therapeutic gene, is often combined with a vector for gene delivery, which enables the gene to enter the target cell and make its gene product. For in vivo gene therapy, physicians typically inject the vector containing the therapeutic gene directly into a patient s tissue, body cavity or bloodstream.

The genes used for disease treatment are typically the normal counterparts of genes that are defective or inadequately expressed in the diseased cell. In some cases, the therapeutic gene will simply act to replace a missing protein or to augment the level of a protein that is otherwise inadequate to prevent disease. In other cases, the therapeutic gene will act to eliminate the diseased cells through a process that scientists refer to as apoptosis. Apoptosis, or cell death, is a normal process that the body uses to eliminate damaged cells and cells that are no longer necessary.

The delivery system must be able to deliver a sufficient dose of genes for disease treatment to the correct tissue in order 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 where they will initiate a program to produce more virus. Scientists can modify these viruses by deleting pieces of the viral genome that are necessary for viral reproduction and replacing the deleted pieces with a therapeutic gene. The resulting viral vector retains the ability of the virus to efficiently deliver its genes, which now include a gene, or genes, for disease treatment, into cells, but has lost the ability to reproduce itself and spread to other 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 systems in order to expand the disease targets that can be treated with gene therapy.

Many of the clinical trials currently ongoing that involve gene therapy use 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

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American Cancer Society estimates the annual direct cost of treating cancer patients in the United States is approximately $61 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 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 therapy, because in contrast to more complex genetic disorders, which may require long-term function of the transferred gene, the treatment for cancer restores just those functions that will lead to the destruction of the cancer cell. The introduction of normal tumor suppressor genes, such as p53, into cancer cells is among the most promising of these approaches.

Tumor Suppressor Genes

Tumor suppressor genes 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 and PTEN genes, among others.

The best known and most studied of the tumor suppressor genes is the p53 gene. Initially mislabeled an oncogene, or cancer-causing gene, p53 is now known to be a powerful tumor suppressor gene that acts to block cancer development by preventing the accumulation of DNA damage. 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. Therefore, the presence of a normally functioning p53 pathway allows the body to naturally suppress tumor growth. Most cancers have found ways to block the normal function of the p53 pathway; approximately 50% of human cancers have done this through mutation of the p53 gene itself. Scientists describe tumors with that mutation as p53 mutant tumors.

Current Treatment of Cancer

Despite advances in cancer research in recent years, better treatments for cancer are urgently needed. The 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 current cancer therapies, the treatment of cancer remains complex. Physicians refer to the first treatment regimen for a newly-diagnosed cancer, usually surgery if possible, or

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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 the effects of the new therapy are more quickly apparent.

Given that established cancer therapies often prove to be incomplete, ineffective or toxic to the patient, there is a need for new treatment modalities that either complement established therapies or replace them by offering better therapeutic outcomes. For example, for 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, additional approaches are needed to improve the toxicity and marginal benefits common to current cancer treatments. Gene therapy directly addresses the cellular dysfunction that causes cancer, compared with small molecule drugs or immunotherapeutic agents, which may act indirectly.

The Introgen Approach

We believe that the emerging field of gene therapy 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 gene therapy 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 therapy 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 gene therapy, establishing a large safety database.

We have developed ADVEXIN gene therapy by inserting the p53 gene into the adenoviral delivery system we have developed and extensively tested. Evidence from laboratory, pre-clinical and clinical trials suggests that the p53 tumor suppressor gene may be sufficient to slow, stop or kill many cancer cell types. We believe that ADVEXIN gene 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 gene 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 therapy 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 Gene Therapy and INGN 241 for Multiple Cancer Indications. We plan to continue developing ADVEXIN gene therapy using the p53 gene and our INGN 241 product using the mda-7 gene in multiple cancer indications. Using ADVEXIN gene therapy, we are conducting pivotal Phase 3 clinical trials in head and neck cancer and Phase 2 clinical trials in non-small cell lung cancer and breast cancer. In cooperation with the National Cancer Institute, or NCI, we have concluded five trials and are presently conducting two Phase 1 clinical trials using ADVEXIN gene therapy. We have also completed enrollment in a Phase 1 clinical trial of ADVEXIN gene

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therapy delivered intravenously. Using INGN 241, we are conducting testing in a Phase 1/2 clinical trial.

Develop Our Portfolio of Gene Therapy and Other Drug Products. Utilizing our significant research, clinical, and regulatory expertise, we are pursuing additional gene therapy and other drug products for various cancers. We have established an efficient process for evaluating new drug candidates and rapidly progressing them from pre-clinical to clinical development. We have identified and licensed multiple technologies, which we intend to combine with our adenoviral vector system and which we believe are attractive development targets for the treatment of various cancers.

Expand Our Delivery System Technologies. We believe no single gene delivery system will be applicable to all clinical needs. At present, we have a broad portfolio of delivery technologies under development. We are leveraging our experience gained with our existing adenoviral vector systems to develop next generation vectors for both viral and non-viral delivery systems. Through our strategic collaboration with VirRx, Inc., we are developing replication-competent viral therapies in which viruses bind directly to cancer cells, replicate in those cells, and cause those cancer cells to die. To further augment our portfolio, we will continue to examine new licensing opportunities and develop collaborations in the area of novel delivery and targeting technologies.

Leverage Our Manufacturing Capabilities to Produce Additional Gene Therapy Drug Products. We have developed significant expertise and infrastructure for process development and manufacturing of therapeutic genes and delivery systems. We have built and validated a manufacturing facility that we believe meets CGMP requirements. We believe that this facility is capable of supporting the market launch of ADVEXIN gene therapy and the clinical testing requirements of INGN 241. We have also established a variety of process methodologies, formulation strategies and quality release assays to produce clinical grade materials at commercial scale. We intend to utilize these processing and production capabilities to advance clinical development and commercialization of our pipeline of gene therapy product candidates, as well as capitalize on opportunities to produce other companies products for them.

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 will address this market by building a direct sales force as part of the ADVEXIN gene therapy commercialization process and by pursuing marketing and distribution agreements with corporate partners for ADVEXIN gene therapy as well as additional gene therapy products.

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

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Product Development Programs

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

Product (Gene)	Cancer Indication	Development Status
ADVEXIN® Gene Therapy (p53)	Head and Neck	Phase 3
	Non-Small Cell Lung	Phase 2 completed
	Breast	Phase 2*
	Prostate	Phase 1 completed
	Intravenous Administration	Phase 1 completed
	Ovarian	Phase 1 completed**
	Bladder	Phase 1 completed**
	Brain (glioblastoma)	Phase 1 completed**
	Bronchoalveolar	Phase 1**
	Rheumatoid Arthritis	Pre-clinical
INGN 241 (mda-7)	Various (solid tumors)	Phase 1/2
	Pancreatic	Pre-clinical
	Breast	Pre-clinical
INGN 251 (PTEN)***	Colorectal	Pre-clinical
	Brain (glioblastoma)	Pre-clinical
BAK Program	Various	Research
FUS-1 Program	Various	Research
p16 Program	Pancreatic	Research
Mebendazole	Gastro-intestinal	Research

* Aventis Pharma provides funding for this trial.

** Conducted in conjunction with the National Cancer Institute.

*** Assigned to our subsidiary Gendux AB.

Indications for ADVEXIN® Gene Therapy (p53)

ADVEXIN gene therapy combines the p53 gene with an adenoviral vector for gene delivery. Physicians typically inject ADVEXIN gene therapy directly into the tumor. The importance of the p53 gene in controlling tumor growth suggests that ADVEXIN gene therapy is applicable to multiple cancers. Our initial development strategy for ADVEXIN gene therapy is to obtain approval for cancer indications, such as head and neck and lung cancer, which have few or no treatment options available and have near-term clinical endpoints.

We have conducted a number of Phase 1 and Phase 2 clinical trials to establish the safety and evaluate the efficacy of ADVEXIN gene therapy both alone and in combination with radiation therapy, chemotherapy and/or surgery. We evaluated efficacy by measuring tumors during each trial to analyze whether tumors had regressed, remained stable or progressed during treatment. We supplemented these analyses, where possible, with microscopic tissue analysis, or biopsy, to determine the presence of residual cancer cells within the treated area. We further evaluated efficacy by measuring the survival time of the patients treated in all of these trials.

Head and Neck Cancer

Head and neck cancer, encompassing cancers of the tongue, mouth, vocal cords and tissues surrounding them, has a worldwide incidence of approximately 400,000 new cases per year. In the United States, the annual incidence of squamous cell cancer, a cancer of cells that line the oral cavity, pharynx and larynx, is

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approximately 37,000 with annual deaths of approximately 11,000. 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 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. Once the disease recurs, few patients survive despite secondary treatment with conventional therapies, with median patient survival of less than 12 months. Although often used as a secondary treatment, there are no chemotherapy drugs available today that have been approved by the FDA for treatment of patients with recurrent head and neck cancer.

Because physicians can administer ADVEXIN gene therapy locally, we believe it is a viable candidate for treatment of head and neck cancer. Based on clinical results from our Phase 1 and Phase 2 clinical trials, we are currently enrolling patients in and conducting two multi-national pivotal Phase 3 clinical trials that the FDA has reviewed, and if successful, will be used to support regulatory approval. We intend these trials to demonstrate the efficacy of ADVEXIN gene therapy for treatment of patients with squamous cell carcinoma of the head and neck, regardless of whether the p53 gene is mutant or non-mutated, in whom standard treatment of surgery and radiation therapy have not been effective and who have recurrent or refractory disease. The first trial compares the efficacy of ADVEXIN gene therapy to a standard chemotherapy treatment in patients with refractory disease. The second trial compares the efficacy of ADVEXIN gene 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.

The first Phase 3 clinical trial is planned for 240 patients with refractory disease. Patients in the control group receive weekly methotrexate, a standard chemotherapy treatment for this condition, while patients in the treatment group receive twice weekly injections of ADVEXIN gene therapy. The trial s primary endpoint, or result that we will principally evaluate, is survival. The investigators will measure a possible survival advantage by comparing how long the ADVEXIN gene therapy group patients live relative to how long the control group patients live. The second Phase 3 clinical trial is planned for 288 patients with recurrent head and neck cancer. These patients will not have previously been treated with chemotherapy. The control group will receive a standard chemotherapy treatment with the drugs cisplatin and 5-fluorouracil and the treatment group will receive the same drugs plus ADVEXIN gene therapy. Each treatment will be repeated every three weeks, which is a standard interval for chemotherapy. The primary endpoint will be the duration of tumor growth control in the head and neck region as measured by a patient s tumor growth beyond the patient s baseline, or tumor size at the beginning of the trial. These trials are complementary, with the primary endpoint in each serving as a secondary endpoint, or result that we will evaluate secondarily, in the other. Both are randomized trials, meaning that neither the doctor nor the patient knows whether the patient will be in the control group or the treatment group at the time the patient is enrolled in either trial. An independent data safety monitoring board oversees safety for the trials and conducts a specified interim data analysis for each trial. Both of these Phase 3 clinical trials are being conducted at numerous cancer centers in the United States, Canada and Europe. Both of these trials have been extensively discussed with the FDA.

We conducted a Phase 2 clinical trial of ADVEXIN gene therapy in 112 patients with either recurrent or refractory head and neck cancers at 18 clinical centers in the United States and Europe, using the highest dose of ADVEXIN gene therapy tested in the Phase 1 clinical trial discussed below. This trial did not have a treatment control arm and the main purpose of the trial was to evaluate the safety, side effects and efficacy of ADVEXIN gene therapy administered alone to tumors of various sizes. The primary measure of efficacy was to assess patient response to ADVEXIN gene therapy by periodically measuring the size of all tumors in the patient compared to their size at the start of treatment. A positive response is defined as the disappearance of the tumor, shrinkage of the tumor or the absence of additional tumor growth beyond 25% of pre-treatment measurements, an accepted indicator of tumor growth control.

In order to design pivotal Phase 3 clinical trials and to identify the patient characteristics most amenable to ADVEXIN gene therapy, we conducted a preliminary analysis on the first 88 patients treated and evaluated in our Phase 2 clinical trial. This analysis showed that approximately 25% of the patients that the investigators injected and evaluated had a positive response to treatment. In addition, because a subset of patients had multiple tumors treated, the preliminary analysis also evaluated individual tumor response. The analysis

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showed that 60% of the individual tumors that the investigators injected and evaluated had a positive response. Tumors with non-mutated p53 genes and those with mutant p53 genes both responded to ADVEXIN gene therapy. The patients in this Phase 2 clinical trial tolerated ADVEXIN gene therapy well, 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.

This preliminary analysis also provided important data with regard to the effect of ADVEXIN gene therapy on the median survival time of the patients. The data showed a median patient survival time from the start of treatment of 7.5 months for a subset of patients with refractory disease and tumors below a specified size. Patients with these characteristics comprise the population for our first Phase 3 clinical trial. Based on an historical expected survival time that our clinical advisors estimate to be four months, this median survival time of 7.5 months suggests an 88% increase in survival time for these patients.

