INTROGEN THERAPEUTICS INC
Form 10-K
March 15, 2005

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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, 2004

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 þ No o

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 $77.1 million based upon the last sale price reported on the Nasdaq National Market for June 30, 2004. 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 11, 2005, the Registrant had 30,750,321 shares of common stock, $0.001 par value, issued and outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Certain information required by Items 10, 11, 12, 13 and 14 of Form 10-K is incorporated by reference to the Registrant s proxy statement (2005 Proxy Statement) for the 2005 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, 2004.

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 Risk Factors in Management s Discussion and Analysis of Financial Condition and Results of Operations and elsewhere in, or incorporated by reference into, this Annual Report on Form 10-K.

Access to Company Information

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

Our Corporate Governance Standards, the charters of our Audit Committee, our Compensation Committee and our Nominating and Corporate Governance Committee, as well as our Corporate Code of Ethics for All Employees and Directors and our Corporate Code of Ethics for Financial Officers (which specifically applies to the Company s Chief Executive Officer, Chief Financial Officer and persons performing similar functions) are available on our website at *www.introgen.com* under Investor Relations Corporate Governance.

Overview

Introgen Therapeutics, Inc. was incorporated in Delaware in 1993. We are a biopharmaceutical company focused on the discovery, development and commercialization of targeted therapies for the treatment of cancer and other diseases. We are developing product candidates to treat a wide range of cancers using non-integrating tumor suppressors, cytokines and molecular gene agents. These agents are designed to increase production of normal cancer-fighting proteins that act to overpower cancerous cells, stimulate immune activity and enhance conventional cancer therapies.

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

We believe the use of genes that do not integrate into the patient s genome and that are cleared from the body after administration in order to induce the production of biopharmaceutical proteins is an emerging field presenting 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 we are able to treat a number of cancers in a way that kills cancer cells without harming normal cells.

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Our lead product candidate, ADVEXIN® therapy, combines the p53 gene with a non-replicating, non-integrating adenoviral gene delivery system we have developed and extensively tested. The p53 gene is one of the most potent members of a group of naturally-occurring tumor suppressor genes, which act to kill cancer cells, arrest cancer cell growth and protect cells from becoming cancerous.

We have received Fast Track designation for ADVEXIN therapy from the U.S. Food and Drug Administration (FDA) under its Protocol Assessment program as a result of the FDA s agreement with the design of our two ongoing Phase 3 clinical trials of ADVEXIN therapy. Under this Fast Track designation, the FDA will take actions to expedite the evaluation and review of a Biologic License Application (BLA) for ADVEXIN therapy. We plan to pursue with the FDA an Accelerated Approval of ADVEXIN therapy, which is one alternative provided under a Fast Track designation. These processes are discussed in more detail in the section below entitled Fast Track Products.

We have conducted a series of meetings with the FDA to develop and implement the filing strategy for the BLA for ADVEXIN therapy, which is the application for approval to market and sell ADVEXIN therapy in the United States. As a result of these meetings, we are developing and pursuing an initial rolling BLA filing strategy based primarily on data from our Phase 2 clinical trials of ADVEXIN therapy for treatment of recurrent squamous cell cancer of the head and neck. The FDA has concurred that preliminary evaluation of this data suggests a level of efficacy consistent with the standard for the initiation of a rolling BLA (a submission process also known as Submission Of a Partial Application or SOPA). The FDA has also concluded that ADVEXIN therapy continued to show promise with respect to an unmet medical need since there are no approved therapies in the United States for recurrent head and neck cancer. The FDA has also concluded that the clinical development program for ADVEXIN therapy for recurrent head and neck cancer continued to meet the criteria for Fast Track designation. In conjunction with the new data, the new analyses, and other newly employed biological techniques, Introgen is hopeful of more specifically targeting patients with recurrent head and neck cancer resulting in even better efficacy than has already been demonstrated.

Accordingly, we have submitted a SOPA request to the FDA Division of Cell and Gene Therapy proposing a rolling BLA for ADVEXIN therapy for the treatment of recurrent head and neck cancer, based primarily on data from our Phase 2 clinical trials. We have further proposed to the FDA that, since the basis of the proposed rolling BLA is Phase 2 clinical data utilizing surrogate endpoints, the rolling BLA be evaluated under the provisions of Subpart H for Accelerated Approval. In order to fully explore all of the review and approval possibilities for ADVEXIN therapy, the FDA has requested we submit existing new data and analyses from the Phase 2 ADVEXIN therapy clinical trials for recurrent head and neck cancer. Given that we have two ongoing Phase 3 clinical trials in head and neck cancer as discussed further below, we and the FDA are evaluating the most effective use of the data from these Phase 2 and 3 clinical trials in the review and approval of ADVEXIN therapy. Regulatory approval approaches may allow Accelerated Approval on the basis of Phase 2 clinical data with subsequent confirmatory data being provided by the Phase 3 clinical studies or, alternatively, a full approval based on data from Phase 2 and certain Phase 3 clinical trials. We will also be exploring with the FDA whether its recently announced Critical Path Initiative, which permits new product evaluation on the basis of specifically targeted (i.e. by prognostic or biologic parameters) clinical trials and/or patient populations, can be used in the ADVEXIN therapy approval process.

ADVEXIN therapy for head and neck cancer has been designated an Orphan Drug under the Orphan Drug Act. This designation may give us up to seven years of marketing exclusivity for ADVEXIN therapy for this indication if approved by the FDA. The Orphan Drug Act is discussed in more detail in the section below entitled Orphan Drug Act.

Our two ongoing Phase 3 clinical trials of ADVEXIN therapy in patients with recurrent squamous cell cancer of the head and neck are multi-national, multi-site trials. These trials involve administration of ADVEXIN therapy, both by itself and in combination with chemotherapy, in recurrent squamous cell cancer of the head and neck.

We have conducted multi-national, multi-site Phase 2 clinical trials of ADVEXIN therapy in 217 patients with recurrent squamous cell cancer of the head and neck treated previously with surgery, radiation or chemotherapy. In the combined analysis of these trials, the overall tumor growth control rate was 59%. Tumor

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growth control rate represents the percentage of treated tumors where there was disappearance of the tumor, shrinkage of the tumor or the absence of additional tumor growth beyond 25% of pre-treatment measurements. In 10% of the treated lesions, there was either complete tumor regression or a reduction of tumor size greater than or equal to 50% of the pre-treatment size. A subpopulation of patients participating in one of these trials had certain defining prognostic, medical and biological characteristics that represent refined targeting of ADVEXIN therapy. Analysis of the data from this patient subpopulation showed that tumor growth control (defined by confirmed complete responses, partial responses with greater than 50% tumor reduction, or stable disease) was observed in 41% of these patients. The confirmed objective response rate (complete responses and partial responses) was 15%. Patients achieving disease control also showed clinical benefit reflected by either lack of progression and/or improvement in disease related morbidity. Median survival of the sub-population was 13.5 months for the patients who achieved tumor growth control and 31.4 months for patients who achieved an objective response. These findings, along with other data, are planned for presentation at future scientific meetings and for future publication in a peer-reviewed medical journal.

