INTROGEN THERAPEUTICS INC
Form 10-K
March 08, 2007

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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, 2006.

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:
Common Stock, $0.001 par value per share
Securities registered pursuant to Section 12(g) of the Act:

Indicate by check mark if the Registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes o No þ

Indicate by check mark if the Registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes o No þ

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 a large accelerated filer, an accelerated filer or a non-accelerated filer. See definition of accelerated filer and large accelerated filer in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer o Accelerated filer þ Non-accelerated filer o

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes o No þ

The aggregate market value of the voting stock (common stock) held by non-affiliates of the Registrant, as of the last day of the Registrant s second fiscal quarter, was approximately $89.1 million based upon the last sale price reported on the Nasdaq Global Market for June 30, 2006. For purposes of this disclosure, shares of common stock held by persons holding more than 5% of the outstanding shares of the Registrant s 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 6, 2007, the Registrant had 43,699,601 shares of common stock, $0.001 par value per share, issued and outstanding.

DOCUMENTS INCORPORATED BY REFERENCE

Certain information required by Items 10, 11, 12, 13 and 14 of Part III of Form 10-K is incorporated by reference to the Registrant s proxy statement (2007 Proxy Statement) for the 2007 Annual Meeting of Stockholders, 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, 2006.

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, as amended (Securities Act) and Section 21E of the Securities Exchange Act of 1934, as amended (Exchange Act). These statements address our future operations, financial condition, business strategies and other prospective items as well as the statements below under Item 1A. Risk Factors, and include, among other subjects, matters concerning our expectations regarding:

- The growth of our operations, business and revenues and the growth rate of our costs and expenses;
- Future increases in our research and development, sales and marketing and general and administrative expenses;
- The sufficiency of our existing cash, cash equivalents, marketable securities and cash generated from operations;
- Our expectations regarding various regulatory applications, procedures and approvals relating to our product candidates, including but not limited to our expectations regarding the timing of such applications, procedures and approvals;
- Better efficacy of our product candidates through the use of biomarkers ; and
- Application of our research and development expertise to other diseases that result from cellular dysfunction and uncontrolled cell growth.

The words believe, expect, anticipate and other similar expressions generally identify forward-looking statements. These forward-looking statements are based on our current expectations and entail various risks and uncertainties. Given these risks and uncertainties, readers are cautioned not to place undue reliance on such forward-looking statements. We undertake no obligation to revise or publicly release the results of any revision to these forward-looking statements. These forward-looking statements are subject to certain risks and uncertainties that could cause our actual results to differ materially from those reflected in the forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this Annual Report on Form 10-K, and in particular, the risks discussed under the heading Risk Factors in Part I, Item 1A of this Annual Report on Form 10-K and those discussed in other documents we file with the Securities and Exchange Commission (SEC). Investors should carefully review the information contained in Item 1A. Risk Factors 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 Exchange Act 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 SEC. 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 our Chief Executive Officer, Chief Financial Officer and persons performing similar functions) are available on our website 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 molecular therapies for the treatment of cancer and other diseases. We are developing product candidates to treat a wide range of cancers using tumor

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suppressors, cytokines and other targeted molecular therapies. 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 targeted molecular therapies that increase production of normal cancer-fighting proteins to induce apoptosis, cell cycle control, cell growth control and gene regulation, including the regulation of angiogenic and immune factors. Our products work 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 specific therapeutic effects.

We believe the use of targeted molecular therapies to induce the production of biopharmaceutical proteins represents a new approach for treating many cancers while avoiding the toxic side effects common to traditional therapies. We have developed significant expertise in developing targeted therapies that may be used to treat disease and in using what we believe are safe and effective delivery systems to transport these agents 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.

Our lead product candidate, ADVEXIN® therapy, combines the p53 tumor suppressor with a non-replicating, non-integrating, adenoviral delivery system we have developed and extensively tested. The p53 molecule is one of the most potent members of a group of naturally-occurring tumor suppressors, which act to kill cancer cells, arrest cancer growth and protect cells from becoming cancerous. We are developing other product candidates for the treatment of cancer using other molecules and delivery systems, such as the mda-7 tumor suppressor.

We believe our research and development expertise gained from our targeted molecular 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 targeted molecular therapy product candidates in the treatment of other diseases.

We typically license the technologies on which our products are based from third parties. These licenses generally grant us exclusive rights for pre-clinical and clinical development, manufacturing, marketing and commercialization of product candidates based on those technologies.

Our product research and development efforts include pre-clinical activities as well as the conduct of Phase 1, 2 and 3 clinical trials. We rely on third parties to treat patients in their facilities under these clinical trials. We produce ADVEXIN therapy and other product candidates in manufacturing facilities we own and operate using production methods we developed. We hold a number of patents or patents pending on certain product candidates and manufacturing processes used to produce certain product candidates.

We have not yet generated any significant revenue from unaffiliated third parties, nor is there any assurance of future product revenue. We earn minimal revenue from contract services activities, grants and interest income, as well as rent from the lease of a portion of our facilities to The University of Texas M. D. Anderson Cancer Center. We do not expect to generate revenue from the commercial sale of our products in the near future. We may never generate revenue from the commercial sale of our products.

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

Background

Targeted Therapeutics

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 molecules, 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

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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 the human genome, 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.

Delivery Systems

Targeted molecular therapies are often combined with a delivery system, referred to as a vector, which enables the therapeutic molecule to enter the target cell. The vector must be able to deliver a sufficient dose of the therapeutic molecule to cause a beneficial effect. Among the delivery systems currently in use are modified versions of viruses such as adenoviruses. Viruses are often used as delivery systems because they have the ability to efficiently infect cells and carry therapeutic molecules into the cells. These viruses can be modified by deleting pieces of the viral genome that are necessary for viral reproduction and replacing the deleted pieces with a therapeutic molecule. The resulting viral vector retains the ability of the virus to efficiently deliver the therapeutic molecule into cells, while losing the ability to reproduce itself and spread to other cells.

While viruses are an efficient means of introducing therapeutic molecules into cells, synthetic substances have been developed, such as nanoparticles, which are nanoscale structures that have no viral components. These synthetic or nanoparticle systems can also deliver therapeutic molecules to host cells through systemic administration. These systems can mimic the characteristics of viral vector systems. We use both viral and synthetic nanoparticle systems in our clinical trials to deliver therapeutic molecules.

An Overview of Cancer

Cancer is a leading cause of death in the United States, where approximately 1.4 million people are newly diagnosed with cancer and approximately 560,000 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 National Institutes of Health (NIH) estimate the annual direct cost of treating cancer patients in the United States is approximately $78.2 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 cause 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 targeted therapies because molecular targets that will lead to the destruction of the cancer cell are understood. The introduction of normal tumor suppressors, 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.

Tumor Suppressors

Tumor suppressors are one class of molecules that play a crucial role in preventing cancer and its spread. This class includes the p53, mda-7, BAK and FUS-1 tumor suppressors, among others.

The best known and most studied of the tumor suppressors is the p53 molecule. The p53 molecule is one of the most potent members of a group of naturally occurring tumor suppressors, which act to kill cancer cells, arrest cancer cell growth and protect cells from becoming cancerous. The p53 tumor suppressor is involved in multiple

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cellular processes, including control of cell division, DNA repair, cell differentiation, genome integrity and 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 tumor suppressor is capable of such wide-ranging effects because it orchestrates the activity of a host of genes and proteins. If a cell suffers DNA damage, p53 responds to the damage by initiating a cascade of protective processes to either repair the DNA damage or to destroy the damaged cell through apoptosis. These p53-mediated processes prevent damaged cells from multiplying and progressing towards cancer.

Current Treatment of Cancer

Conventional therapeutic approaches, including surgery, chemotherapy and radiation therapy, can be 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, and often require additional and costly medications to ameliorate such side effects. Further, certain chemotherapies may not effectively treat 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 conventional cancer therapies, the treatment of cancer remains complex. Physicians refer to the first treatment regimen for a newly-diagnosed cancer, usually surgery if possible, or 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 conventional therapies are not likely to provide them with clinical benefit.