Previously, ADVEXIN gene therapy was tested in a Phase 1 safety clinical trial with patients with recurrent 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 gene 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 gene 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, but only a minority of patients are eligible because early-stage diagnosis is uncommon. Only approximately 30% of these patients will have a complete surgical resection of their disease. The remaining patients typically undergo a combination of surgery, radiation and chemotherapy. This combination treatment is only effective in a small percentage of cases. 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. The opportunity for a new beneficial treatment is great, 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 gene 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 gene 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 gene therapy with radiation was tolerated. Objectives of this trial were to determine if the addition of ADVEXIN gene therapy injected directly into the tumor 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. An evaluation was performed three months after treatment was completed, consisting of a radiograph to assess the size of the treated tumor mass, supplemented by a biopsy 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.

We conducted an analysis of 19 patients that the investigators treated and evaluated in the Phase 2 clinical trial of ADVEXIN gene therapy. This analysis included both the radiographs and the tumor biopsies that we refer to above. The results of this analysis established an acceptable safety profile and showed evidence of local tumor control and reductions in tumor size. Fifteen of the 19 patients that the investigators treated, or 79%, had radiographic evidence of local tumor growth control, including twelve complete or partial responses

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of the tumor that the investigators injected. Furthermore, the preliminary analysis showed that nine of these twelve patients had no living tumor cells in the biopsy that the investigator took from the site of the gene therapy injection. Based on the preliminary results of this Phase 2 clinical trial using gene therapy with radiation therapy, a larger trial is being designed to evaluate whether ADVEXIN gene therapy enhances the effectiveness of radiation therapy and chemotherapy when investigators use them together to treat NSC lung cancer.

We conducted a Phase 1 safety clinical trial of ADVEXIN gene 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 gene therapy injected into a single tumor site. In the other arm, 24 patients received ADVEXIN gene therapy in combination with cisplatin, a commonly used chemotherapeutic agent. The patients in this trial tolerated the ADVEXIN gene therapy well, and the most severe side effects noted were consistent with those experienced with the use of cisplatin alone. Also, the National Cancer Institute (NCI) is initiating a Phase 1 safety clinical trial using ADVEXIN gene therapy in combination with radiation therapy in patients with NSC lung cancer.

Breast Cancer

Physicians diagnose an estimated 213,000 new cases of breast cancer annually in the United States, and approximately 40,000 of these people are estimated to die from the disease each year. We are conducting, and Aventis Pharma SA, or Aventis, is funding, a Phase 2 clinical trial using ADVEXIN gene therapy administered alone and in combination with chemotherapy in women who have locally advanced breast cancers. Also, the NCI has concluded a Phase 1 clinical trial using ADVEXIN gene 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 gene therapy.

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

Other Cancers

There are several other cancer indications for which ADVEXIN gene therapy is in earlier stages of clinical development. To evaluate the possible use of ADVEXIN gene therapy in these indications, we have entered into a Cooperative Research and Development Agreement, or CRADA, with the NCI. Under this program the NCI has conducted certain clinical trials and is conducting other clinical trials with ADVEXIN gene therapy at leading cancer centers using clinical protocols that we have developed in connection with the NCI. These protocols are designed to demonstrate the safety of ADVEXIN gene 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. In approximately 80% of patients with advanced disease, the cancer remains localized within the peritoneal, or abdominal, cavity. This allows ready access to cancer cells for simple intraperitoneal administration, that is, administration into the abdominal cavity of gene therapeutic agents. The NCI has conducted a Phase 1 clinical trial of ADVEXIN gene therapy in this population.

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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 uniform delivery of high concentrations of gene therapeutic agents via catheter. The NCI has conducted a Phase 1 clinical trial using ADVEXIN gene 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 that afflicts children as well as adults. This condition occurs in approximately 30% of all brain cancer patients in the United States. GBM is not effectively treated with conventional therapies because the lesions are deep within the brain and are large and grow rapidly. The NCI has conducted a Phase 1 clinical trial using ADVEXIN gene therapy in recurrent GBM.

Bronchoalveolar Cancer. It is estimated that physicians diagnose an estimated 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 spreads throughout 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 gene therapy administered by directly bathing the airway leading to the diseased lung segments.

Indications for INGN-241 (mda-7)

The mda-7 gene is a promising tumor suppressor gene that we believe, like p53, has broad potential to induce apoptosis in many types of cancer. We have combined the mda-7 gene with our adenoviral vector system to form INGN 241. Our pre-clinical trials have determined that INGN 241 suppresses growth of many cancer cells, including those of the breast, lung, colon, prostate and 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.

Our pre-clinical trials also indicate that in addition to its known activity as a tumor suppressor gene, the mda-7 gene may also stimulate the body s immune system to protect it against cancer, thereby offering the potential of providing an added advantage in treating various cancers because it may attack cancer using two different mechanisms. The mda-7 gene may work effectively as a radiation sensitizer to make several types of human cancer cells more susceptible to the anti-cancer effect of radiation therapy as indicated 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, or programmed cell death, in combination with anti-angiogenesis.

We have an exclusive license to the mda-7 gene for gene therapy applications from Corixa Corporation. We are currently conducting a Phase 1 clinical trial using INGN 241 testing safety and mechanism of action in approximately 15 patients with solid tumors. 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.

Research and Development Programs

In addition to our clinical programs underway with ADVEXIN gene therapy and INGN 241, 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.

We have combined the PTEN tumor suppressor gene with our adenoviral vector system to form INGN 251. Researchers have linked mutations in the PTEN tumor suppressor gene to a variety of common human cancers, including brain, prostate and breast cancers. Preliminary trials have demonstrated that

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INGN 251 can inhibit the growth of colorectal, prostate and brain cancer cells and promote apoptosis in many of these cells. Our pre-clinical program with INGN 251 has included trials with Imperial Cancer Research Technology Limited in London, or ICRT. We obtained an exclusive license to the PTEN gene from ICRT, which we have assigned to our subsidiary Gendux AB.

In addition to our pre-clinical programs, we are conducting research on additional genes, including BAK and p16, 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. This family of genes includes the FUS-1 gene. 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. We are working with M. D. Anderson Cancer Center to further evaluate FUS-1 and other 3p21.3 genes as clinically relevant therapeutics.

As a supplement to our gene 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 mebendezole 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 The University of Texas M. D. Anderson Cancer Center to further evaluate this molecule as a cancer treatment.

Introgen Enabling Technologies

We have a portfolio of technologies, referred to as enabling technologies, for administering gene therapy products to patients and for enhancing the effects of these products, which we plan to exploit to develop additional gene therapy 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 gene 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 is 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.

Viral Gene Expression Modulation System. We are developing this technology to block production of viral proteins in the patient to reduce immune response to the vector, thus prolonging the activity of the disease treatment gene.

Expanded Payload Systems. We are developing these technologies to allow the removal of very large pieces of the genome in order to increase the amount of genetic material that can be carried to the cell, allowing multiple genes to be incorporated into a single vector. Also, since many viral genes are deleted, we expect that the immune response against these vectors will be reduced.

Replication-Competent Systems. Through our strategic collaboration with VirRx, Inc., we are developing replication-competent viral therapies in which viruses bind directly to cancer cells, replicate in those cells,

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and cause those cancer cells to die. 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. Although we are not currently using non-viral vector technology in our clinical programs, we have completed proof-of-concept trials in animal models that suggest that this system may be a useful way to deliver tumor suppressor genes for systemic cancer treatment.

Additional Enabling Technologies

We are also developing a number of additional technologies that expand our capabilities.

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 cells during production. This will facilitate production of the gene therapeutic at higher volumes.

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.

Selective Inhibition of Gene Expression. This technology is designed to block the dysfunctional activity or expression of certain genes, like cancer-promoting oncogenes.

Gene Screen Vector System. This technology is designed to aid in the rapid screening of genes for therapeutic potential. This system should allow us to quickly evaluate genes of unknown function for their potential as cancer treatments.

Manufacturing and Process Development

Commercialization of a gene therapy 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 quality release assays that ensure product quality.

We own and operate a state-of-the-art, validated manufacturing facility that we believe complies with the FDA s CGMP requirements. We produce ADVEXIN gene 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 gene therapy. To date, we have produced over 20 batches of ADVEXIN gene 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 clinical trials.

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Business and Collaborative Arrangements

VirRx, Inc.

We are working with VirRx, Inc. (VirRx) to investigate other vector technologies 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 $525,000 of this stock for cash during 2002, 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 at any time after March 7, 2003, which would also terminate the requirement for us to make any additional stock purchases. Provided the collaboration and license agreement remains in place, we will 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 will 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 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.

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 gene therapy products. 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.

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 gene therapy products. Aventis licensed or transferred to us all of its patents covering the manufacture, sale, offering for sale, importation or use of ADVEXIN gene therapy and other K-ras patents, delivery patents and targeting technologies, as well as all trademarks and goodwill associated with ADVEXIN gene therapy. Aventis also agreed, for a period of seven years, not to conduct any activities directed to the development or commercialization of any gene therapy 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 gene 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.

Separate from the collaboration agreement discussed above, we and Aventis have a sponsored research agreement, pursuant to which we conduct and Aventis funds a Phase 2 clinical trial in breast cancer.

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Gendux, Inc. and Gendux AB

We established our wholly-owned subsidiary, Gendux, Inc., and its wholly-owned subsidiary Gendux AB, which is based in Stockholm, Sweden, in order to create a European presence with which to extend our technology and product development opportunities and enhance our interactions with European academic and commercial institutions. We have assigned to Gendux AB certain rights in the PTEN technologies, as well as a non-exclusive license to use our vector technology in commercializing gene therapy products.

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.

The University of Texas M. D. Anderson Cancer Center

Many of our core technologies were developed by scientists at 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 M. D. Anderson Cancer Center in 1994. It terminates on July 20, 2009. 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 one of the largest corporate sponsors 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 entered into 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 gene therapy against a range of designated cancers, including breast cancer, ovarian cancer, bladder cancer and brain cancer. To date, NCI has conducted five Phase 1 clinical trials and is currently conducting two Phase 1 clinical trials. NCI provided most of the funding for these activities. We supplied NCI with ADVEXIN gene 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 entered into a research and license agreement with Corixa Corporation pursuant to which we acquired an exclusive, worldwide license to the mda-7 gene for gene therapy applications. The agreement is effective until the expiration 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

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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.

Imperial Cancer Research Technology Limited

We have a license agreement with Imperial Cancer Research Technology Limited, or ICRT, for the PTEN gene. We have assigned this license to Gendux AB, our subsidiary in Stockholm, Sweden. ICRT is the technology and licensing unit of the Imperial Cancer Research Fund, which conducts over one-third of all cancer research in the United Kingdom. This agreement is terminable upon either party s breach or insolvency, or by ICRT upon our failure to make required payments.

Marketing and Sales

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 gene therapy commercialization process and by pursuing marketing and distribution arrangements with corporate partners for ADVEXIN gene therapy as well as additional gene therapy products.

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. In addition to our intellectual property license with Aventis, 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, the Imperial Cancer Research Fund 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 protecting 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. 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 appear to express a normal p53 protein.

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Combination Therapy with the p53 Gene

We have also focused our portfolio development on protecting 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 gene therapy products, including that of ADVEXIN gene 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 therapy compositions having a high level of purity, as well as to storage-stable formulations. These applications include procedures for preparing commercial quantities of recombinant adenoviruses for gene therapy and include procedures applicable to the p53 gene, as well as any of the other of our potential gene therapy 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 therapy applications.

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, PTEN, 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 gene therapy vectors for use in gene therapy protocols, gene therapy 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. 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 therapy 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

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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 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 production and marketing of our proposed products and our research and development activities are subject to regulation for safety, effectiveness and quality by numerous governmental authorities in the United States and other countries. In the United States, drugs and research personnel are subject to rigorous FDA and National Institutes of Health, or NIH, regulations. The Federal Food, Drug and Cosmetic Act (the FDC Act), as amended, the regulations promulgated under the FDC Act, and other federal and state statutes and regulations govern, among other things, the testing, manufacture, safety, effectiveness, labeling, storage, record keeping, advertising and promotion of our products. Product development and approval within this regulatory framework takes a number of years and involves the expenditure of substantial resources.

The FDA recently 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 trials. We are not developing products using the process used in those clinical trials, and we do not use retroviral vectors in our ongoing 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 us from this event. Our pharmacovigilance department monitors every patient in our clinical trials for safety and reports all side effects to the FDA and the National Institutes of Health according to applicable regulations. We have witnessed no adverse effects in our clinical trials that even remotely resemble what occurred in the X-SCID trial. Due to the fundamental differences between retrovirus vectors and the adenovirus vector employed in ADVEXIN gene therapy, we believe the likelihood of our encountering an event such as that experienced in the X-SCID trial is remote.