We have completed or are currently conducting numerous Phase 1 and Phase 2 clinical trials of ADVEXIN therapy by itself and in combination with chemotherapy or radiation therapy in a variety of cancers. These clinical trials include:

A Phase 2 clinical trial of ADVEXIN therapy combined with systemic chemotherapy for the treatment of breast cancer prior to surgery and a Phase 1 clinical trial using ADVEXIN therapy in patients with locally recurrent breast cancer involving the chest wall;

A Phase 2 clinical trial of ADVEXIN therapy in squamous cell carcinoma of the oral cavity, or oropharynx, that can be removed surgically, to assess the feasibility, efficacy and safety of administering ADVEXIN therapy at the time of surgery for suppression of remaining tumor cells, followed by a combination of chemotherapy and radiation therapy;

A Phase 2 clinical trial of ADVEXIN therapy administered as a complement to radiation therapy in non-small cell lung cancer;

A Phase 1/early Phase 2 clinical trial of ADVEXIN therapy for the treatment of advanced, unresectable squamous cell esophageal cancer;

A Phase 1/early Phase 2 clinical trial in which a mouthwash or oral rinse formulation of ADVEXIN therapy, which has been designated as INGN 234, is administered to prevent precancerous oral lesions from developing into cancerous lesions;

A Phase 1 clinical trial of ADVEXIN therapy in prostate cancer; and

A Phase 1 clinical trial of ADVEXIN therapy in bronchoalveolar cancer.

To date, clinical investigators at sites in North America, Europe and Japan have treated over 500 patients with ADVEXIN therapy, establishing a large safety database. Findings from several of our clinical trials have been published in *Clinical Cancer Research*, *Proceedings of the American Society for Clinical Oncology* as well as presented at numerous conferences, including the San Antonio Breast Cancer Conference in December 2004 and various meetings of the American Society of Clinical Oncology.

A growing body of data suggests ADVEXIN therapy demonstrates clinical activity in a variety of cancer indications. Safety data from our clinical trials suggests this activity may be achieved without the treatment-limiting side effects frequently associated with many other cancer therapies.

Our clinical trials indicate ADVEXIN therapy is well tolerated as a monotherapy. The addition of ADVEXIN therapy to standard chemotherapy or radiation does not appear to increase the frequency or severity of side effects normally associated with these treatment regimens.

Recent pre-clinical studies provide new insight into the molecular pathways by which the p53 gene, the active component of ADVEXIN therapy, kills tumor cells. These pre-clinical studies were undertaken to provide additional molecular data supporting the activity observed during the clinical development of

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ADVEXIN therapy and to provide additional information regarding the specific pathways that mediate the observed clinical effects of ADVEXIN therapy. The studies were conducted by our collaborators at Okayama University in Japan and at The University of Texas M. D. Anderson Cancer Center and were published in a 2004 issue of *Molecular Cancer Therapeutics.* Other pre-clinical data suggest the enhanced therapeutic effects of a combination of ADVEXIN and Erbitux® therapies in an animal model of human non-small cell lung cancer. Other pre-clinical studies conducted by our collaborators at Wayne State University, the Karmanos Cancer Institute located in Detroit, Michigan and the University of California-Irvine, as published in a 2004 issue of *The Laryngoscope*, show that the combination of ADVEXIN therapy and docetaxel resulted in increased levels of programmed cell death in head and neck tumor cells. Two patients, who were part of our ADVEXIN therapy studies program and who had recently celebrated their five-year survival anniversary, were recently featured in *Conquest* magazine, a publication of M. D. Anderson Cancer Center.

We hold the worldwide rights for pre-clinical and clinical development, manufacturing, marketing and commercialization of ADVEXIN therapy.

Certain other key product candidates we are developing, which are described in greater detail below under Product Development Programs include:

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

INGN 225 uses the p53 tumor suppressor gene as the basis for a highly specific therapeutic cancer vaccine that stimulates a particular type of immune system cell known as a dendritic cell. Findings during pre-clinical testing suggest a vaccine consisting of dendritic cells stimulated by ADVEXIN therapy could have broad utility as a treatment for progression of solid tumors. Introgen academic collaborators are conducting Phase 1 and early stage Phase 2 clinical trials to study INGN 225 small cell lung cancer and breast cancer. Certain patients initially unresponsive to chemotherapy will be re-treated with chemotherapy to study the effect that INGN 225 therapy may have.

INGN 234 for the prevention of oral cancers and the treatment of oral leukoplakia. We are conducting a Phase 1/early Phase 2 clinical trial in which p53 is being administered in an oral mouthwash formulation to prevent precancerous oral lesions from developing into cancerous lesions. We are conducting pre-clinical work on other topical administrations of tumor suppressor genes to control or prevent oral or dermal cancers. We are investigating multiple delivery platforms, including both viral and non-viral approaches. We are also investigating combining gene delivery with rinses, patches, ointments and enhancing polymers. We believe the opportunity exists to develop non-toxic treatments for pre-malignant and malignant cells that can be easily exposed to natural biological tumor suppressor and DNA repairing genes.

INGN 401, our systemically-delivered nanoparticle tumor suppressor therapy that uses the FUS-1 gene, a gene frequently altered or missing in the development of many solid tumors. Pre-clinical studies have shown gene delivery of FUS-1 significantly inhibits the growth of tumors and greatly reduces metastatic spread of lung cancer in animals when delivered to tumor cells via either an adenoviral or non-viral delivery system. INGN 401 is being studied in a Phase1/2 clinical trial for end-stage, non-small cell lung cancer patients.

INGN 402 describes a systemic, nanoparticle formulation containing the p53 tumor suppressor gene and INGN 403 describes a systemic, nanoparticle formulation containing the mda-7 tumor suppressor gene, also known as interleukin 24. Early studies with these new nanoparticle drugs have demonstrated a good safety profile and promising anti-cancer activity in murine lung tumor models. Data from the mda-7 nanoparticle studies was recently published in *DNA and Cell Biology*.

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INGN 007, a replication-competent viral therapy that over-expresses an adenoviral gene and thereby causes rapid disruption of tumor cells in which the adenovirus replicates. Pre-clinical testing indicates INGN 007 can eradicate human tumors in animal models.