Given that established cancer therapies often prove to be incomplete, ineffective and/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. Targeted molecular 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 targeted molecular therapies that increase production of normal cancer-fighting proteins. The resultant proteins engage disease-related molecular targets or receptors to produce specific therapeutic effects. We believe 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 molecules 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.

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We initially focused on advanced cancers lacking effective treatments and in which local tumor growth control, where the tumor stops growing or shrinks, is likely to lead to measurable benefit. We have expanded our focus to include earlier stage cancers and pre-malignancies. We believe our clinical trials have shown that our 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 a leader in the development of targeted molecular tumor suppressor 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 our development programs to commercialize our ADVEXIN therapy, using the p53 tumor suppressor, and our INGN 241 product, using the mda-7 tumor suppressor, also know as interleukin 24 (IL-24), in multiple cancer indications.

Develop Our Portfolio of Targeted Molecular Therapies and Other Drug Products. Utilizing our significant research, clinical, regulatory and manufacturing expertise, we are evaluating development of additional molecular therapies for various cancers, including:

INGN 225, a highly specific cancer immunotherapy;

INGN 234, an oral rinse or mouthwash formulation containing the p53 tumor suppressor;

INGN 401, using the FUS-1 tumor suppressor;

INGN 402 and 403, using nanoparticle formulations for systemic delivery of the p53 and mda-7 tumor suppressors; and

INGN 007, a replication-competent viral therapy.

We have an established 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 pre-clinical and clinical studies with these new nanoparticle drugs have demonstrated a good safety profile and promising anti-cancer activity. In addition to FUS-1, we incorporate the p53 tumor suppressor and the mda-7 tumor suppressor 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, specifically INGN 234 referred to above. 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 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 molecular therapy and vector development to pursue targeted molecular 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.

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ADVEXIN® Therapy (p53)

ADVEXIN Therapy Overview and Regulatory Status

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

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 U.S. Food and Drug Administration (FDA). The European Medicines Agency (EMEA) Committee for Orphan Medicinal Products has granted ADVEXIN therapy an Orphan Medicinal Product Designation in Europe for the treatment of Li-Fraumeni Syndrome (LFS). This designation has been ratified by the European Commission. LFS is an inherited cancer characterized by inherited mutations in the p53 tumor suppressor gene. The Orphan Medicinal Product Designation in Europe confers a number of regulatory benefits to ADVEXIN therapy, including access to protocol assistance, reduced regulatory fees and a 10-year period of marketing exclusivity from the date of approval.

We have an agreement with EMEA to file for marketing approval for ADVEXIN therapy under the EMEA s Exceptional Circumstances (EC) provisions. The application will be for the use of ADVEXIN p53 therapy for the treatment of LFS. Exceptional circumstances provisions are designed to facilitate access to needed treatments for certain Orphan Medicinal Products. A Marketing Authorization Application filed with the EMEA under these provisions can be reviewed on an expedited basis. This EC registration approach is designed by EMEA to be more streamlined than EMEA s Conditional Approval procedures, which are similar to the FDA s Accelerated Approval regulations.

We have two ongoing Phase 3 clinical trials of ADVEXIN therapy in patients with advanced recurrent squamous cell carcinoma of the head and neck (recurrent head and neck cancer). These trials involve administration of ADVEXIN therapy, both independently and in combination with chemotherapy, in recurrent head and neck cancer.

We 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 Biologics 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.

We reviewed historically successful FDA registration strategies for numerous cancer drugs, noting that during the past decade, approximately 14 cancer drugs were initially approved based upon submissions of Phase 2 clinical data. A number of the Phase 2 trials supporting these approvals employed single-arm studies involving relatively small patient populations. Virtually all of those drugs relied on surrogate endpoints for approval and a substantial number of the products were for orphan drug indications.

We 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 head and neck cancer. 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 continues to show promise with respect to an unmet medical need since there are limited treatment alternatives 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 continues to meet the criteria for Fast Track designation. In conjunction with the new data, the new analyses, and other newly employed biological techniques, we are hopeful of more specifically targeting recurrent head and neck cancer in patients using indicators known as biomarkers , as discussed further below, resulting in even better efficacy than has already been demonstrated.

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We submitted a SOPA Request to the FDA Division of Cellular and Gene Therapies 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 proposed to the FDA that, since the basis of the proposed rolling BLA is Phase 2 clinical data utilizing surrogate endpoints, the rolling BLA could 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 new data and analyses from the Phase 2 ADVEXIN therapy clinical trials for recurrent head and neck cancer and consider conducting interim efficacy analyses on one or both of our ongoing Phase 3 trials. Given that we have two ongoing Phase 3 clinical trials in recurrent 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. This initiative also encouraged sponsors to examine novel approaches to define tumor responses that correlate with clinical benefit. We have employed several response criteria to evaluate ADVEXIN efficiency as described below.

We proposed to the FDA and received an acceleration of the initiation of the planned interim safety analysis relative to one of our two ongoing Phase 3 clinical trials of ADVEXIN therapy in patients with recurrent head and neck cancer. This analysis was performed by a Data Safety Monitoring Board and did not result in any changes in the study conduct. We believe such safety information will be useful to the FDA as part of our ongoing BLA submission process. We plan to avail ourselves of the suggestion by the FDA that we consider proposing to them an interim efficacy analysis of one or both of our ongoing Phase 3 clinical trials. As with the acceleration of the interim safety analysis, we believe the results of the interim efficacy analysis from one or both Phase 3 studies will be useful to the FDA in its review of our BLA. With regard to these interactions, the FDA requested we submit a proposal for the Phase 3 interim efficacy analyses. We submitted that proposal and received and accepted comments from the FDA in December 2006. In addition, the FDA has agreed that we may utilize our biomarkers indicating the molecular mechanism of ADVEXIN therapy for the analyses of Phase 2 and Phase 3 clinical data.

During 2007, we plan to complete the interim efficacy analyses of one or both of our two ongoing Phase 3 clinical trials for recurrent head and neck cancer, submit Phase 2 and Phase 3 clinical data to the FDA and EMEA in support of our ADVEXIN registration program and complete filings with the EMEA in support of an Exceptional Circumstance Approval Application for LFS cancers.

We cannot assure you that we will be able to achieve these regulatory milestones during the time period that we currently anticipate. We may encounter delays in the regulatory process relating to these milestones due to additional information requirements from regulatory authorities, unintentional omissions in our applications, additional government regulation or other delays in the review process. We may update our expectations regarding these regulatory milestones from time to time to reflect new information as it becomes available to us.

ADVEXIN Therapy as a Targeted Molecular Therapy

We identified a set of predictive indicators, commonly referred to as biomarkers, associated with high response rates and increased survival in Phase 2 clinical trials of ADVEXIN therapy in patients with recurrent head and neck cancer. These trials are discussed in more detail below under Other ADVEXIN Therapy Activities. These biomarkers support the use of ADVEXIN therapy as a targeted molecular therapy.

The FDA, the National Cancer Institute (NCI), and the Centers for Medicare & Medicaid Services are undertaking the Oncology Biomarker Qualification Initiative to expedite the development of novel cancer treatments. These agencies define biomarkers as clinical or biological indicators of disease or therapeutic effects, which can be measured through dynamic imaging tests, laboratory tests on blood or tissue samples as well as by clinically defined parameters. This initiative was developed to employ biomarkers as a way of speeding the development and evaluation of new cancer therapies.

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The identification of predictive indicators of ADVEXIN therapy activity is responsive to these initiatives by predicting the patient populations most likely to benefit from a specific cancer therapy. The population we identified as benefiting from ADVEXIN therapy includes patients who are less likely to respond to standard therapies such as chemotherapies and radiation.