The Drug Approval Process

The steps required before our proposed products may be marketed in the United States include pre-clinical testing, the submission to the FDA of an investigational new drug, or IND, application for clinical trials, clinical trials to establish the safety and effectiveness of the drug, the submission to the FDA of a BLA (for a biologic) or an NDA (for a drug) and the FDA approval of the BLA or NDA prior to any commercial sale of the drug. Our products will be regulated as biologics. In addition to obtaining FDA approval for each product, each domestic manufacturing establishment must be registered with, and approved by, the FDA. Domestic manufacturing establishments are subject to biennial inspections by the FDA and must comply with CGMP requirements. To supply products for use in the United States, foreign manufacturing establishments, including third party facilities, must comply with CGMP requirements and are subject to periodic inspection

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by the FDA or by corresponding regulatory agencies in such countries under reciprocal agreements with the FDA.

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 IND 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, 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 results of the 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. Phase 2 involves clinical trials in a limited patient population to determine the effectiveness of the drug for specific, targeted indications, determine dosage tolerance and optional dosage and identify possible adverse effects and safety risks. When a compound is found to be effective and to have an acceptable safety profile in Phase 2 evaluations, Phase 3 clinical trials are undertaken to further evaluate clinical effectiveness and to further test for safety within an expanded patient population at geographically dispersed clinical trial sites. Phase 3 clinical trials conducted to seek marketing approval by the FDA are called pivotal trials.

National Institutes of Health

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

Following routine procedure, we report to the FDA and the NIH serious adverse events, whether treatment-related or not, that occur in our clinical trials, including deaths. Often, gene therapy clinical trials 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 clinical trials.

Marketing Applications

After the completion of all three clinical trial phases, if the 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

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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.

Orphan Drug Act

We have received orphan drug designation for ADVEXIN gene 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 will 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*

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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.

FDAMA

The Food and Drug Administration Modernization Act of 1997, or FDAMA, was enacted, in part, to ensure the timely availability of safe and effective drugs, biologics and medical devices, by expediting the FDA review process for new products. FDAMA established a statutory program for the approval of fast track products. The fast track provisions essentially codify FDA s Accelerated Approval regulations for drugs and biologics. A fast track product is defined as a new drug or biologic intended for the treatment of a serious or life-threatening condition that demonstrates the potential to address unmet medical needs for such a condition. Under the new fast track program, the sponsor of a new drug or biologic may request the FDA to designate the drug or biologic as a fast track product at any time during the clinical development of the product. FDAMA specifies that the FDA must determine if the product qualifies for fast track designation within 60 days of receipt of the sponsor s request. Approval of an NDA for a fast track product can be based on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit. Approval of a fast track product may be subject to (1) post-approval trials to validate the surrogate endpoint or confirm the effect on the clinical endpoint and (2) prior review of copies of all promotional material. If a preliminary review of the clinical data suggests efficacy, the FDA may initiate review of sections of an application for a fast track product before the application is complete. This rolling review is available if the applicant provides a schedule for submission of remaining information and pays applicable user fees.

We may seek fast track designation to secure expedited review of 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., Genvec, Inc., Vical Incorporated and Onyx Pharmaceuticals, Inc., which are pursuing other forms of treatment for the diseases ADVEXIN gene therapy and our other product candidates target. 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,

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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 14, 2003, we had approximately 50 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 the pharmaceutical and biotechnology industries.

In addition to our full-time staff, we provide financial support through sponsored research agreements for numerous research scientists and technicians at M. D. Anderson Cancer Center and other institutions who serve as investigators for us on clinical and pre-clinical research projects. We have also entered into part-time consulting arrangements with several M. D. Anderson Cancer Center scientists and clinicians.

Our sponsored research projects with M. D. Anderson Cancer Center involve investigators in a wide range of specialties, including thoracic and cardiovascular surgery, neurology, gynecology, urology and gastrointestinal medicine. The human resources devoted to development of our technology and products are further augmented by our collaborators at the numerous other institutions where sponsored research work is performed.

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 gene therapy to the treatment of cancer. He is the primary inventor of the technology upon which our gene therapy products are based. 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 the President of the American Association for Cancer Research. Dr. Von Hoff is certified in medical oncology by the American Board of Internal Medicine.

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 gene 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 at least the next four years.

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 Factors Affecting Future Operating Results will have a material effect on our business. You can read the discussion of our opposition of the patents under Factors Affecting Future Operating Results.

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 traded 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 closing prices reported on the Nasdaq National Market.

	High	Low
Fiscal Year Ended December 31, 2001:		
First Fiscal Quarter	$8.25	$3.31
Second Fiscal Quarter	7.80	3.20
Third Fiscal Quarter	5.50	2.61
Fourth Fiscal Quarter	6.74	3.24
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

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At December 31, 2002, there were 21,487,116 shares of our common stock issued and outstanding held by 166 stockholders of record. We estimate we have approximately 3,719 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

Our selected consolidated financial data presented below is derived from the consolidated financial statements of Introgen Therapeutics, Inc. and our subsidiaries, which appear in Part IV of this Report. Those consolidated financial statements were derived from the audited consolidated financial statements included in this report and in reports we have previously filed with the SEC, except for the six months ended December 31, 2000 and the year ended December 31, 2001, both which are unaudited. 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,	
	1998	1999	2000	2001	2000	2001	2001	2002
					(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
Collaborative research and development revenues from affiliate	$ 8,606	$ 6,714	$ 6,204	$ 3,016	$ 3,016	$	$	$
Product sales to affiliate	2,505	1,475	2,087	1,500	1,500			
Cost of product sales	1,729	994	1,476	2,488	2,488			
Gross margin on product sales	776	481	611	(988)	(988)			
Other revenue			97	684	391	298	591	1,173
Operating costs and expenses:								
Research and development	10,361	7,539	10,075	15,014	5,153	10,063	19,923	21,512
General and administrative	1,825	2,977	4,701	4,875	2,040	3,526	6,361	6,722
Total operating costs and expenses	12,186	10,516	14,776	19,889	7,193	13,589	26,284	28,234
Loss from operations	(2,804)	(3,321)	(7,864)	(17,177)	(4,774)	(13,291)	(25,693)	(27,061)
Interest income (expense), net	789	675	140	381	403	445	423	(207)
Other income				354		518	871	1,139
Net loss	$ (2,015)	$ (2,646)	$ (7,724)	$ (16,442)	$ (4,371)	$ (12,328)	$ (24,399)	$ (26,129)
Net loss per share, basic and diluted	$ (0.51)	$ (0.66)	$ (1.89)	$ (1.02)	$ (0.39)	$ (0.58)	$ (1.14)	$ (1.22)
Shares used in computing basic and diluted net loss per share	3,923	4,006	4,096	16,163	11,121	21,440	21,440	21,471

	June 30,	December 31,

	1998	1999	2000	2001	2001	2002
			(In thousands)			
Balance Sheet Data:						
Cash, cash equivalents, and short-term investments	$16,848	$ 15,761	$ 11,765	$ 34,977	$ 48,825	$ 23,467
Working capital	15,944	14,226	10,263	54,296	43,175	18,852
Total assets	17,766	25,741	24,855	72,347	60,424	33,316
Long-term debt obligations, net of current portion		3,388	8,021	9,798	9,037	7,435
Accumulated deficit	(8,375)	(11,021)	(18,744)	(35,186)	(47,515)	(73,643)
Stockholders equity	16,322	19,187	13,592	56,069	44,566	19,835

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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 Factors Affecting Future Operating Results. 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 Factors Affecting Future Operating Results.

Overview

We are a leading developer of gene therapy products for the treatment of cancer and other diseases. Our lead product candidate, ADVEXIN® gene therapy, combines the p53 gene, one of the most potent members of a group of naturally occurring tumor suppressor genes, which act to protect cells from becoming cancerous, with an adenoviral gene delivery system that we have developed and extensively tested. We are conducting pivotal Phase 3 clinical trials of ADVEXIN gene therapy in head and neck cancer. We have completed a Phase 2 clinical trial of ADVEXIN gene therapy in non-small cell lung cancer and are conducting a Phase 2 clinical trial of ADVEXIN gene therapy in breast cancer. We are conducting Phase 1 clinical trials, or safety trials, of ADVEXIN gene therapy in other types of cancer. We hold the worldwide rights for pre-clinical and clinical development, manufacturing, marketing and commercialization of ADVEXIN gene therapy.

ADVEXIN gene therapy is designated by the FDA as an orphan drug under the Orphan Drug Act, which gives us seven years of marketing exclusivity for ADVEXIN gene therapy if approved by the FDA. We are developing additional cancer gene therapy product candidates, including those based on the mda-7 and PTEN genes, as well as associated vector technologies for delivering the gene-based products into target cells. Our INGN 241 product candidate, which combines the mda-7 gene with our proprietary gene delivery system, is undergoing safety testing in a Phase 1 clinical trial.

We are investigating other vector technologies for delivering gene-based products into targeted cells, specifically those involving replication-competent viral therapies in which viruses bind directly to cancer cells, replicate in those cells, and cause those cancer cells to die. As a supplement to our gene therapy product programs, we are evaluating the development of mebendazole, our first small molecule candidate. Pre-clinical trials suggest that mebendazole may also be an effective treatment of cancer.

We own and operate a manufacturing facility that we believe complies with the FDA s current Good Manufacturing Practices requirements, commonly known as CGMP requirements. We have produced ADVEXIN gene therapy in this facility for use in our Phase 1, 2 and 3 clinical trials and INGN 241 for use in our Phase 1 clinical trials. We have also produced in a separate facility INGN 241 for use in our Phase 1 clinical trials.

Since our inception in 1993, we have used our resources primarily to conduct research and development activities, primarily for ADVEXIN gene therapy and, to a lesser extent, for other product candidates. At December 31, 2002, we had an accumulated deficit of approximately $73.6 million. It is possible we will incur losses in the future that will be greater than cumulative losses incurred in prior years. At December 31, 2002, we had cash and cash equivalents of $23.5 million. During the year ended December 31, 2002, we used $23.6 million of cash for operating activities. It is possible this cash usage rate could increase in future periods as we continue our ADVEXIN gene therapy Phase 3 clinical trials and expand our research and development of various other gene therapy technologies. We reduced our workforce by approximately one third in February 2003 to lower our cash usage rate. We believe our existing working capital can fund our operations for the next fifteen to eighteen months. Since our inception, our only significant revenues have been payments from Aventis under collaborative research and development agreements for our early-stage development work on ADVEXIN gene therapy and Aventis purchases of ADVEXIN gene therapy product we manufactured for its use in later-stage clinical trials it previously performed. We have also earned interest income on cash placed in short-term investments. We may need to raise additional funds through public or private equity offerings, debt

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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.

Collaborative Relationship With Aventis

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 gene therapy products. 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.

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 gene therapy products. Aventis licensed or transferred to us all of its patents covering the manufacture, sale, offering for sale, importation or use of ADVEXIN gene therapy and other K-ras patents, delivery patents and targeting technologies, as well as all trademarks and goodwill associated with ADVEXIN gene therapy. Aventis also agreed, for a period of seven years, not to conduct any activities directed to the development or commercialization of any gene therapy products using the p53 or K-ras genes.

Under the prior collaboration agreements, we generally received quarterly payments from Aventis for early-stage development activities in advance. We recorded these payments as revenue as we performed the collaboration work and incurred the related expenses. We recorded as deferred revenue collaborative research and development payments that we received but for which the related expenses had not yet been incurred. Under the restructured collaboration, Aventis no longer funds any of our research and development.

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 gene 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. We recorded revenue from ADVEXIN gene therapy product sales to Aventis upon completion of production and delivery and Aventis acceptance of the product. Under the restructured collaboration, we no longer receive research funding from or sell ADVEXIN gene therapy to Aventis.

Separate from the collaboration agreement discussed above, we and Aventis have a sponsored research agreement, pursuant to which we conduct and Aventis funds a Phase 2 clinical trial in breast cancer.

Critical Accounting Policies

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

Short-Term Investments. Short-term investments consisted of investments in short-term, investment-grade securities, which consist primarily of federal and state government obligations, commercial paper and/or corporate bonds with various maturity dates not exceeding one year. All short-term investments have been 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

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based on the fair market value of the investments at the date of sale. Additionally, 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 pivotal Phase 3 clinical trials of ADVEXIN gene therapy, 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 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.

Recent Accounting Pronouncements

In June 2002 the FASB issued SFAS No. 146, Accounting for Costs Associated with Exit or Disposal Activities. SFAS No. 146 requires companies to recognize costs associated with exit or disposal activities when they are incurred rather than at the date of commitment to an exit or disposal plan. This statement is effective for exit or disposal activities initiated after December 31, 2002. The Company does not believe that the adoption of SFAS No. 146 will have a material impact on its financial statements.