Our principal executive offices are located at 301 Congress Avenue, Suite 1850, Austin, Texas 78701. Our telephone number is (512) 708-9310. Our website is located at www.introgen.com.

Background

Gene Function and Genomics

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

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

Molecular Cancer Therapies Using Tumor Suppressors and Gene and Gene-Induced Protein Therapy Products

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

Our gene-based products function differently from this model. Instead of replacing or repairing genes, our products use the proteins expressed by certain genes as therapeutic agents to selectively kill cancer cells while not harming normal cells. Under this approach, the genes expressing the therapeutic proteins do not integrate into the patient s DNA and are cleared from the body after administration. The result is pharmacologic intervention using the proteins produced by genes, such as p53 and mda-7, to create biopharmaceuticals with targeted, drug-like functionality. In some cases, the therapeutic protein expressed by the gene will simply act to replace a missing or dysfunctional protein or to augment the level of a protein that is otherwise inadequate to prevent disease or ameliorate an existing disease or dysfunction. In other cases, the therapeutic protein produced by the gene will act to eliminate the diseased cells through a process that scientists refer to as apoptosis. Apoptosis, or programmed cell death, is a normal process that the body uses to eliminate damaged cells and cells that are no longer necessary. In some circumstances, genes such as mda-7 send a signal for further proteins to be produced in cells beyond those in which the gene was initially expressed. This process is referred to as cytokine activity, which potentially results in an increased number of diseased tissue cells being affected by gene-based therapy. The genes used to provide the protein for disease treatment are typically normal human genes that are either being silenced in the disease tissue or are otherwise being expressed at too

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low a level to achieve the desired pharmacologic effect. Diseases like cancer occur by altering the function and expression of many genes that would otherwise act to protect the body.

In order to perform these processes, a gene for disease treatment, or therapeutic gene, is often combined with a delivery system, referred to as a vector, which enables the gene to enter the target cell and express the therapeutic protein it produces. The vector must be able to deliver a sufficient dose of the genes and the proteins they produce to cause a therapeutic effect. The most common delivery systems currently in use are modified versions of viruses such as adenoviruses. Scientists often use viruses as delivery systems because viruses have the ability to efficiently infect cells and carry their genetic material, or genome, into the cells. Scientists can modify these viruses by deleting pieces of the viral genome that are necessary for viral reproduction and replacing the deleted pieces with an additional gene which can cause the manufacture of a desired therapeutic protein. The resulting viral vector retains the ability of the virus to efficiently deliver the additional gene into cells, while losing the ability to reproduce itself and spread to other cells.

Many gene delivery systems in use today are based on adenoviral vectors. Scientists create adenoviral vectors using adenoviruses, which are among several common cold viruses. These vectors have been modified so that their ability to reproduce and spread in a human host is inhibited. 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.

While viruses are the most efficient means of introducing such genes into cells, scientists have also developed synthetic substances such as nanoparticles, which are nanoscale structures that have no viral components. These synthetic or nanoparticle systems can also deliver genetic material to host cells through systemic administration. Scientists have developed these systems to mimic the characteristics of viral vector systems in order to expand the disease targets that can be treated with genes and their resulting proteins.

Cancer, a Genetic Disease

Cancer is a leading cause of death in the United States. In the United States, approximately 1.4 million people are newly diagnosed with cancer and over 570,000 people die from the disease each year. Although the prevalence of specific cancers varies among different populations, we believe that the overall incidence of cancer worldwide is similar to that experienced in the United States. The American Cancer Society estimates the annual direct cost of treating cancer patients in the United States is approximately $69.4 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 suitable initial applications for gene-induced protein therapies, because in contrast to more complex genetic disorders, which may require long-term function of the transferred gene, the treatment for cancer provides those functions that will lead to the destruction of the cancer cell. The introduction of normal tumor suppressor genes and the proteins they produce, such as p53 and mda-7, into cancer cells leads to the destruction of those cancer cells and is a promising approach to treating cancer.

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Tumor Suppressor Genes

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

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

Current Treatment of Cancer

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

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

Given that established cancer therapies often prove to be incomplete, ineffective or toxic to the patient, there is a need for additional new treatment modalities that either complement established therapies or replace them by offering better therapeutic outcomes. For example, in a limited number of cancers, immunotherapy, which seeks to stimulate a patient s own immune system to kill cancer cells, has rapidly become widely accepted by improving on the shortcomings of existing therapy. However, for a broad range of cancers, additional approaches, especially more specific ones that target specific dysfunctional pathways in the cancer cell, are needed to reduce the toxicity and improve upon marginal benefits common to current cancer treatments. Gene-induced protein therapy applications are designed to address the cellular dysfunction that causes cancer, compared with small molecule drugs or immunotherapeutic agents, which may act indirectly.

The Introgen Approach

Our primary approach for the treatment of cancers is to deliver genes that increase production of normal cancer-fighting proteins. Rather than acting to repair or replace aberrant or missing genes and thereby creating

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a long-term or permanent change to the patient s genome, our products work in a different manner by acting as templates for the transient *in vivo* production of proteins that have pharmacologic properties. The resultant proteins engage disease-related molecular targets or receptors to produce a specific therapeutic effect.

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

Because most cancers are amenable to local treatment and because local cancer treatments are administered far more often than systemic cancer treatments, our locally delivered product candidates, such as ADVEXIN therapy, deposit therapeutic genes directly into a patient s cancerous tumor by hypodermic syringe. In those cases for which a systemic therapy may be indicated, we use a systemically administered nanoparticle formulation system to deliver tumor suppressors and genes.

We have initially focused on advanced cancers that lack effective treatments and in which local tumor growth control, where the tumor stops growing or shrinks, is likely to lead to measurable benefit. We believe our clinical trials have shown that our gene-induced protein therapies can be used alone and in combination with conventional treatments such as surgery, radiation therapy and chemotherapy.

The Introgen Strategy

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

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

Develop Our Portfolio of Gene-Induced Protein Therapy and Other Drug Products. Utilizing our significant research, clinical, regulatory and manufacturing expertise, we are evaluating development of additional gene-induced protein therapies for various cancers, such as INGN 225, a highly specific therapeutic cancer vaccine, INGN 234 , an oral rinse or mouthwash formulation containing the p53 tumor suppressor, INGN 401 using the FUS-1 gene and INGN 007, a replication-competent viral therapy. We have established an efficient process for evaluating new drug candidates and advancing them from pre-clinical to clinical development. We have identified and licensed multiple technologies, which we intend to combine with our adenoviral and non-viral vector systems and which we believe are attractive development targets for the treatment of various cancers. We are also evaluating the development of mebendazole (INGN 601), our first small molecule product candidate. We intend to evaluate additional opportunities to in-license or acquire new technologies.