A molecular biomarker predictive of ADVEXIN therapy activity is abnormal p53 function detected in tumor tissues by a routine immunohistochemistry laboratory test. In patients with the abnormal p53 biomarker, ADVEXIN therapy caused a statistically significant increase in median survival of 11.6 months compared to only 3.5 months for patients without abnormal p53 function. Patients with abnormal p53 function are known to have a poor prognosis when treated with standard therapies. In addition to this molecular biomarker, we have identified clinical prognostic biomarkers that correlate with statistically significant increases in survival, partial and complete tumor responses and durable locoregional disease control (tumor responses or tumor growth arrest for three months or longer in duration) following treatment with ADVEXIN therapy. These clinical biomarkers include prior chemotherapy or radiotherapy consistent with ADVEXIN therapy s mechanism of action of inducing tumor death in cells, or apoptosis, with DNA damage from previous treatments.

The predictive biomarkers define target populations of patients with high tumor response rates and increased survival following treatment with ADVEXIN therapy. In our combined Phase 2 trials of recurrent head and neck cancer (trials T201 and T202 with 163 total patients), we have observed prognostic factors defining targeted subpopulations with tumor response rates up to 29% and durable locoregional disease control rates of 57%. In these studies, tumor response was defined by at least a 50% reduction in tumor size and durable locoregional disease control was defined by reduced tumor size or stable disease of at least three months duration. These tumor responses are associated with a statistically significant increase in median survival. The median survival of patients with durable locoregional disease control in this group was 12.4 months compared to 5.9 months for the entire study population.

In a separate analysis of patients treated in the T201 Phase 2 trial of recurrent head and neck cancer treated with the ADVEXIN therapy dose proposed for regulatory approval, the ADVEXIN therapy tumor response rate, defined by a 30% reduction in tumor area, was 10% for the overall population and 26% for the clinical biomarker defined population, with a progression free interval of greater than 12 months from initial treatment who had prior chemotherapy. The durations of these responses were durable with a median of 5.7 months. In this overall treatment population, tumor response was associated with a statistically significant increase in survival. The median survival of the responders was 16.9 months compared to 5.4 months for non-responders. This difference was statistically significant ($p < 0.0001$). This Phase 2 study evaluated 106 patients utilizing the ADVEXIN therapy dose that is also employed in our Phase 3 clinical trials.

The targeted molecular therapy provided by ADVEXIN therapy is evidenced by its use to successfully treat an LFS cancer patient on a compassionate use basis under a protocol authorized by the FDA. Our treatment of a tumor in an LFS patient with ADVEXIN therapy led to improvement of tumor-related symptoms and resulted in a complete response in the treated lesion as determined by positron emission tomography (PET) computerized tomography (CT) scans. PET-CT scans measure the metabolic activity of tumors and are being increasingly utilized in the management of cancer patients because they provide more sensitive assessments of treatment effects compared to conventional CT and magnetic resonance imaging scans.

This LFS study defined important biomarkers to guide the administration of ADVEXIN therapy to patients with other cancers who display p53 pathway abnormalities. Our molecular analysis of biopsies of the LFS tumor before and after treatment identified key markers of p53 pathway abnormalities that are used to predict and evaluate the effects of ADVEXIN therapy. These markers included detection of abnormal levels of p53 protein that identify aberrant p53 pathways and the induction of molecular markers of tumor growth control and tumor cell death that validate

ADVEXIN therapy s mechanisms of action. We believe these biomarkers can be used to identify patients most likely to benefit from ADVEXIN therapy.

The European Medicines Agency (EMEA) Committee for Orphan Medicinal Products has granted ADVEXIN therapy an Orphan Medicinal Product Designation in Europe for the treatment of LFS. This designation has been ratified by the European Commission. The Orphan Medicinal Product Designation in Europe confers a number of regulatory benefits to ADVEXIN therapy, including access to protocol assistance, reduced regulatory fees and a

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10-year period of marketing exclusivity from the date of approval. We received this designation through Gendux AB, our wholly-owned subsidiary.

We have an agreement with EMEA to file for marketing approval for ADVEXIN therapy under the EMEA s Exceptional Circumstances provisions. The application will be for the use of ADVEXIN therapy for the treatment of LFS. Exceptional circumstances provisions are designed by EMEA to facilitate access to needed treatments for certain Orphan Medicinal Products. A Marketing Authorization Application filed with the EMEA under these provisions can be reviewed on an expedited basis. This registration approach is more streamlined than EMEA s Conditional Approval procedures, which are similar to the FDA s Accelerated Approval regulations. As a result of the encouraging clinical findings in treating LFS, we have made ADVEXIN therapy available on a compassionate use basis to qualified LFS patients with tumors refractory to standard treatment.

LFS is an inherited genetic disorder that greatly increases the risk of developing several types of cancer typically with initial occurrence at a young age. The majority of LFS families have inherited mutations in the p53 tumor suppressor gene. The findings described above have been presented at the annual meetings of the American Society of Gene Therapy (ASGT) and the American Society of Clinical Oncology (ASCO).

Other ADVEXIN Therapy Activities

We performed a Phase 2 clinical trial of ADVEXIN therapy combined with neoadjuvant chemotherapy and surgery in women with locally advanced breast cancer. The results of this study were published in the journal *Cancer.* Objective clinical responses were seen following the combined therapy in 100% of the patients with a median of 80% reduction in tumor size. Following tumor shrinkage, complete tumor removal by subsequent surgery was achieved in 100% of the patients. At a median follow-up of 37 months (range, 30-41 months), four patients (30%) developed systemic recurrence and two patients died. The estimate breast cancer-specific survival rate at three years was 84%. There was no increase in systemic toxicity. Neoadjuvant treatments are administered prior to surgery and represent a novel and increasingly applied approach to making surgical tumor resections less invasive, improving outcomes and facilitating breast conservation.

We completed a Phase 2 clinical trial of ADVEXIN therapy administered as a complement to radiation therapy in non-small cell lung cancer. In the 19 patients who participated in the trial, combined ADVEXIN therapy and radiation treatment resulted in 63% biopsy-proven complete responses at three months, which is approximately four times the expected rate using radiotherapy alone. The results of this study were published in *Clinical Cancer Research.*

We performed a Phase 1/early Phase 2 clinical trial of ADVEXIN therapy for the treatment of advanced, unresectable, squamous cell esophageal cancer. Results of this trial in patients with esophageal cancer refractory to chemotherapy and radiation indicate three of the ten patients treated, or 30%, had negative biopsies after receiving ADVEXIN therapy. The median survival of the patients treated with ADVEXIN therapy was approximately twelve months, which compared favorably to historical controls in which a median survival of less than ten months was observed for patients who did not respond to standard treatments. Six patients, or 60%, were still alive one year after beginning ADVEXIN therapy. This clinical trial was performed at Chiba University in Japan.

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

- 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 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.

We have completed other clinical trials of ADVEXIN therapy, including Phase 1 studies in prostate cancer and bronchoalveolar carcinoma. To date, clinical investigators at sites in North America, Europe and Japan have treated

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over 600 patients with ADVEXIN therapy, establishing a large safety database. Findings from several of our clinical trials have been published in *Clinical Cancer Research* and *Proceedings of the American Society for Clinical Oncology* as well as presented at numerous conferences, including the San Antonio Breast Cancer Conference and various meetings of the ASCO, ASGT and the American Association for Cancer Research.

A growing body of data suggests ADVEXIN therapy demonstrates clinical activity in a variety of cancer indications. Safety data from our clinical trials suggest 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, surgery or radiation does not appear to increase the frequency or severity of side effects normally associated with these treatment regimens.

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

Other 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 *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 lung cancer patients who were part of our ADVEXIN therapy studies program were featured in the Summer 2004 issue of *Conquest* magazine, a publication of M. D. Anderson Cancer Center, in connection with reaching their five-year survival anniversary. In addition, a patient with recurrent head and neck cancer who achieved a complete tumor remission on ADVEXIN therapy continues to be disease-free over eight years later while receiving repeated treatments of ADVEXIN therapy.