In December 2002, the FASB issued SFAS No. 148, Accounting for Stock-Based Compensation Transition and Disclosure, an Amendment of FASB Statement No. 123. This Statement amends FASB Statement No. 123, Accounting for Stock-Based Compensation, to provide alternative methods of transition for an entity that voluntarily changes to the fair value based method of accounting for stock-based employee compensation. It also amends the disclosure provisions of that Statement to require prominent disclosure about the effects on reported net income of an entity s accounting policy decisions with respect to stock-based employee compensation. Finally, this Statement amends APB Opinion No. 28, Interim Financial Reporting, to require disclosure about those effects in interim financial information. Since the Company is continuing to account for stock-based compensation according to APB 25, adoption of SFAS No. 148 requires the Company to provide prominent disclosures about the affects of FAS 123 on reported income (loss) and will require the Company to disclose these affects in the interim financial statements as well.

Results of Operations

Comparison of Years Ended December 31, 2002 and 2001

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 gene therapy in breast cancer.

Costs and Expenses

Research and Development. Research and development expenses, excluding amortization of deferred stock compensation of $399,000 in 2002 and $462,000 in 2001, were $21.1 million in 2002 and $19.5 million in 2001. This 8% increase 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 gene 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.

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General and Administrative. General and administrative expenses, excluding amortization of deferred stock compensation of $978,000 in 2002 and $1.2 million in 2001, were $5.7 million in 2002 and $5.2 million in 2001. This 10% increase in 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 gene 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. For options currently outstanding, we expect to record amortization expense for deferred compensation of $965,000 during 2003 and $11,000 during 2004, after which time deferred compensation for options currently outstanding becomes fully amortized. The amount of deferred compensation expense to be recorded in future periods may decrease if unvested options for which deferred compensation has been recorded are subsequently forfeited or may increase if additional options are issued at prices below the deemed fair value of the common stock.

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

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 gene therapy. We do not expect to generate revenues from the commercial sale of products in the foreseeable future, and we may never generate revenues from the sale of products.

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

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Research and Development. Research and development expenses, excluding 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, were $9.8 million for the six-month period ended December 31, 2001, and $4.9 million for the six-month period ended December 31, 2000. The 100% increase 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 gene therapy under the terms of the restructuring of our collaboration with Aventis.

General and Administrative. General and administrative expenses, excluding 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, were $3.0 million in 2001 and $1.5 million in 2000. The 100% increase 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 gene 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.

Comparison of Fiscal Years Ended June 30, 2001 and 2000

Revenues

Revenue from Collaborations. Collaborative research and development revenues from Aventis were $3.0 million in 2001 and $6.2 million in 2000. This 51% decrease was primarily due to the restructuring of our collaboration with Aventis, which resulted in our not receiving payments from Aventis for early-stage research and development related to p53-based gene therapy products subsequent to December 31, 2000. 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 $1.5 million in 2001 and $2.1 in 2000. This 31% decrease occurred because there were no product sales subsequent to December 31, 2000, due to the restructuring of our collaboration with Aventis. The restructuring eliminated our need to sell product to Aventis since we are using the product internally for the future development of ADVEXIN gene therapy.

Other Revenue. Other revenue was $684,000 in 2001 and $97,000 in 2000. This increase was due to funding received under research grants from U.S. Government agencies and contract manufacturing work for third parties.

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Costs and Expenses

Cost of Product Sales. Cost of product sales was $2.5 million in 2001 and $1.5 million in 2000. This 67% increase was due to a reduction in the number of batches of clinical material in production during the quarter ended December 31, 2000, which resulted in an increase in the amount of the costs of our manufacturing operations that were expensed as incurred instead of capitalized as part of inventory. This situation did not continue subsequent to December 31, 2000, due to the restructuring of the Aventis collaboration that ended sales of clinical materials to Aventis, thereby eliminating our cost of product sales.

Research and Development. Research and development expenses, excluding amortization of deferred stock compensation of $442,000 in 2001 and zero in 2000, were $14.6 million in 2001 and $10.1 million in 2000. This 45% increase was primarily due to (1) increased activity related to the development of INGN 241 and (2) expenses associated with the restructuring of the Aventis collaboration, including (a) $826,000 related to the write-off of accounts receivable, inventory and deferred revenue, (b) $2.2 million related to the assumption of responsibility for Phase 2 and 3 clinical trials for ADVEXIN gene therapy and (c) no costs being capitalized as inventory subsequent to December 31, 2000, as a result of the Aventis collaboration restructuring, which eliminated future inventory sales to Aventis. These increases were offset by a decreased level of early-stage research and development performed by us prior to the restructuring of the Aventis agreement relative to products based on the p53 gene, as such products had evolved into later-stage development, which Aventis performed at that time prior to restructuring of that collaboration.

General and Administrative. General and administrative expenses, excluding amortization of deferred stock compensation of $1.1 million in 2001 and $2.1 million in 2000, were $3.8 million in 2001 and $2.6 million in 2000. This 42% increase 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 costs associated with the Aventis collaboration restructuring.

Amortization of Deferred Compensation. Amortization of deferred stock compensation was $1.6 million in 2001 and $2.1 million in 2000. This 23% decrease was due primarily to 2000 including a one-time compensation charge related to the accelerated vesting of options held by a member of our Board of Directors concurrent with the individual s resignation from our Board of Directors.

Interest Income and Interest Expense. Interest income was $1.2 million in 2001 and $722,000 in 2000. This 70% 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 $849,000 in 2001 and $582,000 in 2000. This 46% increase was primarily due to balances under notes payable to finance our new facilities and equipment being outstanding for all of 2001 as compared to being outstanding for only a portion of 2000.

Other Income. Other income was $354,000 in 2001 and zero in 2000. This increase was due to 2001 being the first year in which we earned rental income related to our sublease to M. D. Anderson Cancer Center of research laboratories in our facilities.

Liquidity and Capital Resources

We have incurred annual operating losses since our inception, and at December 31, 2002, we had an accumulated deficit of $73.6 million. Since inception through December 31, 2002, we have financed our operations primarily 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, $14.6 million of private equity sales, net of offering costs, to others, $7.5 million of sales of ADVEXIN gene therapy product to Aventis for use in later-stage clinical trials, $9.2 million in mortgage financing from banks for our facilities, $4.3 million in leases from commercial leasing companies to acquire equipment pledged as collateral for those leases and $5.7 million from interest income earned on cash and short- and long-term investments.

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

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operations. For at least the next two years, we expect to focus our activities primarily on conducting Phase 3 clinical trials, conducting data analysis, preparing regulatory documentation including FDA submissions and conducting pre-marketing activities for ADVEXIN gene therapy. We also expect to continue our research and development of various other gene therapy technologies. The majority of our expenditures over this two-year period will most likely relate to the clinical trials of ADVEXIN gene 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 the year ended December 31, 2002. We believe our existing working capital can fund our operations for the next fifteen to eighteen months, although unforeseen events could shorten that time period. We are taking measures to reduce the amount of cash used in our operating activities. Our existing resources may not be sufficient to support the commercial introduction of any of our product candidates. We may 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 $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 gene 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 increased 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 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. 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, cash equivalents and short-term investments available to fund operating activities.

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

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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.

We have an ongoing agreement that began in 2002 with VirRx, Inc. to purchase shares of VirRx s Series A Preferred Stock. We purchased $525,000 of this stock for cash during 2002. 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 VirRx and us for the development of VirRx s technologies. We may unilaterally terminate this collaboration and license agreement with 90 days prior notice after March 7, 2003, which would also terminate our requirement to make any additional stock purchases. Provided the collaboration and license agreement remains in place, we will 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 will 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:	
2003	$ 2,173
2004	1,395
2005	1,268
2006	842
2007	537
Thereafter	9,133
Total debt service and lease payments	15,348
Less portion representing interest	(6,326)
Total principal balance at December 31, 2002	$ 9,022
Principal balance presented on the December 31, 2002 balance sheet as liabilities in these categories:	
Current portion of obligations under capital leases and notes payable	$ 1,587
Capital lease obligations, net of current portion	125
Notes payable, net of current portion	7,310
Total principal balance at December 31, 2002	$ 9,022

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 2002 with significantly smaller rent payments that we also account for

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as operating leases. Future annual rental payments due under all operating leases are as follows (in thousands):

Year ending December 31,	
2003	$ 279
2004	281
2005	202
2006	144
2007	144
Thereafter	2,707
Total minimum lease payments under operating leases	$3,757

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 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.

We pay consulting fees of approximately $175,000 per annum to a company that is owned by the Chairman of our Board of Directors and that formerly employed one of our directors. 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 an individual primarily responsible for the creation of the technology upon which ADVEXIN gene therapy is based, who is also a stockholder of ours. This agreement provides for payments of approximately $182,000 per annum until September 30, 2003, and $200,000 per annum thereafter 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. Had we terminated this agreement as of December 31, 2002, we would have been obligated to make final payments to this individual totaling $186,000.

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

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 gene therapy. The smaller increase in accounts receivable and the absence of the decrease in inventory was due to the elimination of sales of ADVEXIN gene 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.

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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.

Comparison of Fiscal Years Ended June 30, 2001 and 2000

At June 30, 2001, we had cash and short-term investments of approximately $35.0 million, compared with $11.8 million at June 30, 2000. Net cash used by operating activities was $8.8 million and $5.5 million for the years ended June 30, 2001 and 2000, respectively. This increase in cash used by operating activities was primarily due to a higher net loss from operations and a decrease in deferred revenue, offset partially by an increase in accrued liabilities. Deferred revenue decreased as a result of no longer receiving collaborative research revenue from Aventis as a result of the restructuring of our collaboration agreement with them. The increase in accrued liabilities arose from our assumption of responsibility for the Phase 3 clinical trials for ADVEXIN gene therapy under that collaboration restructuring.

Net cash provided by investing activities was $14.4 million for the year ended June 30, 2001, and $2.6 million for the year ended June 30, 2000. This change is primarily due to a higher level of purchases of short-term investments due to the availability of funds from our initial public offering in October 2000.

Net cash provided by financing activities was $35.6 million and $2.6 million for the years ended June 30, 2001 and 2000, respectively. This was primarily due to the receipt of proceeds from our initial public offering of common stock in October 2000 offset by a decline in the amount of new notes payable and capital lease borrowings since our new facilities and related equipment were complete, outfitted and initially financed in 2000. At June 30, 2001, we had $9.1 million outstanding under notes payable for our facilities and $2.1 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, 2001 and 2002. 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, 2001	June 30, 2001	Sept. 30, 2001	Dec. 31, 2001	March 31, 2002	June 30, 2002	Sept. 30, 2002	Dec. 31, 2002
	(Unaudited) In thousands, except per share amounts							
Statement of Operations Data:								
Contract services, grant and other revenue	24	269	15	283	229	322	453	170
Operating expenses:								
Research and development	3,784	6,077	5,045	5,018	6,699	5,805	4,633	4,375
General and administrative	1,204	1,631	1,685	1,841	1,755	1,679	1,729	1,559
Loss from operations	(4,964)	(7,439)	(6,715)	(6,576)	(8,225)	(7,162)	(5,909)	(5,764)
Interest income (expense), net	(116)	95	375	70	(28)	(38)	(45)	(96)
Other income	162	191	237	281	316	333	261	229
Net loss	$ (4,918)	$ (7,153)	$ (6,103)	$ (6,225)	$ (7,937)	$ (6,867)	$ (5,693)	$ (5,631)
Basic and diluted net Loss per share	$ (0.23)	$ (0.34)	$ (0.28)	$ (0.29)	$ (0.37)	$ (0.32)	$ (0.27)	$ (0.26)
Shares used in computing basic and diluted net loss per share	21,268	21,335	21,435	21,445	21,450	21,463	21,465	21,471

Pre-Approval of Non-Audit Services

Pursuant to Section 10A(i)(2) of the Securities Exchange Act of 1934, as added by Section 202 of the Sarbanes-Oxley Act of 2002, we are responsible for disclosing the approval of non-audit services approved by the Audit Committee of our Board of Directors to be performed by Ernst & Young LLP, our independent auditors. Non-audit services are defined as services other than those provided in connection with an audit or a review of our financial statements. Except as set forth below, the services approved by the Audit Committee are each considered by the Audit Committee to be audit-related services that are closely related to the financial audit process. Each of the audit-related services was pre-approved by the Audit Committee.

The Audit Committee has also pre-approved additional engagements of Ernst & Young LLP for the non-audit services of preparation of state and federal tax returns.

Factors Affecting Future Operating Results

We may encounter delays or difficulties in clinical trials for our product candidates, which may delay or preclude regulatory approval of some or all of our product candidates.

In order to commercialize our product candidates, we must obtain 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.