Develop a Nanoparticle Systemic Administration Platform. Early studies with these new nanoparticle drugs have demonstrated a good safety profile and promising anti-cancer activity. We incorporate the p53 tumor suppressor and the mda-7 gene in these nanoparticle formulations.

Develop the Topical Use of Tumor Suppressors. We plan to continue developing topical product candidates for the treatment or prevention of oral and dermal cancers. We believe these treatments are a logical extension of our loco-regional delivery of cancer therapies and represent attractive product candidates since pre-malignant and malignant cells can be exposed to natural, biological tumor suppressors and DNA repairing agents.

Establish Targeted Sales and Marketing Capabilities. The oncology market can be effectively addressed by a small, focused sales force because it is characterized by a concentration of specialists in

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relatively few major cancer centers. We believe we can address this market by a combination of building a direct sales force as part of the ADVEXIN therapy commercialization process and pursuing marketing and distribution agreements with corporate partners for ADVEXIN therapy as well as additional products.

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

Product Development Programs

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

Product (Gene)**	Cancer Indication	Development Status
ADVEXIN Therapy (p53)	Head and Neck (both monotherapy and combined with chemotherapy)	Phase 3
	Non-Small Cell Lung (combined with XRT)	Phase 2 completed
	Breast (combined with chemotherapy)	Phase 1-2 completed
	Perioperative (and surgery)	Phase 1-2
	Esophageal	Phase 1-2
	Prostate	Phase 1 completed*
	Intravenous Administration	Phase 1 completed*
	Ovarian	Phase 1 completed*
	Bladder	Phase 1 completed*
	Bronchoalveolar	Phase 1 completed*
	Brain (glioblastoma)	Phase 1 completed*
	Rheumatoid Arthritis	Pre-clinical
INGN 225 (p53 vaccine)	Small Cell Lung	Phase 1-2
	Breast	Phase 1-2
INGN 234 (p53 topical)	Oral Cancer Prevention (mouthwash)	Phase 1-2*
INGN 241 (mda-7)	Various (solid tumors)	Phase 1-2 completed
	Melanoma	Phase 1-2
	Pancreatic	Pre-clinical
	Breast	Pre-clinical
INGN 401 (FUS-1 program)	Lung	Phase 1
INGN 402 nanoparticle formulation (p53)	Various cancers	Pre-clinical
INGN 403 nanoparticle formulation (mda-7)	Various cancers	Pre-clinical
INGN 007 (Replication-Competent viral therapy)	Various (solid tumors)	Pre-clinical

* Conducted in conjunction with the National Cancer Institute.

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

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Indications for ADVEXIN® Therapy (p53)

ADVEXIN therapy combines the p53 gene with an adenoviral vector for delivery in order to introduce the therapeutic p53 protein or gene to the cancer cell. The p53 gene works through multiple mechanisms of action including apoptosis, or programmed cell death, inhibition of cancer cell growth, and reducing the blood supply to tumors through a process known as anti-angiogenesis. Molecular pathways normally controlled by the p53 gene are abnormal in the vast majority of cancers. Patients may receive multiple doses of ADVEXIN therapy, and some patients have received ongoing ADVEXIN treatments for several years. Physicians typically inject ADVEXIN therapy directly into the tumor. The importance of the protein produced by the p53 gene in controlling tumor growth suggests that ADVEXIN therapy is applicable to multiple cancers. Our initial development strategy for ADVEXIN therapy is to obtain approval for cancer indications, such as head and neck and lung cancer, which have near-term clinical endpoints and where current treatment is inadequate.

Head and Neck Cancer

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

We are developing ADVEXIN therapy as a treatment for squamous cell cancer of the head and neck. Based on clinical results from our Phase 1 and Phase 2 clinical trials, we are conducting two multi-national, multi-site Phase 3 clinical trials, which we refer to as our 301 and 302 trials.

We have received Fast Track designation for ADVEXIN therapy from the FDA under its Protocol Assessment program as a result of the FDA s agreement with the design of our two ongoing Phase 3 clinical trials of ADVEXIN therapy. Under this Fast Track designation, the FDA will take actions to expedite the evaluation and review of the BLA for ADVEXIN therapy. We plan to pursue with the FDA an Accelerated Approval of ADVEXIN therapy, which is one alternative provided under a Fast Track designation. These processes are discussed in more detail in the section below entitled Fast Track Products.

We have conducted a series of meetings with the FDA to develop and implement the filing strategy for the ADVEXIN therapy BLA. As a result of these meetings, we are developing and pursuing an initial rolling BLA filing strategy based primarily on data from our Phase 2 clinical trials of ADVEXIN therapy for treatment of recurrent squamous cell cancer of the head and neck. The FDA has concurred that preliminary evaluation of this data suggests a level of efficacy consistent with the standard for the initiation of a rolling BLA (a submission process also known as Submission Of a Partial Application or SOPA). The FDA has also concluded that ADVEXIN therapy continued to show promise with respect to an unmet medical need since there are no approved therapies in the United States for recurrent head and neck cancer. The FDA has also concluded that the clinical development program for ADVEXIN therapy for recurrent head and neck cancer continued to meet the criteria for Fast Track designation. In conjunction with the new data, the new analyses, and other newly employed biological techniques, Introgen is hopeful of more specifically targeting patients with recurrent head and neck cancer resulting in even better efficacy than has already been demonstrated.

Accordingly, we have submitted a SOPA request to the FDA Division of Cell and Gene Therapy proposing a rolling BLA for ADVEXIN therapy for the treatment of recurrent head and neck cancer, based primarily on data from our Phase 2 clinical trials. We have further proposed to the FDA that, since the basis of the proposed rolling BLA is Phase 2 clinical data utilizing surrogate endpoints, the rolling BLA be evaluated under the provisions of Subpart H for Accelerated Approval. In order to fully explore all of the review and

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approval possibilities for ADVEXIN therapy, the FDA has requested we submit existing new data and analyses from the Phase 2 ADVEXIN therapy clinical trials for recurrent head and neck cancer. Given that we have two ongoing Phase 3 clinical trials in head and neck cancer as discussed further below, we and the FDA are evaluating the most effective use of the data from these Phase 2 and 3 clinical trials in the review and approval of ADVEXIN therapy. Regulatory approval approaches may allow Accelerated Approval on the basis of Phase 2 data with subsequent confirmatory data being provided by the Phase 3 clinical studies or, alternatively, a Full Approval based on data from Phase 2 and certain Phase 3 clinical trials. We will also be exploring with the FDA whether its recently announced Critical Path Initiative, which permits new product evaluation on the basis of specifically targeted (i.e. by prognostic or biologic parameters) clinical trials and/or patient populations, can be used in the ADVEXIN therapy approval process.