We hold a worldwide, exclusive license to a family of patent applications directed to combination therapy using ADVEXIN therapy with inhibitors of epidermal growth factor receptors (EGFr inhibitors) such as Erbitux®, Vectibix®, Tarceva® and Iressa®. We licensed this family of patents from M. D. Anderson Cancer Center. This important technology is based on the discovery by scientists at M. D. Anderson Cancer Center that p53 therapies (which is the basis for our ADVEXIN therapy) and mda7 therapies (which is the basis for our INGN 241 product candidate discussed below) can work synergistically with inhibitors of epidermal growth factor receptors to arrest tumor growth. Preclinical studies have shown that this therapeutic approach results in a greater level of cancer cell death than when either therapy is used alone.

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

INGN 241 (mda-7)

INGN 241 uses mda-7, a promising tumor suppressor, 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 tumor suppressor with our adenoviral delivery system to form INGN 241. Our pre-clinical trials have shown 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 the growth of normal cells. Because INGN 241 kills cancer cells even if other tumor suppressors, including p53, are not functioning properly, it appears mda-7 functions via a novel mechanism of tumor suppression.

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 indicated that in patients with solid tumors, INGN 241 was well tolerated, was biologically active and displayed minimal toxicity associated

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with its use. We are conducting later stage clinical trials using INGN 241 in patients with metastatic melanoma and recurrent head and neck cancer. We are conducting a Phase 3 clinical trial using INGN 241 in combination with radiation therapy for solid tumors.

Data from our Phase 1 trial of INGN 241 in patients with solid tumors demonstrate that direct injection of INGN 241 induced programmed cell death in 100% of the tumors treated, even in patients who had failed prior therapy with other anti-cancer drugs. Clinical responses were observed in 44% of the treated lesions, including complete and partial responses in two patients with melanoma. Patients treated with INGN 241 had increases in a subset of T-cells that help to destroy cancer cells, which is consistent with the role of the mda-7 protein as a member of the interleukin family of immune stimulating proteins.

We have conducted pre-clinical work indicating that in addition to its known activity as a tumor suppressor, the protein produced by mda-7 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 tumor suppressor may act as a cytokine, or immune system modulator, it is also known as interleukin 24, or IL-24. The mda-7 molecule may also work as a radiation sensitizer to make several types of human cancer cells more susceptible to radiation therapy. We have seen evidence of this effect in pre-clinical and clinical settings.

We have identified the molecular pathways by which mda-7, the active component of INGN 241, induces growth arrest and programmed cell death or apoptosis in cancer cells. Pre-clinical studies using lung cancer cells have demonstrated the mda-7 protein binds to a critical cellular enzyme known as PKR. The binding of mda-7 to PKR is essential for the anti-cancer activity of INGN 241. The identification of this binding partner demonstrates a significant advancement in understanding how this therapeutic can be effective against cancer. Additional studies have identified bystander killing of pancreatic cancer cells by the mda-7 protein. Bystander killing involves the killing of neighboring tumor cells by the mda-7 protein released from adjacent INGN 241-treated tumor cells.

Pre-clinical data indicate INGN 241 works synergistically with celecoxib, marketed by Pfizer as Celebrex®, to inhibit the growth and increase killing of breast cancer cells. The combination of celecoxib and INGN 241 showed greater than additive increases in cell death compared with either therapy alone and also resulted in the suppression of tumor cell growth.

Pre-clinical data indicate INGN 241 and bevacizumab, marketed by Roche Holding AG and Genentech, Inc. (Genentech) as Avastin®, each inhibit tumor angiogenesis through distinct mechanisms in models of lung cancer. Study results demonstrate that the combination of INGN 241 and Avastin® significantly increases anti-tumor activity compared with either agent used separately. We have observed synergistic activity resulting in a positive therapeutic effect in the treatment of lung cancer in laboratory animals following the combination of the two agents. In contrast, treatment with Avastin® alone demonstrated only minor tumor regression in those animals. These findings have been published in *Molecular Therapy*, the journal of ASGT.

Pre-clinical data indicate the combination of INGN 241 and Tarceva®, marketed by Genentech, more significantly inhibits tumor cell growth than Tarceva® administered alone. The preclinical data suggest the two agents work in concert to inhibit activity of the epidermal growth factor receptor, a potent driver for cell growth in many types of cancer.

Our pre-clinical work indicates INGN 241 effectively kills cancer cells that are resistant to cisplatin, one of the most commonly used chemotherapeutic agents. These pre-clinical studies also identified a novel defect in a protein degradation pathway in the cisplatin-resistant cells. This defect enhances the activity of INGN 241, suggesting that INGN 241 may have particular utility in treating cancers that do not respond to cisplatin.

In pre-clinical studies, we have observed the expression of mda-7 in ovarian cancer cells activates a cell death or apoptotic pathway regulated by the Fas signaling system. This activation resulted in significant increases in apoptosis and inhibition of cancer cell proliferation that were specific to cancer cells. These effects were not observed in normal ovarian tissue, supporting previous data showing a cancer-selective effect of INGN 241.

We have 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. The data demonstrate INGN

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241 can inhibit production of the VEGF protein, a potent inducer of angiogenesis, within lung cancer cells, which in turn inhibits tumor angiogenesis, a key requirement for tumor growth.

Pre-clinical work has demonstrated administration of INGN 241 results in the development of systemic immune responses against tumor cells and suggests INGN 241 could be used as a novel cancer molecular immunotherapy. In pre-clinical studies, implantation of INGN 241-treated tumor cells into mice resulted in significant inhibition of tumor growth. Significantly, mice immunized with INGN 241-treated cells showed inhibition of tumor growth after a subsequent challenge with additional tumor cells.

We have conducted pre-clinical studies with INGN 241 in breast cancer cell lines as a single agent, as well as in combination with radiation therapy, with chemotherapy (Taxotere® or Adriamycin®), with the hormone inhibitor Tamoxifen® and with Herceptin®, a biologic cancer therapy. In all settings, INGN 241 reduced cell growth and increased programmed tumor cell death (apoptosis). This effect was enhanced when combined with drugs currently used to treat breast cancer. In animal models of breast cancer, treatment with INGN 241 alone or in combination with radiation therapy resulted in significant decreases in tumor growth. In particular, our pre-clinical studies have shown 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 while Herceptin® exhibited no activity on Her-2/neu negative cells, INGN 241 did induce cell death in these cells.

Pre-clinical studies indicate the mda-7 protein released from cells treated with INGN 241 can kill nearby, untreated breast cancer cells resulting in additional therapeutic effect. This bystander effect occurs when the therapeutic protein binds to certain receptors on nearby cancer cells. We believe this bystander effect is significant because it could indicate the number of cancer cells INGN 241 can kill is greater than the number of cells that take up this novel investigational cancer therapy.

Pre-clinical studies have demonstrated that INGN 241 can induce human lung cancer cells to undergo apoptosis, or programmed cell death, through the synergistic action of INGN 241 and a class of tumor-targeted drugs known as heat shock protein 90 (Hsp90) inhibitors. We have observed that the combination of INGN 241 and two Hsp90 inhibitors can result in the enhancement of cell death in lung cancer cells. This combination treatment inhibited tumor cell movement, suggesting an anti-metastatic effect.

Findings and results arising from our development of INGN 241 have been published in the *Journal of Leukocyte Biology*, *Cancer Gene Therapy*, *Cancer Research*, *Molecular Therapy*, *Oncogene*, *Surgery*, and *International Immunopharmacolgy.* Data from this work have also been presented at the annual San Antonio Breast Cancer Symposium.

We have an exclusive license from GlaxoSmithKline plc (GlaxoSmithKline) to the mda-7 tumor suppressor for our therapeutic applications. This license was originally from Corixa Corporation (Corixa), which was acquired by GlaxoSmithKline. Pre-clinical studies regarding the active component of INGN 241 have included research at The University of Texas M. D. Anderson Cancer Center and Columbia University. We have an exclusive license to a family of patent applications covering methods and compositions of the mda-7 tumor suppressor with several types of currently available therapies, including conventional chemotherapies, vascular endothelial growth factor inhibitors, such as Avastin® (bevacizumab), non- steroidal anti-inflammatory drugs, which include COX-2 inhibitors such as Celebrex®, (celecoxib) and proteasome inhibitors, which can increase therapeutic functionality, such as Velcade® (bortezemib).