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

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While we are conducting a Phase 1/2 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 gene 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 gene therapy 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 gene 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 gene 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 failure of the product candidate to be more effective 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 though the product candidate may not have caused 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 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. Failure to comply with applicable FDA or other applicable regulatory requirements may result in criminal prosecution, civil penalties, recall or seizure of products, total or partial suspension of production or injunction, as well as other regulatory action against our product candidates or us.

Outside the United States, our ability to market a product is contingent upon receiving clearances from the appropriate regulatory authorities. This foreign regulatory approval process includes all of the risks associated with FDA clearance described above.

We have a history of operating losses and expect to incur significant additional operating losses.

We have generated operating losses since we began operations in June 1993. As of December 31, 2002, we had an accumulated deficit of approximately $73.6 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. 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 M. D. Anderson Cancer Center. Prior to December 31, 2000, we earned revenue from Aventis under collaborative agreements for research and development and sales of ADVEXIN gene therapy for use in Aventis clinical trials, which are revenues we no longer receive. We do not expect to generate revenues from the commercial sale of products in the foreseeable 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.

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Developing a new drug and conducting clinical trials for multiple disease indications is expensive. We expect that we will fund our operations over the next fifteen to eighteen months with our current working capital, resulting primarily from the net proceeds from our initial public offering in October 2000, the sale of Series A Non-Voting Convertible Preferred Stock to Aventis in June 2001, 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, due to a number of factors, including:

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

slower than expected progress in developing ADVEXIN gene 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 our manufacturing capability;

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

slower than expected progress in reducing our operating costs.

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 cannot maintain our corporate and academic arrangements and enter into new arrangements, product development could be delayed.

Our strategy for the research, development and commercialization of our product candidates may require us to enter into contractual arrangements with corporate collaborators, academic institutions and others. We have entered into sponsored research and/or collaborative arrangements with several entities, including M. D. Anderson Cancer Center, ICRT, the National Cancer Institute, VirRx and Corixa Corporation. Our success depends upon our collaborative partners performing their responsibilities under these arrangements. We cannot control the amount and timing of resources our collaborative partners devote to our research and testing programs or product candidates, 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 gene 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 successfully sell, market and distribute our products. 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 successfully commercialize our products.

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

Serious unwanted side effects attributable to treatment, which physicians classify as treatment-related adverse events, occurring in the field of gene therapy may result in greater governmental regulation and negative public perception of our product candidates, as well as potential regulatory delays relating to the testing or approval of our product candidates. The FDA recently 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 trials. We are not developing products using the process used in those clinical trials, and we do not use retroviral vectors in our ongoing 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 us from this event. Our pharmacovigilance department monitors every patient in our clinical trials for safety and reports all side effects to the FDA and the National Institutes of Health according to applicable regulations. We have witnessed no adverse effects in our clinical trials that even remotely resemble what occurred in the X-SCID trial. Due to the fundamental differences between retrovirus vectors and the adenovirus vector employed in ADVEXIN gene therapy, we believe the likelihood of our encountering an event such as that experienced in the X-SCID trial is remote.

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 National Institutes of Health, or 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. 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.

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

To date no governmental authority has approved any gene therapy product for sale in the United States or internationally. The commercial success of our products will depend in part on public acceptance of the use of gene therapies, 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 is unsafe, and gene therapy may not gain the acceptance of the public or the medical community. Negative public reaction to gene therapy could also result in greater government regulation and stricter clinical trial oversight.

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 or patent applications. 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 and they 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

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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 therapy, 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 gene 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 radiation, one issued United States patent covering the use of adenoviral p53 in cancer therapy, an issued United States patent covering adenoviral p53 as a product and an issued United States patent covering the core DNA of adenoviral p53. 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. 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.

We have been notified by the European Patent Office, or EPO, that Schering-Plough has filed an opposition against the issuance of 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. We expect that the EPO will hold an initial oral proceeding to determine whether the patent should be maintained in late 2003 or early 2004. Resolution of this opposition will require that we expend time, effort and money. If the party opposing the patent ultimately prevails in having our European patent revoked in whole or in part 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. 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.

While we believe that our potential products do not infringe any valid claim of the Canji p53 patents, Canji or Schering-Plough could assert a claim against us. 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

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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 Canji p53 issued United States patent, 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. 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. In the second opposition, involving a patent directed to therapeutic and other applications of the p53 gene 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 will have an opportunity to appeal 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 upcoming. 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.

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., Genvec, Inc., Vical Incorporated and Onyx Pharmaceuticals, Inc., which are pursuing other forms of treatment for the diseases ADVEXIN gene therapy and our other product candidates target. 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 gene therapy, INGN 241 or other product candidates, we may not be able to commercialize them profitably.

Our profitability will depend on the market s acceptance of ADVEXIN gene therapy, INGN 241 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;

we produce and sell them at a profit; and

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

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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.

The completion of our clinical trials and commercialization of our product candidates requires access to, or development of, facilities to manufacture a sufficient supply of our product candidates. We use a manufacturing facility in Houston, Texas, which we constructed and own, to manufacture ADVEXIN gene therapy, INGN 241 and other product candidates for currently planned clinical trials. This facility will be used for the initial commercial launch of ADVEXIN gene therapy. We have no experience manufacturing ADVEXIN gene 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 few contract manufacturers who currently have the capability to produce ADVEXIN gene 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 gene 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 CGMP 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 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 facility 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 destruction, then our ability to manufacture ADVEXIN gene therapy or any other product candidates would be significantly hampered and we would incur delays in our pre-clinical testing, clinical trials and commercialization efforts.

Canji controls a United States patent and 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 upon 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 some of the materials used in the manufacturing of ADVEXIN gene therapy, INGN 241 and our other product candidates. Some of these materials are available from only one supplier or vendor. 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. Any delay or interruption would likely lead to a delay or interruption in our manufacturing operations, which could negatively affect our operations.

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The CellCube™ Module 100 bioreactor, which Corning (Acton, MA) manufactures, and Benzonase®, which EM Industries (Hawthorne, NY) manufactures, are currently available only from these suppliers. Any significant interruption in the supply of either of these items would require a material change in our manufacturing process. We maintain inventories of these items, but we do not have a supply agreement with either manufacturer.

If product liability lawsuits are successfully brought against us, we may incur substantial damages and demand for the products 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;

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 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 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:

the announcement of new products or services 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, including factors unrelated to our operating performance or the operating performance of our competitors.

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. Many factors may have a significant adverse effect on the market price of our common stock, including:

results of our pre-clinical and clinical trials;

announcement of technological innovations or new commercial products by us or our competitors;

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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; and

quarterly fluctuations in our revenues and other financial results.

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.

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, 2002 would decrease our interest income by approximately $290,000.

At December 31, 2002, 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.

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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.

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 and Section 16(a) Beneficial Ownership Reporting Compliance contained in the 2003 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 2003 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 2003 Proxy Statement.

Equity Compensation Plan Information

Plan Category	(a)Number of Securities to be Issued Upon Exercise of Outstanding Options, Warrants and Rights (in Thousands)	(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)
Equity compensation plans approved by security holders	3,986	$2.18	1,123
Equity compensation plans not approved by security holders	0	0	0
Total	3,986	$2.18	1,123

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 2003 Proxy Statement.

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Item 14. Controls and Procedures

Within 90 days prior to the date of filing this Report, an evaluation was performed under the supervision and with the participation of our management, including our Chief Executive Officer and Chief Financial Officer, of the effectiveness of our disclosure controls and procedures (as defined in Rules 13a-14(c) and 15d-14(c) under the Securities Exchange Act of 1934, as amended). Based on and as of the time of such evaluation, our management, including the Chief Executive Officer and Chief Financial Officer, concluded that our disclosure controls and procedures were effective in timely alerting them to material information relating to the company required to be included in our reports filed or submitted under the Securities Exchange Act of 1934, as amended. There have been no significant changes in our internal controls or in other factors that could significantly affect internal controls and procedures subsequent to the time of such evaluation.

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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
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)	Registration Rights Agreement, dated October 31, 1997
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

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Exhibit Number	Description of Document
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
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 gene 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.

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Exhibit Number	Description of Document
10.30 (3)	Delivery Technology License Agreement, effective as of January 1, 1999, by and between Introgen and Gendux, Inc.
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.
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
24.1	Power of Attorney (See page 52)
99.1	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.

(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.

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(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.

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**

We did not file any Current Reports on Form 8-K during the last quarter of our fiscal year ended December 31, 2002.

(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 31, 2003.

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 31, 2003
/s/ JAMES W. ALBRECHT, JR. (James W. Albrecht, Jr.)	Chief Financial Officer (Principal Financial and Accounting Officer)	March 31, 2003
/s/ JOHN N. KAPOOR, PH.D. (John N. Kapoor, Ph.D.)	Chairman of the Board and Director	March 31, 2003
/s/ WILLIAM H. CUNNINGHAM, PH.D. (William H. Cunningham, Ph.D.)	Director	March 31, 2003
/s/ CHARLES E. LONG (Charles E. Long)	Director	March 31, 2003
/s/ ROBERT L. MOORE	Director	March 31, 2003

(Robert L. Moore)		
/s/ MAHENDRA G. SHAH, PH.D.	Director	March 31, 2003
(Mahendra G. Shah, Ph.D.)		

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CERTIFICATIONS

I, David G. Nance, certify that:

1. I have reviewed this annual report on Form 10-K of Introgen Therapeutics, Inc.;

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

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

4. Introgen s other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-14 and 15d-14) for Introgen and we have:

(a) designed such disclosure controls and procedures to ensure that material information relating to Introgen, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this annual report is being prepared;

(b) evaluated the effectiveness of Introgen s disclosure controls and procedures as of a date within 90 days prior to the filing date of this annual report (the Evaluation Date); and

(c) presented in this annual report our conclusions about the effectiveness of the disclosure controls and procedures based on our evaluation as of the Evaluation Date;

5. Introgen s other certifying officer and I have disclosed, based on our most recent evaluation, to Introgen s auditors and the audit committee of Introgen s board of directors (or persons performing the equivalent function):

(a) all significant deficiencies in the design or operation of internal controls which could adversely affect Introgen s ability to record, process, summarize and report financial data and have identified for Introgen s auditors any material weaknesses in internal controls; and

(b) any fraud, whether or not material, that involves management or other employees who have a significant role in Introgen s internal controls; and

6. Introgen s other certifying officer and I have indicated in this Annual Report whether or not there were significant changes in internal controls or in other factors that could significantly affect internal controls subsequent to the date of our most recent evaluation, including any corrective actions with regard to significant deficiencies and material weaknesses.

By: /s/ DAVID G. NANCE

David G. Nance
Chief Executive Officer

Date: March 31, 2003

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I, James W. Albrecht, Jr., certify that:

1. I have reviewed this annual report on Form 10-K of Introgen Therapeutics, Inc.;

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

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

4. Introgen s other certifying officer and I are responsible for establishing and maintaining disclosure controls and procedures (as defined in Exchange Act Rules 13a-14 and 15d-14) for Introgen and we have:

(a) designed such disclosure controls and procedures to ensure that material information relating to Introgen, including its consolidated subsidiaries, is made known to us by others within those entities, particularly during the period in which this annual report is being prepared;

(b) evaluated the effectiveness of Introgen s disclosure controls and procedures as of a date within 90 days prior to the filing date of this annual report (the Evaluation Date); and

(c) presented in this annual report our conclusions about the effectiveness of the disclosure controls and procedures based on our evaluation as of the Evaluation Date;

5. Introgen s other certifying officer and I have disclosed, based on our most recent evaluation, to Introgen s auditors and the audit committee of Introgen s board of directors (or persons performing the equivalent function):

(a) all significant deficiencies in the design or operation of internal controls which could adversely affect Introgen s ability to record, process, summarize and report financial data and have identified for Introgen s auditors any material weaknesses in internal controls; and

(b) any fraud, whether or not material, that involves management or other employees who have a significant role in Introgen s internal controls; and

6. Introgen s other certifying officer and I have indicated in this annual report whether or not there were significant changes in internal controls or in other factors that could significantly affect internal controls subsequent to the date of our most recent evaluation, including any corrective actions with regard to significant deficiencies and material weaknesses.

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

James W. Albrecht, Jr.
Chief Financial Officer

Date: March 31, 2003

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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 sheet of Introgen Therapeutics, Inc. and subsidiaries as of December 31, 2002, and the related consolidated statements of operations, stockholders equity, and cash flows for the year 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 years ended June 30, 2001 and 2000, were audited by other auditors whose report dated January 18, 2002, expressed an unqualified opinion on those statements.

We conducted our audit 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 audit provides 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 at December 31, 2002, and the consolidated results of their operations and their cash flows for the year then ended in conformity with accounting principles generally accepted in the United States.