Clinical trial 301 is a Phase 3 clinical trial that compares the efficacy of ADVEXIN therapy to a standard chemotherapy treatment in patients with recurrent squamous cell cancer of the head and neck in whom standard treatment of surgery, radiation therapy and the more commonly used chemotherapies have not been curative. As a result, these patients are typically referred to as refractory patients. Clinical trial 301 is planned to enroll approximately 240 patients with recurrent, non-resectable, refractory disease. Patients in the control group receive weekly treatments of methotrexate, a standard chemotherapy treatment for this condition, while patients in the treatment group receive twice weekly intratumoral injections of ADVEXIN therapy. The clinical trial s primary endpoint is survival.

Clinical trial 302 is a Phase 3 clinical trial that compares the efficacy of ADVEXIN therapy when it is used in combination with a standard chemotherapy treatment to that of standard chemotherapy treatment used alone in patients with recurrent disease. Clinical trial 302 is planned to enroll approximately 255 patients with recurrent, non-resectable squamous cell head and neck cancer. Patients in the control group receive the chemotherapy drugs cisplatin and 5-fluorouracil, while the patients in the treatment group receive the same drugs plus intratumoral ADVEXIN therapy. Each treatment is repeated every four weeks, which is a standard interval for chemotherapy. The clinical trial s primary endpoint is time to progression of the treated lesions as measured by a patient s tumor growth beyond the patient s baseline, or tumor size at the beginning of the trial. Survival is the secondary endpoint. The 301 and 302 clinical trials are designed to be complementary, with the primary endpoint in each serving as a secondary endpoint, or result that we will evaluate secondarily, in the other. Both of these studies are randomized, and are being conducted at numerous cancer centers in the United States, Canada and Europe.

ADVEXIN therapy was previously studied in three independent, multi-national, multi-site Phase 2 clinical trials of ADVEXIN therapy in 217 patients with recurrent squamous cell head and neck cancers. Starting in 2001 with the restructuring of our collaboration with Aventis Pharmaceuticals Products, Inc., (Aventis), we began collecting and analyzing clinical data from the three Phase 2 clinical trials conducted by Aventis. We and Aventis previously reported interim findings by Aventis from two of those Phase 2 clinical trials comprising approximately 112 patients. Additional Phase 2 clinical trial data from over 100 patients had not been previously included in a combined analysis of the ADVEXIN therapy Phase 2 clinical trials for head and neck cancer. The case report forms and data from all three, independent, multi-institutional and multi-national studies were collected by us during the past several years and have provided us with the opportunity to closely examine the clinical trial information. We obtained independent confirmation of the Aventis Phase 2 clinical trial response data. In addition, we have obtained and are continuing to obtain expert analysis from statistical, clinical, regulatory and oncology specialists.

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

In the combined analysis of the three multi-national, multi-site Phase 2 clinical trials, the overall tumor growth control rate was 59%. Tumor growth control rate represents the percentage of treated tumors where there was disappearance of the tumor, shrinkage of the tumor or the absence of additional tumor growth

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beyond 25% of pre-treatment measurements. In 10% of the treated lesions, there was either complete tumor regression or a reduction of tumor size greater than or equal to 50% of the pre-treatment size. A subpopulation of patients participating in this trial had certain defining prognostic, medical and biological characteristics that represent refined targeting of ADVEXIN therapy. Analysis of the data from this patient subpopulation showed that tumor growth control (defined by confirmed complete responses, partial responses with greater than 50% tumor reduction, or stable disease) was observed in 41% of these patients. The confirmed objective response rate (complete responses and partial responses) was 15%. Patients achieving disease control also showed clinical benefit reflected by either lack of progression and/or improvement in disease related morbidity. These clinical findings are consistent with the results of multiple pre-clinical and clinical trials where tumor growth control was observed.

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

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

Non-Small Cell Lung Cancer

Lung cancer is the most common cause of cancer-related death in the United States, with an estimated 173,000 new cases diagnosed annually. An estimated 164,000 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 87% of all lung cancer cases. Surgery can be an effective treatment in the early stages of disease, but only a minority of patients are eligible because early-stage diagnosis is uncommon. Up to 70% of NSC lung cancer patients have disease that is too far advanced for complete surgical resection. The remaining patients typically undergo a combination of surgery, radiation and chemotherapy. This combination treatment is only effective in a small percentage of cases. Clinical data has shown that of patients who have unresectable disease, approximately 80% will again have active cancer cells three months after completing a full course of radiation. Due to the ineffective treatment of NSC lung cancer in many patients, a significant, unmet need for better treatments exists, particularly if it can be combined with existing treatments without increasing the toxicity of those treatments.

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

We conducted an analysis of the 19 patients that the investigators treated and evaluated in the Phase 2 clinical trial of ADVEXIN therapy. This analysis included both radiographs to assess the size of the treated tumor mass and tumor biopsies to assess for living cancer cells within the tumor at the site of treatment. The patients were then followed without further treatment for clinical evidence of disease progression. The results of this analysis established an acceptable safety profile and showed evidence of local tumor growth control and reductions in tumor size. Twelve of the 19 patients that the investigators treated and evaluated, or 63%, had

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radiographic evidence of local tumor growth control, including 12 complete or partial responses of the tumor that the investigators injected. Furthermore, the preliminary analysis showed that nine of these 12 patients had no living tumor cells in the biopsy that the investigator took from the site of the injection. This study was published in the January 2003 issue of *Clinical Cancer Research.*

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

Breast Cancer

Physicians diagnose an estimated 213,000 new cases of breast cancer annually in the United States, and approximately 41,000 people are estimated to die from the disease each year. We conducted a Phase 1-2 trial evaluating ADVEXIN therapy combined with neoadjuvant chemotherapy in women with locally advanced breast cancer. Neoadjuvant treatments are administered prior to surgery and represent a novel and increasingly applied approach to make surgical tumor resections either more complete, thus improving outcomes, or less invasive, thereby facilitating breast conservation. Updated results of this trial were presented at the annual San Antonio Breast Cancer Conference in December 2004. Data from this clinical trial indicated that objective clinical responses (regression resulting in a greater than 50% reduction in tumor size) were seen following the combined therapy in all of the patients. Complete tumor removal by subsequent surgery was achieved in 100 percent of the patients. Activation of a local immune response at the site of the tumor was observed. Treated tumors were infiltrated with cells of the immune system that are known to participate in immune responses against tumors, which may be useful in controlling local disease as well as disease outside the breast. This clinical trial is part of our ADVEXIN therapy development plan, which is to administer ADVEXIN therapy in the setting of primary, multi-modality local therapy of cancer in conjunction with surgery, chemotherapy and radiation therapy. In addition, the National Cancer Institute (NCI) has concluded a Phase 1 clinical trial using ADVEXIN therapy in patients with locally recurrent breast cancer involving the chest wall.