INGN 225 (p53 molecular immunotherapy)

We are developing INGN 225 using the p53 tumor suppressor in a different manner to create a molecular immunotherapy for cancer 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 the p53 tumor suppressor 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 tumor suppressor, which suggests a molecular immunotherapy consisting of dendritic cells stimulated by p53 could have broad utility as a treatment for progression of tumors.

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We have completed a Phase 1/2 clinical trial in collaboration with the Moffitt Cancer Center at the University of South Florida in patients with small cell lung cancer. We are also conducting a Phase 1/2 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.

The results from the Phase 1/2 trial in patients with extensive small cell lung cancer who were previously treated with chemotherapy indicate that 52% of the evaluable patients in the study treated with INGN 225 had objective responses to subsequent chemotherapy and 41% of the evaluable patients were still alive one year after receiving this therapy. Historically, the expected objective response rate in similar patients to further chemotherapy is between approximately 5% and 30%. Patients with this type of lung cancer typically have a grave prognosis with a median survival of approximately six months, but treated patients in this study who developed an immune response to p53 had a median survival of approximately twelve months.

We believe the data indicate INGN 225 may sensitize tumors to the effects of platinum and taxane chemotherapies. Of particular interest is the observation that patients with highly aggressive disease (termed platinum resistant) showed improved response rates and increased survival compared to historical controls. These findings are consistent with the results observed in lung and breast cancer patients treated with ADVEXIN therapy that increased the expected effects of cisplatin, taxane and doxorubicin chemotherapies. As platinum, taxanes and doxorubicin are among the most common types of cancer chemotherapies, these findings may have important implications for improving the efficacy of these widely utilized cancer treatments.

INGN 234 (p53 topical)

We are developing INGN 234 for the prevention of oral cancers and the treatment of oral leukoplakia. We are conducting a Phase 1 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 suppressors 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 delivery of our therapies 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 molecules.

We have entered into an alliance agreement with Colgate-Palmolive to develop and potentially market oral healthcare products. See Part I, Item 1. Business Business and Collaborative Arrangements Alliance with Colgate-Palmolive Company below for further discussion of this alliance agreement.

INGN 401 (FUS-1)

INGN 401 uses a nanoparticle vector system to deliver the tumor suppressor 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.

Pre-clinical data suggest that INGN 401 may have utility as a monotherapy in lung cancer. We have observed significant inhibition of tumor growth in lung cancer animal models following INGN 401 monotherapy treatment when compared with untreated animals.

Pre-clinical data suggests that a combination of ADVEXIN therapy and INGN 401, administered intravenously in nanoparticle formulations, is capable of significantly shrinking metastatic tumors in models of human lung cancer. The data indicates that while ADVEXIN therapy and INGN 401 are each effective as a monotherapy, more powerful results were observed when the treatments were combined. The data also indicates that the nanoparticle treatments had no demonstrable adverse effects on normal cells. The results of the study that produced this data are published in *Cancer Research.*

INGN 401 has demonstrated synergistic activity with gefitinib (Iressa®), a novel class of anti-cancer agents that decrease tumor growth by inhibiting growth factor receptors that promote tumor proliferation. While gefitinib

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can produce dramatic responses in a small subset of lung cancer patients, most lung cancers are refractory to its effects. The data indicate nanoparticle delivery of INGN 401 can synergize with Gefitinib in killing lung tumor cells resistant to gefitinib alone. Furthermore, in gefitinib-sensitive tumors, INGN 401 delivery significantly enhanced anti-cancer activity.

A Phase 1/early Phase 2 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 published in *Cancer Gene Therapy* and *Cancer Research.*

INGN 402 and INGN 403 (nanoparticle formulations of p53 and mda-7, respectively)

We are developing two nanoparticle formulations for systemic delivery. INGN 402 contains the p53 tumor suppressor and INGN 403 contains the mda-7 tumor suppressor, also known as interleukin 24 (IL-24). Early studies with these new nanoparticle drug candidates have demonstrated a good safety profile and promising anti-cancer activity in murine lung tumor models. Data from the mda-7 nanoparticle studies was published in *DNA and Cell Biology* and presented at the annual meetings of the ASGT and ASCO.

INGN 007 (oncolytic viral therapy)

We are developing INGN 007, a replication-competent viral therapy, which is also called an oncolytic virus, in which viruses bind directly to cancer cells, replicate in those cells, and cause those cancer cells to die. Pre-clinical testing in animal models indicates INGN 007 over-expresses a molecule that allows the vector to saturate the entire tumor. This testing has demonstrated that INGN 007 has a favorable safety profile and significantly inhibits tumor growth. Findings from this work to develop INGN 007 have been published in *Cancer Research* and were presented at a meeting of the ASCO. We are developing this replication-competent viral therapy through our strategic collaboration with VirRx.

Other Research and Development Programs

We are conducting a number of pre-clinical and research programs involving a variety of targeted therapies for the treatment of cancer. These programs involve molecules that act through diverse mechanisms to inhibit the growth of or kill cancer cells.

We license from M. D. Anderson Cancer Center a group of molecules known as the 3p21.3 family. Pre-clinical research performed on these molecules by collaborators at The University of Texas Southwestern Medical Center and M. D. Anderson Cancer Center suggests that the 3p21.3 family plays a critical role in the suppression of tumor growth in lung and other cancers. This family of molecules includes the FUS-1 tumor suppressor we are testing as INGN 401 and the NPRL2 gene. We are working with M. D. Anderson Cancer Center to further evaluate other 3p21.3 family molecules as clinically relevant therapeutics.

The NPRL2 gene is believed to be important in the genesis of multiple types of cancer, including lung cancer and renal cell cancer. Preclinical data with the NPRL2 tumor suppressor gene demonstrated that systemic treatment using NPRL2 nanoparticles in combination with cisplatin resulted in a 90% inhibition of tumor growth in human lung cancer cells compared to control treatments. The ability to use a biomarker assay for NPRL2 to identify patients who might not experience significant benefit from treatment with cisplatin alone could represent an important advance in cancer treatment. Development of NPRL2 systemic nanoparticles may help patients whose tumors are resistant to cisplatin by re-sensitizing tumors to this commonly used therapy. Study results involving the NPRL2 treatment have been published in *Cancer Research*, a biomedical journal, and *Cancer Wise*, an electronic publication of M. D. Anderson Cancer Center.

We are evaluating additional molecules, including BAK, which hold promise as therapeutic candidates. BAK is a pro-apoptotic molecule 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 therapeutic molecule. We have exclusive rights to use the BAK molecule under a license with LXR Biotechnology, Inc. (LXR), with the LXR rights being subsequently sold to Tanox, Inc. (Tanox).

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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 were published in *Clinical Cancer Research* and *Molecular Cancer Therapeutics.*

We believe our research and development expertise gained from our molecular 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 molecular 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 targeted molecular products to patients and for enhancing the effects of these products. We plan to utilize these technologies to develop additional products to treat cancer and other diseases which, like cancer, result from cellular dysfunction and uncontrolled cell growth.

Nanoscale 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 delivery. These systems also may be applicable to indications where activity of the therapeutic molecule for disease treatment is required for longer periods of time or where systemic administration may be necessary.

Nanoparticle Systemic Delivery Platform

We hold an exclusive, worldwide license to a portfolio of patents from M. D. Anderson Cancer Center focused on the delivery of biologically active proteins, polypeptides and peptides using novel nanoparticle delivery complexes. These systemically-delivered nanoparticles are applicable to a wide variety of bioactive protein-derived molecules. This technology is directed to specially designed nanoparticles that carry and deliver therapeutic bioactive proteins, polypeptides and peptides to targeted cells, such as cancer cells.

These nanoparticle formulations have certain therapeutic advantages. While peptides alone may be rapidly removed from circulation, requiring frequent administration and high doses, our nanoparticle-polypeptide formulations can increase therapeutic activity and protect against rapid degradation normally associated with peptide therapy. In addition, our peptide nanoparticles can include special targeting molecules to further enhance cellular uptake and to improve therapeutic efficacy.