/s/ Ernst & Young LLP

Austin, Texas

January 21, 2003

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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 YEAR 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,	
	2001	2002
ASSETS		
Current Assets:		
Cash and cash equivalents	$ 37,397	$ 23,467
Short-term investments	11,428	
Prepaid expenses and other current assets	811	812
Total current assets	49,636	24,279
Property and equipment, net of accumulated depreciation of $6,406 and $8,228, respectively	10,443	8,742
Other assets	345	295
Total assets	$ 60,424	$ 33,316
LIABILITIES AND STOCKHOLDERS EQUITY		
Current Liabilities:		
Accounts payable	$ 946	$ 1,774
Accrued liabilities	4,029	1,997
Deferred revenues from affiliate		69
Current portions of capital lease obligations and notes payable	1,486	1,587
Total current liabilities	6,461	5,427
Capital lease obligations, net of current portion	957	125
Notes payable, net of current portion	8,079	7,310
Deferred revenue, long-term	361	619
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; 21,446, and 21,487 shares issued and outstanding in 2001 and 2002, respectively	21	21
Additional paid-in capital	94,544	94,430
Deferred compensation	(2,485)	(974)
Accumulated deficit	(47,515)	(73,643)
Total stockholders equity	44,566	19,835
Total liabilities and stockholders equity	$ 60,424	$ 33,316

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,		Six Months Ended December 31,		Year Ended December 31,
	2000	2001	2000	2001	2002
			(Unaudited)		
Contract services, grant and other Revenue	$ 97	$ 684	$ 391	$ 298	$ 1,173
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	21,512
General and administrative	4,701	4,875	2,040	3,526	6,722
Total operating costs and expenses	14,776	19,889	7,193	13,589	28,234
Loss from operations	(7,864)	(17,177)	(4,774)	(13,291)	(27,061)
Interest income	722	1,230	783	912	596
Interest expense	(582)	(849)	(380)	(467)	(803)
Other income		354		518	1,140
Net loss	$ (7,724)	$ (16,442)	$ (4,371)	$ (12,328)	$ (26,128)
Net loss per share, basic and diluted	$ (1.89)	$ (1.02)	$ (0.39)	$ (0.58)	$ (1.22)
Shares used in computing basic and diluted net loss per share	4,096	16,163	11,120	21,440	21,471

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

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INTROGEN THERAPEUTICS, INC. AND SUBSIDIARIES

CONSOLIDATED STATEMENTS OF STOCKHOLDERS EQUITY

	Series A, B, C and D Convertible Preferred Stock		Series A Non-Voting Convertible Preferred Stock		Common Stock		Additional Paid-In Capital	Deferred Compensation	Accumulated Deficit	Total
	Shares	Amount	Shares	Amount	Shares	Amount				
					(Amounts in thousands)					
Balance, June 30, 1999	6,419	$ 6		$	4,006	$ 4	$31,975	$(1,778)	$(11,021)	$ 19,187
Issuance of common stock in connection with Exercise of stock options and warrants					128		58			58
Deferred compensation relating to issuance of stock options, net of reversals							3,929	(3,929)		
Amortization of deferred compensation and stock-based compensation							574	1,497		2,071
Net loss									(7,724)	(7,724)
Balance, June 30, 2000	6,419	$ 6		$	4,134	$ 4	$36,536	$(4,210)	$(18,745)	$ 13,592
Issuance of common stock in connection with initial public offering, net of offering costs of $4,575					4,600	5	32,221			32,226
Conversion of preferred stock to common stock	(6,419)	(6)			12,326	12	(6)			
Issuance of common stock in connection with Exercise of stock options and warrants					331		204			204
Issuance of preferred stock in June 2001 in accordance stock purchase agreement with affiliate, net of offering costs of $100			100	1			24,900			24,900
Deferred compensation relating to issuance of stock options, net of reversals							720	(720)		
Amortization of deferred compensation and stock-based compensation								1,589		1,589
Net loss									(16,442)	(16,442)
Balance, June 30, 2001		$	100	$ 1	21,391	$ 21	$94,575	$(3,341)	$(35,187)	$ 56,069
Issuance of common stock in connection with Exercise of stock options and warrants					55		26			26
Deferred compensation relating to issuance of stock options, net of reversals							(57)	57		

Amortization of deferred compensation and stock-based compensation								799		799
Net loss									(12,328)	(12,328)
Balance, December 31, 2001		$	100	$ 1	21,446	$ 21	$94,544	$(2,485)	$(47,515)	$ 44,566
Issuance of common stock in connection with Exercise of stock options and warrants					41		21			21
Deferred compensation relating to issuance of stock options, net of reversals							(135)	135		
Amortization of deferred compensation and stock-based compensation								1,376		1,376
Net loss									(26,128)	(26,128)
Balance, December 31, 2002		$	100	$ 1	21,487	$ 21	$94,430	$ (974)	$(73,643)	$ 19,835

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

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INTROGEN THERAPEUTICS, INC. AND SUBSIDIARIES

CONSOLIDATED STATEMENTS OF CASH FLOWS

	Year Ended June 30,		Six Months Ended December 31,		Year Ended December 31,
	2000	2001	2000	2001	2002
			(Unaudited) (Amounts in thousands)		
Cash flows from operating activities:					
Net loss	$ (7,724)	$(16,442)	$ (4,371)	$(12,328)	$(26,128)
Adjustments to reconcile net loss to net cash used in operating activities:					
Depreciation	1,711	2,226	1,066	1,191	1,801
Compensation related to issuance of certain stock options	2,071	1,589	746	800	1,511
Changes in assets and liabilities:					
Decrease (increase) in receivable from affiliate			(709)		
Decrease (increase) in inventory	(110)	1,734	984		
Decrease (increase) in other assets	(908)	(437)	(371)	(294)	49
Increase (decrease) in accounts payable	(1,752)	113	582	568	829
Increase (decrease) in accrued liabilities	763	3,376	479	(372)	(2,032)
Increase (decrease) in deferred revenue	407	(917)	(155)	73	326
Net cash used in operating activities	(5,542)	(8,758)	(1,749)	(10,362)	(23,644)
Cash flows from investing activities:					
Purchases of property and equipment	(1,022)	(3,581)	(2,954)	(127)	(121)
Purchases of short-term investments	(21,585)	(83,143)	(47,076)	(19,400)	(71,734)
Maturities of short-term investments	25,224	72,343	20,075	28,749	83,184
Net cash provided by (used in) investing activities	2,617	(14,381)	(29,955)	9,222	11,329
Cash flows from financing activities:					
Proceeds from sale of preferred and common stock, net of offering costs	59	33,105	33,070	25,026	(114)
Proceeds from issuance of note payable	2,814	3,263	1,932		
Principal payments under capital lease obligations and notes payable	(305)	(818)	(387)	(689)	(1,501)
Net cash provided by financing activities	2,568	35,550	34,615	24,337	(1,615)
Net increase (decrease) in cash	(357)	12,411	2,911	23,197	(13,930)
Cash, beginning of period	2,146	1,789	1,789	14,200	37,397
Cash, end of period	$ 1,789	$ 14,200	$ 4,700	$ 37,397	$ 23,467
Supplemental disclosure of cash flow information:					
Cash paid for interest	$ 608	$ 917	$ 280	$ 459	$ 803

Supplemental disclosure of non-cash investing and financing activities:					
Purchases of equipment under capital lease obligations	$ 2,780	$	$	$	$
Retirement of fully-depreciated assets	$ 484	$	$	$	$
Receivable for issuance of preferred stock	$	$ 25,000	$	$	$
Offering costs deferred in 2000, netted against initial public offering proceeds in 2001	$	$ 776	$ 776	$	$

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

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INTROGEN THERAPEUTICS, INC. AND SUBSIDIARIES

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS

December 31, 2002
(Information pertaining to the six-month period ending December 31, 2000 is unaudited)

1. Formation and Business of the Company

Introgen Therapeutics, Inc., a Delaware corporation, and its subsidiaries (Introgen) is a leading developer of gene therapy products for the treatment of cancer and other diseases. Our lead product candidate, ADVEXIN® gene therapy, combines the p53 gene, one of the most potent members of a group of naturally occurring tumor suppressor genes, which act to protect cells from becoming cancerous, with our adenoviral delivery system. We are conducting pivotal Phase 3 clinical trials of ADVEXIN gene therapy in head and neck cancer. We have completed a Phase 2 clinical trial of ADVEXIN in non-small cell lung cancer and are conducting a Phase 2 trial of ADVEXIN gene therapy in breast cancer. We are conducting Phase 1 clinical trials, or safety trials, of ADVEXIN gene therapy in other types of cancer. We are developing additional cancer gene therapy product candidates, including those based on the mda-7 and PTEN genes, as well as associated vector technologies for delivering the gene-based products into target cells. Our INGN 241 product candidate, which combines the mda-7 gene with our proprietary gene delivery system, is undergoing safety testing in a Phase 1 clinical trial. We hold the worldwide rights for pre-clinical and clinical development, manufacturing, marketing and commercialization of ADVEXIN gene therapy. ADVEXIN gene therapy is designated by the FDA as an orphan drug under the Orphan Drug Act, which gives us seven years of marketing exclusivity for ADVEXIN gene therapy if approved by the FDA.

We are investigating other vector technologies for delivering gene-based products into targeted cells, specifically those involving replication-competent viral therapies in which viruses bind directly to cancer cells, replicate in those cells, and cause those cancer cells to die. As a supplement to our gene therapy product programs, we are evaluating the development of mebendazole, our first small molecule candidate. Pre-clinical trials suggest that mebendazole may also be an effective treatment of cancer.

We own and operate a manufacturing facility that we believe complies with the FDA s current Good Manufacturing Practices requirements, commonly known as CGMP requirements. We have produced ADVEXIN gene therapy in this facility for use in our Phase 1, 2 and 3 clinical trials and INGN 241 for use in our Phase 1 clinical trials.

We have not yet generated any significant revenues from unaffiliated third parties, nor is there any assurance of future product revenues. Our research and development activities involve a high degree of risk and uncertainty, and our ability to successfully develop, manufacture and market our proprietary products is dependent upon many factors. These factors include, but are not limited to, the need for additional financing, the reliance on collaborative research and development arrangements with corporate and academic affiliates, and the ability to develop manufacturing, sales and marketing experience. Additional factors include uncertainties as to patents and proprietary technologies, competitive technologies, technological change and risk of obsolescence, development of products, competition, government regulations and regulatory approval, and product liability exposure. As a result of the aforementioned factors and the related uncertainties, there can be no assurance of our future success.

Prior to June 30, 2001, we developed therapeutics based on p53 and on K-ras pathway inhibition under two collaboration agreements originally entered into in October 1994 with Rhône-Poulenc Rorer Pharmaceuticals Inc., which ultimately became part of Aventis Pharma, or Aventis. In June 2001, we and Aventis restructured this collaborative relationship whereby we assumed responsibility for the worldwide development of all p53 and K-ras products and acquired all worldwide marketing and commercialization rights with respect to those products. We assumed responsibility for the control and performance of ongoing clinical trials for p53- and K-ras-based products and for the development and clinical trials for new gene therapy products. Aventis licensed or transferred to us all of its patents covering the manufacture, sale, offering for sale, importation or use of ADVEXIN gene therapy and other K-ras patents, delivery patents and targeting technologies, as well as all trademarks and goodwill associated with ADVEXIN gene therapy. Aventis also

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INTROGEN THERAPEUTICS, INC. AND SUBSIDIARIES

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

agreed, for a period of seven years, not to conduct any activities directed to the development or commercialization of any gene therapy products using the p53 or K-ras genes. In connection with this restructuring, 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 they incurred in facilitating the transition of control and performance of these clinical trials from Aventis to us.

Since our inception in 1993, we have used our resources primarily to conduct research and development activities, primarily for ADVEXIN gene therapy and, to a lesser extent, for other product candidates. At December 31, 2002, we had an accumulated deficit of approximately $73.6 million. It is possible we will incur losses in the future that will be greater than cumulative losses incurred in prior years. We expect that cash needed for operating activities will increase as we continue to expand our research and development of various gene therapy technologies. Since inception, our only significant revenues have been payments from Aventis under the collaborative agreements discussed above for Aventis early-stage development work on ADVEXIN gene therapy and Aventis purchases of ADVEXIN gene therapy product we manufactured for Aventis use in later-stage clinical trials it previously performed. We no longer receive these revenues. We have also earned revenue from federal research grants, contract manufacturing and process development activities and interest income on cash placed in short-term investments.

Unless indicated otherwise, amounts disclosed in these footnotes are rounded to the nearest thousand.

2. Summary of Significant Accounting Policies

Basis of Presentation

The accompanying consolidated financial statements include our accounts and all of our subsidiaries. Intercompany transactions and balances are eliminated in consolidation. In October 2001, we announced a change in the ending date of our accounting year from June 30 to December 31.

Use of Estimates

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

Cash and Cash Equivalents

Cash and cash equivalents include amounts on deposit with financial institutions and investments with original maturities of 90 days or less.