Prostate Cancer

Prostate cancer is one of the most common forms of cancer. Approximately 232,000 new cases occur annually in the United States and approximately 30,000 people are estimated to die from the disease each year. Most prostate cancer patients are treated with either surgery or radiation therapy. Because newer and simpler methods of diagnosis that detect the disease at an earlier stage exist today, a significant number of patients who are diagnosed with prostate cancer before it has metastasized may benefit from local treatment therapies such as ADVEXIN therapy.

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

Other Cancers

There are several other cancer indications for which ADVEXIN therapy is in earlier stages of clinical development. To evaluate the possible use of ADVEXIN therapy in these indications, we collaborate with the NCI under a Cooperative Research and Development Agreement, or CRADA. Under this program the NCI has conducted and is conducting clinical trials with ADVEXIN therapy at leading cancer centers using clinical protocols that we have developed with the NCI. These protocols are designed to demonstrate the safety of ADVEXIN therapy in these indications and by various routes of administration.

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Ovarian Cancer. There are an estimated 22,000 new cases of ovarian cancer and 16,000 deaths attributed to ovarian cancer in the United States each year. Approximately 80% of patients with advanced disease can be treated with simple intraperitoneal administration, that is, administration of gene therapeutic agents into the abdominal cavity. The NCI has conducted a Phase 1 clinical trial of ADVEXIN therapy in this population.

Bladder Cancer. There are an estimated 63,000 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 13,000. The anatomy of the bladder allows delivery of gene therapeutic agents via catheter. The NCI has conducted a Phase 1 clinical trial using ADVEXIN therapy in this indication.

Brain Cancer (Glioblastoma). An estimated 13,000 people die from cancers of the brain and central nervous system in the United States each year. Glioblastoma multiforme, or GBM, is a particularly deadly form of primary brain cancer and represents approximately 55% of all brain cancer cases in the United States. GBM is not effectively treated with conventional therapies because the lesions are deep within the brain, are often large and grow rapidly. The NCI has conducted a Phase 1 clinical trial using ADVEXIN therapy in recurrent GBM.

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

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

Pre-Cancerous Conditions

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

Indications for INGN 241 (mda-7)

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

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

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

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

Findings and results arising from our development of INGN 241 have been recently published in *Molecular Therapy, Oncogene, Surgery* and *International Immunopharmacolgy.*

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

Indications for INGN 225 (p53 vaccine)

As a supplement to our gene-induced therapeutic protein programs, we are developing INGN 225 using the p53 gene to create a highly specific therapeutic cancer vaccine that stimulates a particular type of immune system cell known as a dendritic cell. Research published in *Current Opinion in Drug Discovery & Development* concluded that ADVEXIN therapy can be used with a patient s isolated dendritic cells as an antigen delivery and immune enhancing therapeutic strategy. Pre-clinical testing has shown that the immune system can recognize and kill tumors after treatment with dendritic cells stimulated by the p53 gene, which suggests a vaccine consisting of dendritic cells stimulated by the p53 gene could have broad utility as a treatment for progression of solid tumors. We are conducting a Phase 1/ Phase 2 trial, performed in collaboration with the University of South Florida and the Moffitt Cancer Center, in patients with small-cell lung cancer and a Phase 1/ Phase 2 trial in patients with breast cancer in collaboration with the University of Nebraska. In both trials, INGN 225 is administered after the patients have been treated with standard chemotherapy.

Indications for INGN 401 (FUS-1)

INGN 401 uses a nanoparticle vector system to deliver the tumor suppressor gene FUS-1, which we exclusively license from M. D. Anderson Cancer Center. Pre-clinical studies have shown that FUS-1, delivered using an adenoviral or a non-viral delivery system through either intravenous (systemic) administration or direct intratumoral injection, significantly inhibits the growth of tumors and greatly reduces the metastatic spread of lung cancer in animals. A Phase 1 clinical trial is ongoing at M. D. Anderson Cancer Center testing INGN 401 in patients with advanced non-small cell lung cancer who have previously been treated with chemotherapy. Data and findings from our work to develop INGN 401 have been recently published in *Cancer Gene Therapy* and *Cancer Research.*

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Research and Development Programs

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

We are evaluating additional genes, including BAK, which hold promise as therapeutic candidates. BAK is a pro-apoptotic gene that kills cancer cells. We are working with our collaborators at M. D. Anderson Cancer Center to identify and develop both viral and non-viral vectors containing this gene. We had exclusive rights to use the BAK gene under a license with LXR Biotechnology, Inc., the rights of which were subsequently sold to Tanox, Inc.

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

We are conducting pre-clinical and clinical work on topical administrations of tumor suppressor genes to control or prevent oral and dermal cancers. We are considering multiple delivery platforms, including both viral and non-viral approaches. We are evaluating combining tumor suppressors with rinses, patches, ointments and polymers. We believe the opportunity exists to develop non-toxic treatments for pre-malignant and malignant epithelial and dermal cells that can be easily exposed to natural biological tumor suppressor and DNA repairing agents.

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

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

Introgen Enabling Technologies

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

Viral Delivery Systems

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

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Nanoparticle Systemic Delivery Platform

We have in-licensed and are developing a non-viral, nanoparticle delivery platform as a complementary delivery technology for certain types of cancers, or clinical indications, particularly those that require systemic administration. We are currently using this technology in INGN 401 to deliver the FUS-1 gene in a Phase 1 clinical trial in collaboration with M. D. Anderson Cancer Center.

Based upon results in preclinical studies and in clinical studies using the INGN 401 nanoparticle system, we have expanded this program to study two additional tumor suppressors in our portfolio. INGN 402 utilizes the p53 tumor suppressor and INGN 403 utilizes the mda-7 gene, both in a nanoparticle formulation. Early studies with these new nanoparticle systems have demonstrated a good safety profile and promising anti-cancer activity in murine lung tumor models. Data from the mda-7 nanoparticle studies was recently published in *DNA and Cell Biology.*

Replication Competent Viral Delivery Systems

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

Additional Enabling Technologies

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

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

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 apoptotic gene to kill producer cells during production. This system could facilitate higher volume production of pro-apoptotic agents.

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

Manufacturing and Process Development

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

We own and operate a state-of-the-art, validated manufacturing facility we believe complies with the FDA s current Good Manufacturing Practices requirements, commonly known as CGMP requirements. We produce ADVEXIN therapy in this facility for use in our Phase 1, 2 and 3 clinical trials. The design and processes of this facility have been reviewed with the FDA. The validation of our manufacturing processes is ongoing. We plan to use this facility for our market launch of ADVEXIN therapy. To date, we have produced over 20 batches of ADVEXIN therapy clinical material, including all clinical material used in the Phase 2 and Phase 3 clinical trials for this product candidate.