We have 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 using this technology in INGN 401, INGN 402 and INGN 403.

Data published in *DNA and Cell Biology* highlight the potential utility of combining our nanoparticle delivery system with the mda-7 tumor suppressor for the treatment of lung cancer. This data demonstrate that combining this innovative delivery system with the mda-7 tumor suppressor results in potent anti-cancer effects and systemic tumor

growth inhibition in an animal model of lung cancer. We believe combining potent anti-cancer tumor suppressors, such as mda-7 or p53, with our nanoparticle delivery system could allow development of clinical strategies to attack metastatic cancers.

Replicating Viral Delivery Systems

Through our strategic collaboration with VirRx, we are developing replication-competent viral therapies, also known as oncolytic viruses, in which viruses bind directly to cancer cells, replicate in those cells, and cause those cancer cells to die. This technology forms the basis for our INGN 007 product development. We anticipate pursuing

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clinical confirmation as to whether this self-amplifying delivery system can complement our existing adenoviral delivery system, which is replication disabled, in selected therapeutic scenarios, in applications beyond INGN 007.

Additional Enabling Technologies

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

Multi-Molecule Vector System. This technology is designed to combine multiple therapeutic molecules 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 molecular therapy at a time for disease treatment.

Pro-Apoptotic Molecule Delivery System. This technology is designed to allow the activity of pro-apoptotic, or apoptosis-inducing, molecules during treatment only, while temporarily suppressing the ability of the apoptotic molecule 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 promote the activity of the therapeutic molecule in only those cells which have been affected by the disease being targeted. It is intended to be applied to both viral and non-viral vectors.

Manufacturing and Process Development

Commercialization of a targeted molecular therapy 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 state-of-the-art manufacturing facilities, including a commercial-scale, validated manufacturing facility designed to comply with the FDA s Current Good Manufacturing Practice requirements, commonly known as CGMP requirements. We have produced numerous batches of ADVEXIN therapy clinical material for use in our Phase 1, 2 and 3 clinical trials. The design and processes of the facility used for ADVEXIN therapy production have been reviewed with the FDA. We plan to use our facilities for the market launch of ADVEXIN therapy. We also use our facilities to produce INGN 241 and other investigative materials for use in clinical trials of those product candidates. From time to time, as requirements for our own products allow, we also manufacture pre-clinical and clinical materials for outside parties for a fee under contract services arrangements.

Business and Collaborative Arrangements

Alliance with Colgate-Palmolive Company

In November 2005, we entered into an alliance agreement with Colgate-Palmolive to develop and potentially market oral healthcare products. In connection with the alliance agreement and pursuant to a common stock purchase agreement, Colgate-Palmolive purchased 3,610,760 shares of our common stock at a price of $5.539 per share for a total of approximately $20.0 million. Under the common stock purchase agreement, Colgate-Palmolive agreed to vote these shares and any other shares of our capital stock owned by it in favor of corporate actions approved by our Board of Directors. This voting agreement is subject to suspension or termination upon certain events specified in the common stock purchase agreement.

Pursuant to the alliance agreement, we will conduct research and development activities involving specialized formulations of our molecular therapies (such as p53, mda-7 and FUS-1) targeted at precancerous conditions of the oral cavity and at oral cancer. The objective is to market these formulations as oral healthcare products. The alliance agreement excludes certain of our cancer product candidates, including ADVEXIN therapy, INGN 241, INGN 225 and INGN 401.

Colgate-Palmolive has a first right to negotiate development, manufacturing, marketing and distribution rights with us for specifically designed oral healthcare products for use in the human oral cavity that may result from these

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research and development activities. We agreed to use commercially reasonable efforts to develop one or more specialized oral formulations through completion of Phase 2 clinical trials within the seven-year term of the alliance agreement. We can terminate our development efforts earlier under certain circumstances, including if the prospects for these products do not warrant further investment, or if we expend $15.0 million in this effort. In calculating the amount of our expenditures on these efforts, we may include grant funding received by us or our collaborators for work performed by third parties (e.g., universities and other institutions) that is directly related to program activities, as specified in the alliance agreement. The term of the alliance agreement continues to November 2012, unless earlier terminated by the parties as provided in the alliance agreement.

VirRx, Inc.

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

Under an agreement with VirRx, we purchased $2,475,000 of VirRx s Series A Preferred Stock for cash, of which we purchased $150,000 and $600,000 during the years ended December 31, 2006 and December 31, 2005, respectively. We are not obligated to make any additional such purchases at this time. We recorded these purchases as research and development expense.

Provided the agreement with VirRx 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, 2 and 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 will receive no VirRx stock, upon approval by the FDA of a BLA 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 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.

SR Pharma plc

We own approximately 6.6% of the issued share capital of SR Pharma. We purchased these shares for approximately $3.0 million in July 2005. The shares we own had a quoted market value of $6.9 million at December 31, 2006 and $9.7 million at March 7, 2007. SR Pharma is a European biotechnology company publicly traded on the Alternative Investment Market of the London Stock Exchange (LSE) that is developing oncology and other products.

Academic and Other Collaborations

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

The University of Texas M. D. Anderson Cancer Center

Many of our core technologies were developed by scientists at 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.

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We have exclusive license agreements with The Board of Regents of the University of Texas System and M. D. Anderson Cancer Center covering many of the core technologies and products we are developing, including ADVEXIN therapy. These license agreements generally terminate on the date of expiration of the last to expire patents covered by these agreements (or earlier if no patent rights are applicable), and are terminable upon either party s breach, upon notice on a patent by patent basis or should we become insolvent.

To maintain the exclusivity of these licenses, we are required to conduct ongoing research and development of, and/or use commercially reasonable efforts to, commercialize these technologies. We have agreed to pay M. D. Anderson Cancer Center royalties on sales of products utilizing these technologies. We are obligated to reimburse any of M. D. Anderson Cancer Center s costs that may be incurred in connection with obtaining patents related to the licensed technologies. Our strategy for product development is designed to take advantage of the significant multidisciplinary resources available at M. D. Anderson Cancer Center. These efforts have resulted in our becoming a significant corporate sponsor of activities at M. D. Anderson Cancer Center in recent years and have yielded to us exclusive patent and licensing rights to numerous technologies.

National Cancer Institute

We have a cooperative research and development agreement, or CRADA, with the NCI. The CRADA has a flexible duration, but is terminable upon the mutual consent of the parties or upon 30 days notice of either party. Under the CRADA, the 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, the NCI has conducted numerous Phase 1 clinical trials for ADVEXIN therapy. The NCI provided most of the funding for these activities. We supplied the 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.

Research and License Agreement for the mda-7 Tumor Suppressor

We have a research and license agreement with GlaxoSmithKline, pursuant to which we acquired an exclusive, worldwide license to the mda-7 tumor suppressor for the therapeutic applications we are pursuing. This agreement was originally with Corixa, which subsequently was acquired by GlaxoSmithKline. 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 tumor suppressor. Corixa originally licensed the mda-7 tumor suppressor from Columbia University.

Moffitt Cancer Center

We are collaborating with the H. Lee Moffitt Cancer Center and Research Institute to advance our INGN 225 molecular cancer immunotherapy 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 molecular immunotherapy field.

London Stock Exchange

We are evaluating the feasibility of listing our common stock on the LSE, which would be in addition to the listing of our common stock on the Nasdaq Global Market in the United States. We believe an LSE listing may allow us to better leverage our assets on a global basis and, specifically, in Europe and Asia.

Research and Development Expense

Our research and development expense was $18.2 million, $21.4 million and $20.5 million for the years ended December 31, 2006, 2005 and 2004, respectively.

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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.