Short-Term Investments

Our short-term investments consist of investments in short-term, investment-grade securities in the form of federal and state government obligations, commercial paper and/or corporate bonds with various maturity dates not exceeding one year. All short-term investments have been 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. Additionally, we could incur future losses on investments if the investment issuer becomes impaired or the investment is downgraded.

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INTROGEN THERAPEUTICS, INC. AND SUBSIDIARIES

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

Property and Equipment

Property and equipment are carried at cost, less accumulated depreciation. Maintenance, repairs and minor replacements are charged to expense as incurred. Significant renewals and betterments are capitalized. Depreciation is provided generally using accelerated methods based on useful lives of fifteen years for research, manufacturing and administrative facilities and five to seven years for equipment. Interest incurred during construction of facilities is capitalized as a cost of those facilities.

Property and equipment consists of the following items (in thousands):

	December 31,	
	2001	2002
Facilities	$11,570	$11,594
Equipment	5,279	5,376
Total property and equipment	16,849	16,970
Less accumulated depreciation	(6,406)	(8,228)
Net property and equipment	$10,443	$ 8,742

As of December 31, 2001 and 2002, $3,077,000 of equipment was held under capital lease obligations and is being depreciated over the applicable lease term (see Note 7).

Federal Income Taxes

We recognize deferred tax liabilities and assets for the expected future tax consequences of events that have been recognized differently between the financial statements and tax returns. Under this method, deferred tax liabilities and assets are determined based on the difference between the financial statement carrying amounts and tax bases of liabilities and assets using enacted tax rates and laws in effect in the years in which the differences are expected to reverse. Deferred tax assets are evaluated for realization based on a more-likely-than-not criteria in determining if a valuation should be provided.

Accrued Liabilities

Accrued liabilities consist of the following significant items (in thousands):

	December 31,	
	2001	2002
Pre-clinical costs due to unrelated parties	$ 960	$ 490
Property taxes	213	314
Clinical costs due affiliate	1,163	300
Vacation	218	284
Clinical costs due unrelated parties	365	275
Legal fees	500	150
Other	610	184

Total accrued liabilities	$4,029	$1,997

In conducting our pivotal Phase 3 clinical trials of ADVEXIN gene therapy, we procure services from multiple 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. Some of our vendors do not necessarily bill us for their services on a regular basis and, accordingly, make it difficult for us to determine the costs we have incurred relative to their services for any given accounting period. As a result, we make significant accounting

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INTROGEN THERAPEUTICS, INC. AND SUBSIDIARIES

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

estimates as to the amount of costs we have incurred relative to these vendors in each accounting period. These estimates are based on many factors, including, among others, costs set forth in our contracts with these vendors, the period of time over which the vendor has rendered 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.

Revenue Recognition

Contract services revenue is recognized as the related contract services are performed. Deferred revenue is recorded for cash received for which the related expenses had not been incurred.

In accordance with the terms of the grant, grant revenue is recognized as research expenses relating to the grant are incurred, provided that the amounts received are not refundable if the research is not successful.

Collaborative research payments received prior to the restructuring of the Aventis collaboration were recognized as revenue as we performed our obligations related to such research agreements. Deferred revenue was recorded for cash received for which the related expenses had not been incurred. We have not received such payments subsequent to December 31, 2000.

Prior to the restructuring of the Aventis collaboration, we sold gene-therapy based products to Aventis at specified prices and payment terms with no rights to return delivered and accepted product. Revenue from product sales to the affiliate was recognized upon completion of production and delivery requirements and acceptance by Aventis and when collection was reasonably assured. Deferred revenue was recorded for cash received for product which had not been delivered to and accepted by Aventis. We have not sold product to Aventis subsequent to December 31, 2000.

Rental income from the sublease of laboratory space to third parties under leases that have variable monthly rent amounts over the term of the lease is recognized on a straight-line basis over the term of the lease. Any cash payments received in excess of rental income recognized is recorded as deferred revenue. Rental income is included in other income in the accompanying consolidated statement of operations.

Research and Development Costs

Research and development costs include the costs of conducting basic research, developing product applications, conducting pre-clinical investigations and performing clinical trials to obtain data for regulatory filings for product approvals. Research and development costs are expensed as incurred.

Net Loss Per Share

Net loss per share is computed using the weighted average number of shares of common stock outstanding. Due to losses incurred in all periods presented, the shares associated with stock options, warrants and non-voting convertible preferred stock are not included because they are anti-dilutive.

Stock-Based Compensation

Statement of Financial Accounting Standards (SFAS) No. 123, Accounting for Stock-Based Compensation, allows companies to adopt one of two methods for accounting for stock options. We have elected the method that requires disclosure only of stock-based compensation. Because of this election, we continue to account for our employee stock-based compensation plans, using the intrinsic value method, under Accounting Principles Board (APB) Opinion No. 25, Accounting for Stock Issued to Employees, as clarified by Interpretation No. 44, Accounting for Certain Transactions Involving Stock Compensation. Accordingly,

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INTROGEN THERAPEUTICS, INC. AND SUBSIDIARIES

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

deferred compensation is recorded for stock-based compensation grants based on the excess of the fair market value of the common stock on the measurement date over the exercise price. The deferred compensation is amortized over the vesting period of each unit of stock-based compensation grant, generally four years. If the exercise price of the stock-based compensation grants is equal to the estimated fair value of our stock on the date of grant, no compensation expense is recorded.

The fair value of options granted for all periods presented was estimated on the applicable grant dates using the Black-Scholes option pricing model. Significant weighted average assumptions used to estimate fair value for all years include: risk-free interest rates ranging from 4.8 percent to 6.7 percent; expected lives of seven to ten years; no expected dividends; and volatility factors ranging from 58.0 percent to 110.8 percent. Had compensation expense been determined consistent with the provisions of SFAS No. 123, our net loss would have been increased to the following pro forma amounts (in thousands, except per share information):

	Year Ended June 30,		Six Months Ended December 31,	Year Ended December 31,
	2000	2001	2001	2002
Net loss, as reported	$(7,724)	$(16,442)	$(12,328)	$(26,128)
Add: Stock-based employee compensation expense included in reported net loss	$ 1,497	$ 1,589	$ 799	$ 1,377
Deduct: Total stock-based employee compensation expense determined under fair value based method for all awards	$(1,555)	$ (1,883)	$ (1,693)	$ (1,902)
Pro forma net income	$(7,782)	$(16,736)	$(13,222)	$(26,653)
Earnings per share:				
Basic and Diluted as reported	$ (1.89)	$ (1.02)	$ (0.58)	$ (1.22)
Basic and Diluted pro forma	$ (1.90)	$ (1.04)	$ (0.62)	$ (1.24)

Because SFAS No. 123 does not apply to options granted prior to July 1, 1995, the resulting pro forma compensation costs may not be representative of the costs to be expected in future years.

Other Comprehensive Loss

Our other comprehensive loss consists of net loss, as there are no other comprehensive loss items.

Recent Accounting Pronouncements

In June 2002 the FASB issued SFAS No. 146, Accounting for Costs Associated with Exit or Disposal Activities. SFAS No. 146 requires companies to recognize costs associated with exit or disposal activities when they are incurred rather than at the date of commitment to an exit or disposal plan. This statement is effective for exit or disposal activities initiated after December 31, 2002. We do not believe that the adoption of SFAS No. 146 will have a material impact on our financial statements.

In December 2002, the FASB issued SFAS No. 148, Accounting for Stock-Based Compensation Transition and Disclosure, an Amendment of FASB Statement No. 123. This Statement amends FASB Statement No. 123, Accounting for Stock-Based Compensation, to provide alternative methods of transition for an entity that voluntarily changes to the fair value based method of accounting for stock-based employee compensation. It also amends the disclosure provisions of that Statement to require prominent disclosure about the effects on reported net

income of an entity s accounting policy decisions with respect to stock-based employee compensation. Finally, this Statement amends APB Opinion No. 28, Interim Financial Report-

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INTROGEN THERAPEUTICS, INC. AND SUBSIDIARIES

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

ing, to require disclosure about those effects in interim financial information. Since we are continuing to account for stock-based compensation according to APB 25, adoption of SFAS No. 148 requires us to provide prominent disclosures about the affects of FAS 123 on reported income (loss) and will require us to disclose these affects in the interim financial statements as well.

3. Stockholders Equity

Stock Split

In August 2000, our Board of Directors approved a stock dividend to effect a stock split of 1.6 shares for every one share of common stock outstanding. An amount equal to the increased par value of the common shares has been reflected as a transfer from additional paid-in capital to common stock. Retroactive effect has been given to the stock split in stockholders equity and in all share and per share data as of the earliest date presented in the accompanying consolidated financial statements.

Initial Public Offering

In October 2000, we completed an initial public offering of 4,600,000 newly-issued shares of our common stock at a price of $8.00 per share. We received $32.2 million in cash proceeds from the initial public offering, net of underwriting discounts, commissions and other offering costs.

Convertible Preferred Stock

Simultaneous with the closing of the initial public offering, our convertible preferred stock then outstanding, consisting of 3,011,423 shares of Series A Convertible Preferred Stock, 1,757,063 shares of Series B Convertible Preferred Stock, 551,410 shares of Series C Convertible Preferred Stock and 1,100,000 shares of Series D Convertible Preferred Stock, was automatically converted into 12,326,173 shares of common stock.

Series A Non-Voting Convertible Preferred Stock

In connection with the restructuring of the Aventis collaboration and pursuant to a stock purchase agreement with Aventis executed on June 30, 2001, we issued and sold to Aventis 100,000 unregistered shares of a new class of $0.001 par value, Series A Non-Voting Convertible Preferred Stock in exchange for $25.0 million. At June 30, 2001, we had a receivable of $25.0 million from Aventis for this sale, for which we received payment in July 2001. These shares are convertible at any time, at our option or the option of Aventis, into 2,343,721 shares of our common stock. Under a voting agreement, Aventis must vote these shares in the same manner as the shares voted by a majority of the other stockholders on any corporate action put to a vote of our stockholders. This voting requirement terminates at the earliest of the tenth anniversary of the voting agreement, registration of these shares with the Securities and Exchange Commission or the sale of these shares to an Aventis non-affiliate, as defined in the voting agreement. A registration rights agreement grants the holder of a majority of the common stock issuable upon conversion of the Series A Non-Voting Convertible Preferred Stock three demand registrations and three piggyback registrations.

Employee Stock Purchase Plan

Under our 2000 Employee Stock Purchase Plan (the Stock Purchase Plan), 780,000 shares of common stock are reserved for purchase by eligible employees, at 85 percent of the appropriate market price. The Stock Purchase Plan provides for an increase on each January 1 in the number of shares available for issuance, in an amount equal to the lesser of 480,000 shares, 1.5 percent of the outstanding shares of common stock on the date of the annual increase or such lesser amount as may be determined by the Board of Directors. The Stock Purchase Plan provides that eligible employees may authorize payroll deductions of up to 10 percent of their

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

qualified compensation. The maximum number of shares that an employee may purchase in a single offering period is 10,000 shares. The Stock Purchase Plan will terminate in 2010 and may be amended or terminated by the Board of Directors. During the year ended June 30, 2001, 22,561 shares of common stock were purchased by employees under this plan. There have been no common stock purchases since that time, as we have suspended operation of the Stock Purchase Plan until further notice by the Board of Directors.

Stock Option Plans

The 2000 Stock Option Plan (the Stock Option Plan) was initiated in October 2000 and all stock option grants since that time have been under this plan. The Stock Option Plan provides for the granting of options, either incentive or non-statutory, or stock purchase rights to our employees, directors and consultants to purchase shares of our common stock. At December 31, 2002, there were 5,109,000 shares of common stock reserved for option grants under this plan. This plan provides for annual increases in the number of shares available for issuance beginning in fiscal 2001, equal to the lesser of 1,600,000 shares, five percent of the outstanding shares on the date of the annual increase, or a lesser amount as may be determined by the Board of Directors. The exercise price for all option grants shall be no less than the fair value of our common stock at the date of grant, with the exception of incentive stock options granted to holders of shares representing more than ten percent of our voting power, in which case the exercise price shall be no less than 110 percent of the fair value. In the event of a merger, reorganization or change in our controlling ownership, all options outstanding under the Stock Option Plan become fully vested and immediately exercisable unless the successor corporation assumes or substitutes other options in their place. The Stock Option Plan will terminate in 2010 and may be amended or terminated by the Board of Directors.

Prior to October 2000, stock options were granted under our 1995 Stock Plan. We no longer issue options under this plan. The terms of this plan are substantially the same as the Stock Option Plan. No shares of common stock were reserved for option grants under this plan at December 31, 2002.

We record the fair value of options issued to non-employee consultants at the fair value of the options issued. We have not incurred significant compensation expense relating to non-employee consultant grants. Any expense is recognized over the service period or at the date of issuance if the options are fully vested and no performance obligation exists.