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We recently completed construction of a separate facility for continued production of investigative materials for use in clinical trials. This new facility allows us to produce INGN 241 and other product candidates in an environment separate from that used for production of ADVEXIN therapy.

Business and Collaborative Arrangements

VirRx, Inc.

We are working with VirRx to investigate other vector technologies, specifically replication-competent viral therapies, for delivering gene-based products into targeted cells. These technologies form the basis for our INGN 007 product candidate.

We have an agreement with VirRx, which began in 2002, to purchase shares of VirRx s Series A Preferred Stock. From inception of this agreement through December 31, 2004, and during the year ended December 31, 2004, we have purchased $1,725,000 and $600,000, respectively, of this stock for cash. These purchases are 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 VirRx and us for the development of VirRx s technologies. We may unilaterally terminate this collaboration and license agreement with 90 days prior notice, which would also terminate the requirement for us to make any additional stock purchases.

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

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

We entered into a license agreement with The Board of Regents of the University of Texas System and M. D. Anderson Cancer Center in 1994. The license agreement terminates on July 20, 2009 (if no patent rights are applicable) or upon the last to expire of the relevant patents. The agreement is also terminable upon our insolvency, either party s breach or upon our notice on a patent-by-patent basis. The technologies we have licensed from M. D. Anderson Cancer Center, under the exclusive license agreement, relate to p53 and the 3p21.3 family of genes. Under the agreement, we have agreed to pay M. D. Anderson Cancer Center royalties

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on sales of products utilizing these technologies. We are obligated to reimburse any of M. D. Anderson Cancer Center s costs that may be incurred in connection with obtaining patents related to the licensed technologies. Our strategy for product development is designed to take advantage of the significant multidisciplinary resources available at M. D. Anderson Cancer Center. These efforts have resulted in our becoming a significant corporate sponsor of activities at M. D. Anderson Cancer Center in recent years and have yielded to us exclusive patent and licensing rights to numerous technologies.

National Cancer Institute

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

Corixa Corporation

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

The University of South Florida and the Moffitt Cancer Center

We are collaborating with the H. Lee Moffitt Cancer Center and Research Institute to advance our INGN 225 therapeutic cancer vaccine program. Moffitt Cancer Center has conducted pre-clinical research with us, and they are currently treating patients in the ongoing INGN 225 clinical study. We are designing additional studies in collaboration with Moffitt Cancer Center personnel to continue clinical research in the dendritic cell vaccine field.

Research and Development Expense

Our research and development expenses were $20.5 million, $15.0 million and $21.5 million for the years ended December 31, 2004, 2003 and 2002, respectively.

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. As regulatory approval of one or more of our product candidates for commercial sale approaches, we will address the methods of sales and marketing available to us. We will continue to evaluate the merits of building our own direct sales force, pursuing marketing and distribution arrangements with corporate partners or some combination of both.

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Patents and Intellectual Property

Our Portfolio

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

We currently own or have an exclusive license to a large number of issued and pending United States and foreign patents and patent applications. If we do not seek a patent term extension, the currently issued United States patents that we own or have exclusively licensed will expire between the years 2010 and 2021. The exclusive licenses that give us rights on the patents, and applications that such licenses cover, will expire no earlier than the life of any patent covered under the license.

Adenoviral p53 Compositions and Therapies

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

Combination Therapy with the p53 Gene

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

Adenovirus Production, Purification and Formulation

Another focus of our research has involved the development of procedures for the commercial scale production of our potential adenoviral-based products, including that of ADVEXIN therapy. In this regard, we own three issued United States patents as well as a number of pending United States applications, and corresponding international applications, directed to highly purified adenoviral compositions, commercial scale

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

Other Tumor Suppressor Genes

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

Other Therapeutic, Composition and Process Technologies

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

Benzimidazole Small Molecule Cancer Therapy Program

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

Trade Secrets

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

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

Government Regulation

The Drug Approval Process

Prescription pharmaceutical products and biologics are subject to extensive pre- and post- marketing regulation by the FDA, including regulations that govern the testing, manufacturing, safety, efficacy, labeling, storage, recordkeeping, advertising and promotion of the products under the Federal Food, Drug, and Cosmetics Act (FDC Act), and the Public Health Services Act, and by comparable regulatory agencies in most foreign countries. The process required by the FDA before a new drug, or biologic may be marketed in the United States generally involves:

Completion of preclinical laboratory and animal testing;

Submission of an investigational new drug application, or IND, which must become effective before clinical trials may begin;

Performance of adequate and well controlled human clinical trials to establish the safety and efficacy of the proposed drug or biologic s intended use; and

In the case of a new drug, approval by the FDA of a New Drug Application (NDA) or of a BLA for a biologic. Our products will be regulated as biologics.

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

Pre-Clinical Testing

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

Clinical Trials

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

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Clinical trials are typically conducted in three sequential phases, but the phases often overlap. In Phase 1, the initial introduction of the drug into healthy volunteers or patients, the drug is tested for safety or adverse effects, dosage tolerance, absorption, distribution, metabolism, excretion and clinical pharmacology. Phases 2 and 3 involve clinical trials in patient populations to determine the effectiveness of the drug for specific, targeted indications, determine dosage tolerance and optimal dosage. Phase 3 clinical trials typically contain control groups and are undertaken to further evaluate clinical effectiveness, to further test for safety within an expanded patient population at geographically dispersed clinical trial sites and may be utilized to seek marketing approval by the FDA.

National Institutes of Health

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

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

Marketing Applications

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

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

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

Satisfaction of FDA premarket approval requirements for new drugs and biologics typically takes several years and the actual time required may vary substantially based upon the type, complexity and novelties of the product or disease. Government regulation may delay or present marketing of potential products for a

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considerable period of time and impose costly procedures upon our activities. Success in early stage clinical trials and on prior versions of the products does not assure success in later stage clinical trials. Data obtained from clinical activities is not always conclusive and may be susceptible to varying interpretations that could delay, limit or prevent regulatory approval.

Orphan Drug Act

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

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

Off-Label Use

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

Fast Track Products

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

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

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

Priority Review. Under FDA policies, a product is eligible for priority review, or review within a six-month time frame from the time an NDA or BLA is accepted for filing, if the product provides a significant improvement compared to marketed products in the treatment, diagnosis, or prevention of a disease. A Fast Track designated product would ordinarily meet the FDA s criteria for priority review. We cannot guarantee any of our products will receive a priority review designation, or if a priority designation is received, that review or approval will be faster than conventional FDA procedures.