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, which was acquired by GlaxoSmithKline, Aventis Pharmaceutical Products, Inc. (Aventis), which is now Sanofi-Aventis, Columbia University, VirRx and LXR, with the LXR rights being subsequently sold to Tanox. 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. Currently, the last to expire patents key to our ADVEXIN therapy expire in 2020, however, we have applications pending that could extend our coverage for our ADVEXIN therapy beyond these dates. Patents key to our INGN 241 product, using the mda-7 tumor suppressor, expire in the time frame of 2013 to 2016, although we have pending patent cases that could extend our protection beyond these expiration dates. 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 patents and patent applications directed to adenoviruses that contain p53, referred to as adenoviral p53, adenoviral p53 DNA, adenoviral p53 pharmaceutical compositions, the production of adenoviral p53 compositions and the use of such compositions in various cancer therapies and protocols.

We have exclusively licensed from Aventis patent applications directed to adenoviral p53 and its clinical applications. We have an exclusive license to a United States patent application and corresponding international applications directed to the use of the p53 tumor suppressor in the treatment of cancer patients whose tumors express a normal p53 protein.

Combination Therapy with Tumor Suppressors, including p53 and mda-7/IL24

Our portfolio development includes seeking protection for clinical therapeutic strategies that combine the use of either the p53 tumor suppressor or the mda-7/IL-24 tumor suppressor 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 a number of issued United States patents and applications with corresponding international patents and applications directed to cancer therapy using either the p53 tumor suppressor or the mda-7/IL-24 tumor suppressor in combination with conventional radiotherapy and/or other anti-cancer compounds. Such compounds include:

DNA-damaging agents and conventional chemotherapies;

Immunotherapeutics (e.g., Herceptin®);

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COX-2 inhibitors (e.g., celecoxib);

Hsp90 inhibitors;

Proteasome inhibitors;

VEGF inhibitors (e.g., Avastin®); and

EGFr inhibitors (e.g., Tarceva®, Iressa®).

These United States patents and applications and corresponding international patents and applications concern the therapeutic application of the p53 tumor suppressor or the mda-7/IL-24 tumor suppressor before, during or after treatment with radiotherapy or other anti-cancer compounds.

To further extend our portfolio as it relates to combinatorial anti-cancer therapy, we have licensed from Aventis a United States patent and corresponding international patents and applications directed to therapy using the p53 tumor suppressor together with taxanes such as Taxol® or Taxotere®. We have exclusively licensed a United States patent application and corresponding international applications directed to the use of the p53 tumor suppressor 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. We own three issued United States patents and related European patents, as well as a number of pending United States applications and corresponding international applications directed to highly purified adenoviral compositions, commercial-scale processes for producing adenoviral-based compositions having a high level of purity and storage-stable formulations. These patents and patent applications include procedures for preparing commercial quantities of recombinant adenovirus products and include procedures applicable to the p53 tumor suppressor, as well as any of our other potential products.

We have licensed from Aventis in the p53 field a United States patent and corresponding international applications directed to processes for the production of purified adenoviruses, which are useful for our product applications. With respect to storage-stable formulations, we were issued a United States patent directed to compositions and methods concerning improved, storage-stable adenovirus formulations. This patent is not limited to our ADVEXIN therapy product candidate and may eventually replace formulations currently in use.

Other Tumor Suppressors

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

Other Therapeutic, Composition and Process Technologies

We own or have exclusively licensed a number of United States and international patent applications on a range of additional technologies. These licenses include various applications and patents relating to p53, combination therapy with 2-methoxyestradiol, anti-proliferative factor technologies, retroviral delivery systems, stimulation of anti-p53 and

screening and product assurance technologies.

We have exclusively licensed a number of United States and international applications directed to various improved vector applications employing more than one molecular therapy for disease treatment, as well as applications directed to the delivery of molecular therapies for disease treatment without the use of a vector, or non-viral therapy. For example, a United States patent, exclusively licensed to us, was issued that is directed to adenoviruses that exhibit tissue specific replication. We have exclusive rights in an issued United States patent and corresponding international applications directed to a low toxicity analogue of IL-24, also called F42K. We also

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have been issued exclusively licensed patents in Europe directed to our nanoparticle delivery system for delivering tumor suppressor genes.

Benzimidazole Small Molecule Cancer Therapy Program

We 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 tumor suppressor.

Trade Secrets

We rely on trade secrets law to protect technology where we believe patent protection is not appropriate or obtainable. Trade secrets are difficult to protect. We generally require employees, academic collaborators and consultants to enter into confidentiality agreements covering our trade secrets and other confidential information. 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 the case of technologies that we have licensed, we do not have the ability to make the final decisions on how the patent application process is managed, and accordingly are unable to exercise the same degree of control over this intellectual property as we exercise over our internally developed technology.

Our research collaborators and scientific advisors have rights to publish data and information in which we have rights. If we cannot maintain the confidentiality of our technology and other confidential information in connection with our collaborations, then our ability to receive patent protection or protect our proprietary information will be diminished.

Government Regulation

The 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 (our products will be regulated as biologics) 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.

A complex, lengthy, cumbersome and expensive process such that we cannot be certain that we will receive FDA approval for any of our products.

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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 (1) the results of previous testing, (2) how, where and by whom the clinical trials will be conducted, (3) the chemical structure of the compound, (4) the method by which it is believed to work in the human body; (5) any toxic effects of the compound found in the animal trials and (5) how the compound is manufactured.

Clinical Trials

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

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

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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. The actual time required may vary substantially based upon the type, complexity and novelties of the product or disease. Government regulation may delay or present marketing of potential products for a considerable period of time and impose costly procedures upon our activities.

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

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. Legislative proposals have been introduced from time-to-time 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.

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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. Current 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

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

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

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

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

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 product, the FDA will take actions to expedite the evaluation and review of the application for approval of ADVEXIN therapy. The Fast Track designation for ADVEXIN therapy from the FDA does not guarantee a faster development process, review process or approval compared to conventional FDA procedures.

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We may seek Fast Track designation for our other products. We may be prevented from seeking, approval under the Accelerated Approval process for any of our 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.

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.

In Europe, we have been granted Orphan Drug status for the use of ADVEXIN therapy in LFS. We intend to pursue an Exceptional Circumstances Approval for this product and seek Conditional Approval for the use of ADVEXIN therapy in head and neck cancer.

We cannot be sure that international 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 will continue to face, competition in the development and marketing of our product candidates from academic institutions, government agencies, research institutions and biotechnology and pharmaceutical companies. Competition may arise from other drug development technologies, methods of preventing or reducing the incidence of disease, including molecular immunotherapies, 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 the Chinese pharmaceutical companies SiBiono GeneTech, Inc. (SiBiono GeneTech) and Shanghai Sunway Biotech Co. Ltd. have announced they have received regulatory approval from the Chinese drug regulatory authorities to market an adenoviral p53 product and an oncolytic virus product, respectively, both only in China. We are also aware of other pharmaceutical and biotechnology companies, including Canji, Inc. (Canji), Genvec, Inc. (Genvec) and ImClone Systems, Inc., which are pursuing forms of treatment for the diseases ADVEXIN therapy and our other product candidates target.

We are aware that ImClone and Bristol Myers Squibb have obtained marketing approval based on a supplemental application to the FDA for a monoclonal antibody product (Erbitux) for the treatment of certain kinds of head and neck cancer. Erbitux was approved for two stages of treatment of the cancer, one for an early, as yet untreated form, and a second for refractory head and neck cancer already treated with chemotherapy.

We are aware that Sanofi-Aventis has obtained marketing approval for the use of Taxotere® in combination with cisplatin and 5FU for the treatment of certain kinds of head and neck cancer.

We are aware that Canji, with its parent Schering-Plough Corporation (Schering-Plough), 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.

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We expect 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 depends upon our ability to obtain required regulatory approvals, 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 7, 2007, we had approximately 74 employees and contracted personnel engaged in research and development, regulatory affairs, clinical affairs, manufacturing and quality, finance and corporate development activities. Several of our employees hold 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 Innovative Cancer Therapies at M. D. Anderson Cancer Center where he holds the Bud Johnson Clinical Distinguished Chair. Dr. Roth was one of our founders and is our Chief Medical Advisor. Dr. Roth is a widely-recognized pioneer in the application of targeted molecular therapies to the treatment of cancer. He is the primary inventor of the technology supporting our tumor suppressor products. He received his M.D. from The Johns Hopkins University School of Medicine.