Aggregate deferred compensation recorded related to stock options was $4,177,000 and $792,000 during the years ended June 30, 2000 and 2001, respectively, $600,000 and zero during the six months ended December 31, 2000 and 2001, and zero during the year ended December 31, 2002.

Amortization to expense of deferred compensation related to stock options was $1,497,000 and $1,589,000 during the years ended June 30, 2000 and 2001, respectively, $746,000 and $799,000 for the six months ended December 31, 2000 and 2001, respectively, and $1,377,000 during the year ended December 31, 2002.

Reversals of deferred compensation and additional paid-in capital for unamortized deferred compensation related to the forfeiture of non-vested options by terminated employees was $248,000 and $73,000 for the years ended June 30, 2000 and 2001, respectively, and $56,000 and $56,000 for the six months ended December 31, 2000 and 2001, respectively, and $134,000 during the year ended December 31, 2002. For each respective year, total amortization expense was revised to the extent amortization had previously been recorded for non-vested options.

In December 1999, we accelerated the vesting of options held by a member of the Board of Directors concurrent with the individual s resignation from our Board of Directors. We accelerated these options in recognition of the individual s contributions to the Board of Directors and recognized approximately $574,000 of compensation expense for the fair value of the previously unvested options as of the re-measurement date.

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INTROGEN THERAPEUTICS, INC. AND SUBSIDIARIES

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

The following is a summary of option activity under these plans:

	Options Outstanding	Weighted Average Exercise Price Per Share
Balance, June 30, 1999	2,431,111	$0.47
Granted	399,306	0.94
Exercised	(108,745)	0.46
Cancelled	(124,517)	0.51
Balance, June 30, 2000	2,597,155	0.55
Granted	704,498	4.30
Exercised	(308,212)	0.42
Cancelled	(17,357)	0.74
Balance, June 30, 2001	2,976,084	1.27
Granted	379,300	4.35
Exercised	(55,238)	0.44
Cancelled	(38,350)	1.21
Balance, December 31, 2001	3,261,796	1.80
Granted	989,514	3.62
Exercised	(40,331)	0.54
Cancelled	(224,886)	3.46
Balance, December 31, 2002	3,986,093	2.18
Exercisable at December 31, 2002	2,457,447	1.28

The weighted average fair value of options granted during the years ended June 30, 2000 and 2001 was $11.18 and $5.61, respectively, for the six months ended December 31 2001 was $3.96, and for the year ended December 31, 2002 was $3.07. All options granted during the six months ended December 31, 2000 and thereafter have an exercise price equal to the fair value of our common stock as of date of grant.

The following table summarizes information about stock options outstanding as of December 31, 2002:

Options Outstanding				Options Exercisable	
Range of Exercise Price	Outstanding as of December 31, 2002	Weighted Average Remaining Contractual Life (In Years)	Weighted Average Exercise Price	Exercisable as of December 31, 2002	Weighted Average Exercise Price
$0.39-$1.99	2,137,107	4.92	$0.56	1,936,845	$0.53
2.00- 3.91	575,750	8.95	2.68	205,900	2.86
4.02- 5.88	1,273,236	8.65	4.64	314,702	4.86

3,986,093	6.69	2.18	2,457,447	1.28

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INTROGEN THERAPEUTICS, INC. AND SUBSIDIARIES

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

4. Federal Income Taxes

The reconciliation of the statutory federal income tax rate to our effective income tax rate is as follows:

	Year Ended June 30,		Six Months Ended December 31,		Year Ended December 31,
	2000	2001	2000	2001	2002
Federal statutory rate	(34.0)%	(34.0)%	(34.0)%	(34.0)%	(34.0)%
State taxes, net of federal benefit					(2.8)
Increase in deferred tax valuation allowance	24.8	30.6	30.8	32.9	37.1
Stock option compensation not deductible	9.1	3.3	3.1	2.2	1.8
Research and development tax credits				(1.4)	(0.2)
Other	0.1	0.1	0.1	0.3	(4.7)
	%	%	%	%	%

The components of our deferred tax assets are as follows:

	December 31,	
	2001	2002
Net operating loss carryforwards	$ 11,708,500	$ 21,602,000
Research and development tax credits	226,900	282,800
Technology license	50,200	25,900
Tax basis of property and equipment in excess of book basis	1,578,400	1,849,800
Accrued liabilities	432,500	248,900
Capital leases	137,900	
Other	209,000	35,600
Total deferred tax assets	14,343,400	24,045,000
Less Valuation allowance	(14,343,400)	(24,045,000)
Net deferred tax assets	$	$

As of December 31, 2002, we have generated net operating loss (NOL) carryforwards of approximately $58.4 million and research and development credits of approximately $283,000 available to reduce future income taxes. These carryforwards begin to expire in 2007. A change in ownership, as defined by federal income tax regulations, could significantly limit our ability to utilize these carryforwards. Our ability to utilize current and future NOLs to reduce future taxable income and tax liabilities may be limited. Additionally, because United States tax laws limit the time during which these carryforwards may be applied against future taxes, we may not be able to take full advantage of these attributes for federal income tax purposes. As we have had cumulative losses and there is no assurance of future taxable income, a valuation allowance has been established to fully offset the deferred tax asset. The valuation allowance increased $1.9 million and $5.0 million for the years ended June 30, 2000 and 2001, respectively, and $2.8 million and $4.1 million for the six months ended December 31, 2000 and 2001, respectively, and $9.7 million during the year ended December 31, 2002. These valuation allowance increases were primarily due to losses from operations.

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INTROGEN THERAPEUTICS, INC. AND SUBSIDIARIES

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

5. Notes Payable

We have notes payable with banks to finance our facilities, which are pledged as security for these notes. There are two notes with the following terms:

Note payable with an original principal balance of $6,000,000 and an outstanding balance of $5,826,000 and $5,732,000 at December 31, 2001 and 2002, respectively. Interest is fixed at 7.5 percent until November 2004, at which time it is subject to a one-time adjustment to a rate equal to the then-current rate of the five-year United States Treasury bond note plus 2 percent, with such adjusted interest rate not to exceed 8.5 percent. Interest plus principal based on a 25-year amortization period are payable monthly until November 2009, at which time the remaining outstanding principal is due and payable.

Note payable with an original principal balance of $3,263,000 and an outstanding balance of $2,938,000 and $2,332,000 at December 31, 2001 and 2002, respectively. Interest is at prime, adjustable annually. Principal and interest, fully amortized over a five-year period, is payable monthly through June 2006.

Interest was capitalized as a cost of facilities during the time those facilities to which those notes relate were under construction. Interest capitalized was $103,000 and $84,000 during the years ended June 30, 2000 and 2001, respectively, $60,000 and zero during the six months ended December 31, 2000 and 2001, respectively, and zero during the year ended December 31, 2002.

Aggregate annual maturities on notes payable as of December 31, 2002, are as follows (in thousands):

Year ending December 31,	
2003	$ 755
2004	789
2005	825
2006	434
2007	142
Thereafter	5,119
Total	$8,064

We believe the fair market value of our debt approximates its carrying value as of all balance sheet dates presented herein.

6. License and Research Agreements

Patent and Technology License Agreement With The University of Texas System

We have a license agreement with the Board of Regents of The University of Texas System (the System) and M. D. Anderson Cancer Center, a component institution of the System, whereby we have an exclusive, worldwide license to use certain technology. Beginning with the first commercial sale of a product incorporating the licensed technologies, we will pay M. D. Anderson Cancer Center, for the longer of fifteen years or the life of the patent, a royalty based on net sales by us or our affiliates or by sublicense agreement of products incorporating any of such technologies. We are obligated by the agreement 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.

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VirRx, Inc.

We are working with VirRx, Inc. (VirRx) to investigate other vector technologies 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 $525,000 of this stock for cash during 2002, which we 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 at any time after March 7, 2003, which would also terminate the requirement for us to make any additional stock purchases. Provided the collaboration and license agreement remains in place, we will 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 will make a $5.0 million cash milestone payment to VirRx, for which we receive no VirRx stock, upon approval by the United States Food and Drug Administration 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.

Other Technology Option and License Agreements

We have technology option and license agreements with various other third parties and, in particular, agreements related to the mda-7 and PTEN genes. These agreements require us to make milestone and license payments to these parties if and when we achieve certain prescribed clinical trial and product development milestones. We have technology option and license agreements with two additional third parties covering certain enabling technologies, both of which require annual payments of $20,000 until cancelled at our option.

Sponsored Research

We fund certain research performed by M. D. Anderson Cancer Center to further the development of technologies that could have potential commercial viability. By sponsoring and funding this research, we have the right to include certain patentable inventions arising therefrom under its patent and technology license agreement with The University of Texas System. The expense for this research was approximately $816,000 and $634,000 during the years ended June 30, 2000 and 2001, respectively, $230,000 and $632,000 during the six months ended December 31, 2000 and 2001, respectively, and $809,000 for the year ended December 31, 2002.

7. Commitments and Contingencies

Lease Commitments

We are obligated under various capital and operating leases for land, office and laboratory space and equipment that expire at various dates through September 2026. The amounts payable under capital leases were drawn under two lease lines of credit with commercial leasing companies which were used to finance equipment acquisitions. Amounts drawn under both lines are payable monthly over 48 months from the time of the draw. The lines of credit bear interest at fixed interest rates ranging from 11.3% to 13.25% at December 31, 2002. The lease lines of credit are secured by the equipment being financed.

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NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

Operating leases consist primarily of a ground lease for the land on which our new facility is located. The annual rent due under this lease is $144,000. The primary term of this lease continues through September 2026.

Lease expense was $380,000 and $315,000 for the years ended June 30, 2000 and 2001, respectively, and $157,000 and $155,000 for the six months ended December 31, 2000 and 2001, respectively, and $303,000 for the year ended December 31, 2002. Future minimum lease payments under non-cancelable operating leases and the present value of future minimum capital lease payments as of December 31, 2002, are as follows (in thousands):

	Operating Leases	Capital Leases
Year ending December 31,		
2003	$ 279	$ 905
2004	281	128
2005	202	
2006	144	
2007	144	
Thereafter	2,707	
Total minimum lease payments	$3,757	1,033
Less amount representing interest		(76)
Capital lease obligations		$ 957

Insurance and Litigation

We are subject to numerous risks and uncertainties because of the nature and status of our operations, and we are subject to claims and legal actions arising in the normal course of business. We maintain insurance coverage for events and in amounts that we deem appropriate. Management believes that uninsured losses, if any, would not be materially adverse to our financial position or results of operations.

We were previously named as a defendant in a complaint filed by Canji, Inc against Sidney Kimmel Cancer Center (SKCC), ourselves and others. In June 2002, Canji, SKCC and we entered into an agreement to settle all claims to the litigation. As part of the agreement, SKCC agreed to reimburse us for certain costs, and we granted to Canji a limited, non-exclusive sublicense under our license of intellectual property from SKCC. The SKCC intellectual property is not material to our business.

Employment Agreement

We have an employment agreement with our President and Chief Executive Officer that provides for a base salary and bonuses through July 31, 2003.

8. Related Parties

The Chairman of our Board of Directors owns, and another member of our Board of Directors is a former employee of, a company to which we pay consulting fees of approximately $175,000 per year. We are obligated to continue paying this fee until such time as we, at our option, terminate the services of that company. As of December 31, 2002, these two individuals held options to purchase 416,000 shares of our common stock.

We have a consulting agreement with an individual primarily responsible for the creation of the technology upon which ADVEXIN gene therapy is based, who is also a stockholder. Under this consulting

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INTROGEN THERAPEUTICS, INC. AND SUBSIDIARIES

NOTES TO CONSOLIDATED FINANCIAL STATEMENTS (Continued)

agreement, we paid this individual fees of $150,000 and $150,000 during the years ended June 30, 2000 and 2001, respectively, $75,000 and $78,750 during the six months ended December 31, 2000 and 2001, respectively, and $171,000 during the year ended December 31, 2002. This consulting agreement provides for payments of $181,500 per annum until September 30, 2003, and $200,000 per annum thereafter 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.

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. This lease began in February 2001, after which time rental income related to this lease is included in other revenue. Rental income was $354,000 for the year ended June 30, 2001, $515,000 for the six months ended December 31, 2001 and $1,104,000 for the year ended December 31, 2002.

In 2002, we entered into an agreement with Aventis Pharmaceuticals Products, Inc. (APP) under which APP provides funding for a Phase 2 clinical trial for breast cancer conducted under our supervision. APP may fund up to $795,000 for this trial of which we received $197,000 through December 31, 2002. Amounts received under this agreement are recorded as deferred revenue until the related expenses are incurred. APP is an affiliate of Aventis, one of our stockholders.

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EXHIBIT INDEX

Exhibit Number	Description of Document
23.1	Consent of Ernst & Young LLP, independent auditors
23.2	Information Regarding Consent of Arthur Andersen LLP
24.1	Power of Attorney (See page 52)
99.1	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