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

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

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

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

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

International

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

Competition

The biotechnology and pharmaceutical industries are subject to rapid and intense technological change. We face, and will continue to face, competition in the development and marketing of our product candidates from academic institutions, government agencies, research institutions and biotechnology and pharmaceutical companies. Competition may arise from other drug development technologies, methods of preventing or

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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 are aware that a Chinese pharmaceutical company, SiBioNo GeneTech, Inc., has announced that it has received regulatory approval from the Chinese drug regulatory agency to market an adenoviral p53 product only in China. We are also aware of other pharmaceutical and biotechnology companies, including Canji, Inc. and Genvec, Inc., which are pursuing forms of treatment for the diseases ADVEXIN therapy and our other product candidates target. We are aware that Canji, with its parent Schering-Plough Corporation, has in the past been involved in research and/or development of adenoviral p53 products and owns or controls patents and patent applications directed to adenoviral p53 therapy. We understand that Canji/ Schering-Plough has stopped its adenoviral p53 clinical trials, and it is unknown whether these parties are continuing their adenoviral p53 research and/or development efforts. There are many other companies, both publicly and privately held, including well-known pharmaceutical companies, engaged in developing products for human therapeutic applications. We also compete with universities and other research institutions in the development of products, technologies and processes. In many instances, we compete with other commercial entities in acquiring products or technologies from universities and other research institutions.

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

Human Resources

As of March 15, 2005, we had approximately 75 employees and contracted personnel engaged in research and development, regulatory affairs, clinical affairs, manufacturing and quality, finance and corporate development activities. Our employees include eight holders of a Ph.D. or M.D. degree. Many of our employees have extensive experience in pharmaceutical and biotechnology industries.

Scientific Advisory Board

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

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

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

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

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Elizabeth Grimm, Ph.D., is a professor of experimental therapeutics 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.

Item 2. ***Properties***

Our primary operations are conducted from facilities in Houston, Texas, totaling approximately 42,000 square feet in two buildings. These buildings consist of a 12,000 square foot CGMP production facility designed to support an ADVEXIN therapy product launch and a 30,000 square foot building containing our research and development laboratories and administrative offices. We own these facilities through TMX Realty Corporation, our wholly-owned subsidiary. Our corporate offices are located in Austin, Texas. We expect our current facilities to satisfy our requirements for the foreseeable future.

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

We sublease to M. D. Anderson Cancer Center approximately 10,000 square feet in the facilities described above. This lease provides for rent payments at prevailing market rates and has an initial term expiring in 2009.

In addition to the facilities described above, we lease other space in Houston, Texas on which we constructed and operate a second production facility. We use that facility to produce investigative material for INGN 241 and other product candidates in an environment separate from that used for production of ADVEXIN therapy.

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 a European patent controlled by Canji discussed under Risk Factors , will have a material effect on our business. You can read the discussion of our opposition of the patents under Risk Factors.

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

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

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PART II

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

Market and Equityholder Information

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

	High	Low
Fiscal Year Ended December 31, 2003:		
First Fiscal Quarter	$ 3.36	$ 1.97
Second Fiscal Quarter	10.16	2.00
Third Fiscal Quarter	11.24	5.26
Fourth Fiscal Quarter	10.20	6.95
Fiscal Year Ended December 31, 2004:		
First Fiscal Quarter	$ 10.37	$ 7.29
Second Fiscal Quarter	9.20	4.20
Third Fiscal Quarter	7.10	2.96
Fourth Fiscal Quarter	9.81	5.00

At December 31, 2004, there were 30,622,806 shares of our common stock issued and outstanding held by approximately 152 stockholders of record. A substantially greater number of holders of our common stock are street name or beneficial holders, whose shares are held of record by banks, brokers and other financial institutions.

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. We do not anticipate paying any cash dividends in the foreseeable future.

Sales of Unregistered Securities

On October 22, 2004, we acquired all of the outstanding capital stock of Magnum Therapeutics Corporation (Magnum), a company for which Dr. Robert Sobol, our Senior Vice President, Medical and Scientific Affairs, was the sole stockholder. We paid approximately $1.75 million for the Magnum stock by (1) issuing approximately 252,000 shares of our common stock valued at approximately $1.48 million at the acquisition date and (2) assuming liabilities of approximately $272,000. With respect to the common stock we issued pursuant to the acquisition, 50% of the shares are being held in escrow for a period of one year subsequent to the acquisition date to satisfy the indemnification obligations of the selling shareholder under terms of the purchase agreement. The shares were issued to Dr. Sobol, as the sole stockholder of Magnum, pursuant to Section 4(2) under the Securities Act of 1933. Magnum s primary asset is the right to receive future funding under a grant from the National Institutes of Health.

Stock Repurchases

We did not repurchase any shares of capital stock during the fourth quarter of the fiscal year covered by this Report.

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

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, 2001(b)	Six Months Ended December 31,		Year Ended December 31,			
		2000(c)	2001(b)	2001(c)	2002(a)	2003(a)	2004(a)
		(Unaudited)		(Unaudited)			
	(In thousands except per share amounts)						
Statement of Operations Data:							
Contract services, grants and other revenue	$ 684	$ 391	$ 298	$ 591	$ 1,173	$ 304	$ 1,808
Collaborative research and development revenues from affiliate	3,016	3,016					
Product sales to affiliate	1,500	1,500					
Cost of product sales	2,488	2,488					
Gross margin on product sales	(988)	(988)					
Operating costs and expenses:							
Research and development	15,014	5,153	10,063	19,923	21,512	14,973	20,474
General and administrative	4,875	2,040	3,526	6,361	6,722	6,102	6,597
Total operating costs and expenses	19,889	7,193	13,589	26,284	28,234	21,075	27,071
Loss from operations	(17,177)	(4,774)	(13,291)	(25,693)	(27,061)	(20,771)	(25,263)
Interest income (expense), net	381	403	445	423	(207)	393	(191)
Other income	354		518	871	1,140	1,052	1,067
Net loss	$ (16,442)	$ (4,371)	$ (12,328)	$ (24,399)	$ (26,128)	$ (19,326)	$ (24,387)
	$ (1.02)	$ (0.39)	$ (0.58)	$ (1.14)	$ (1.22)	$ (0.84)	$ (0.91)

Net loss per share, basic and diluted							
Shares used in computing basic and diluted net loss per share	16,163	11,121	21,440	21,440	21,471	22,902	26,943

			December 31,				
			June 30, 2001(b)	**2001(b)**	**2002(b)**	**2003(a)**	**2004(a)**
					(In thousands)		
Balance Sheet Data:		&nbs					