Carol L. Prives, Ph.D., is DaCosta Professor of Biology at Columbia University and American Cancer Society Professor. She is a member of the advisory boards of Memorial Sloan Kettering Cancer Center and of the American Association for Cancer Research. She serves on the editorial boards of prominent journals including Cell and Genes & Development. She received her Ph.D. in biochemistry from McGill University.

Daniel D. Von Hoff, M.D., F.A.C.P., is the Physician in Chief and Senior Investigator for the Translational Genomics Research Institute (TGen) and Clinical Professor of Medicine at the University of Arizona, Arizona Cancer Center, Arizona Health Sciences Center. Dr. Von Hoff is also Chief Scientific Officer for US Oncology and Scottsdale Clinical Research Institute. Dr. Von Hoff is certified in medical oncology by the American Board of Internal Medicine. He received his M.D. from The Columbia College of Physicians and Surgeons.

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

Item 1A. ***Risk Factors***

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

Our ability to achieve and sustain operating profitability depends on our ability to successfully commercialize ADVEXIN therapy in various markets for multiple indications, which depends in large part on our ability to

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

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

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

We have completed or are conducting clinical trials of our lead product candidate, ADVEXIN therapy, for the treatment of various cancers. Current or future clinical trials may demonstrate ADVEXIN therapy is neither safe nor effective.

We have completed or are conducting clinical trials of INGN 241, a product candidate based on the mda-7 tumor suppressor. We will need to continue conducting significant research and animal testing, referred to as pre-clinical testing, to support performing clinical trials for our other product candidates. It will take us many years to complete pre-clinical testing and clinical trials, and failure could occur at any stage of testing. Current or future clinical trials may demonstrate INGN 241 or our other product candidates are neither safe nor effective.

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

- the product candidate is less effective and/or more toxic than current therapies;
- the presence of unforeseen adverse side effects of a product candidate, including its delivery system;
- a longer than expected time required to determine whether or not a product candidate is effective;
- the death of patients during a clinical trial, even if the product candidate did not cause those deaths;
- the failure to enroll a sufficient number of patients in our clinical trials;
- the inability to produce sufficient quantities of a product candidate to complete the trials; or
- the inability to commit the necessary resources to fund the clinical trials.

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

Despite the FDA s designation of ADVEXIN therapy as a Fast Track product, we may encounter delays in the regulatory approval process due to additional information requirements from the FDA, unintentional omissions in our BLA for ADVEXIN therapy, or other delays in the FDA s review process. Similarly, although we have an agreement with the European Medicines Agency (EMEA) to file for marketing approval for ADVEXIN therapy under the EMEA s Exceptional Circumstances provisions, we may encounter delays in the regulatory approval process due to additional information requirements from the EMEA, unintentional omissions in our Marketing Authorization Application filed with the EMEA, or other delays in the EMEA s review process. We may encounter delays or rejections in the regulatory approval process because of additional government regulation from future legislation or administrative action or changes in FDA or EMEA policy during the period of product development, clinical trials and FDA and EMEA regulatory review.

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Despite the initiation of the BLA process for ADVEXIN therapy under the FDA s accelerated approval regulations, the FDA could determine that accelerated approval is not warranted and that a traditional BLA filing must be made. Such a determination could delay regulatory approval. Additionally, accelerated approval of an application could 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 could cause the product to be withdrawn from the market by the FDA on an expedited basis.

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

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

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

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

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

We have generated operating losses since we began operations in June 1993. As of December 31, 2006, we had an accumulated deficit of approximately $172.3 million. We expect to incur substantial additional operating expense and losses over the next several years as our research, development, pre-clinical testing and clinical trial activities increase. As we expand our operations and develop systems to support commercialization of our product candidates, these losses, among other things, have had, and are expected to continue to have, an adverse impact on our total assets, stockholders equity and working capital.

We have no products that have generated any commercial revenue. Presently, we earn minimal revenue from contract services activities, grants, interest income and rent from the lease of a portion of our facilities to M. D. Anderson Cancer Center. We do not expect to generate revenue from the commercial sale of products in the near future, and we

may never generate revenue from the commercial sale of products.

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

Developing a new drug and conducting clinical trials is expensive. Our product development efforts may not lead to commercial products, either because our product candidates fail to be found safe or effective in clinical trials or because we lack the necessary financial or other resources or relationships to pursue our programs through commercialization. Our capital and future revenue may not be sufficient to support the expense of our operations, the development of commercial infrastructure and the conduct of our clinical trials and pre-clinical research.

We expect we will fund our operations over approximately the next 21 to 24 months with our current working capital, which we accumulated primarily from sale of equity securities, income from contract services and research grants, debt financing of equipment acquisitions, the lease of a portion of our facilities to M. D. Anderson Cancer Center and interest on invested funds. We intend to raise additional capital sooner, however, under various circumstances, including if we experience:

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

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

higher than expected costs to obtain regulatory approvals;

higher than expected costs to pursue our intellectual property strategy;

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

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

faster than expected rate of progress and cost of our research and development and clinical trial activities;

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

higher than expected costs of preparing an application for FDA or foreign regulatory approval of ADVEXIN therapy;

higher than expected costs of developing the processes and systems to support FDA or foreign regulatory approval of ADVEXIN therapy;

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

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

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

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

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

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

Our strategy for the research, development and commercialization of our product candidates may result in our entering into contractual arrangements with corporate collaborators, academic institutions and others. We have

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entered into sponsored research, license and/or collaborative arrangements with several entities, including M. D. Anderson Cancer Center, the NCI, Chiba University in Japan, VirRx and Corixa, which was acquired by GlaxoSmithKline, as well as numerous other institutions that conduct clinical trials work or perform pre-clinical research for us. Our success depends upon our collaborative partners performing their responsibilities under these arrangements and complying with the regulations and requirements governing clinical trials. We cannot control the amount and timing of resources our collaborative partners devote to our research and testing programs or product candidates, or their compliance with regulatory requirements which can vary because of factors unrelated to such programs or product candidates. These relationships may in some cases be terminated at the discretion of our collaborative partners with only limited notice to us. We may not be able to maintain our existing arrangements, enter into new arrangements or negotiate current or new arrangements on acceptable terms, if at all. Some of our collaborative partners may also be researching competing technologies independently from us to treat the diseases targeted by our collaborative programs.

If we do not continue to receive grant funding from federal agencies and others, we may be unable to continue our research and development programs for certain of our product candidates at current levels or in the manner we have planned for the future.

We rely on grants from third parties, generally federal agencies, to provide the funding necessary to conduct our research and development programs for some of our technologies and product candidates. Funding of these grants is typically subject to government appropriations. These grants often contain provisions that allow for termination at the convenience of the government. Further, these grants are subject to complex federal guidelines and regulations. If federal agencies or regulatory authorities determine that we, or the programs for which we desire to receive or have received grant funding, do not qualify for funding, our scientific or product development programs could be slowed or stopped and we may suffer financial losses and be unable to successfully commercialize our products.

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

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

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

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

The United States Senate has held hearings concerning the adequacy of regulatory oversight of recombinant DNA therapy clinical trials, as well as the adequacy of research subject education and protection in clinical research in general, and to determine whether additional legislation is required to protect volunteers and patients who participate in such clinical trials. The Recombinant DNA Advisory Committee, which acts as an advisory body to the NIH, has expanded its public role in evaluating important public and ethical issues in recombinant DNA therapy

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clinical trials. Implementation of any additional review and reporting procedures or other additional regulatory measures could increase the costs of or prolong our product development efforts or clinical trials.

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

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

Patient enrollment may be slow and patients may discontinue their participation in clinical studies, which may negatively impact the results of these studies, and extend the timeline for completion of our and our collaborator s development programs for our product candidates.

The time required to complete clinical trails is dependent upon, among other factors, the rate of patient enrollment. Patient enrollment is a function of many factors, including:

the size of the patient population;

the nature of the clinical protocol requirements;

the diversion of patients to other trials or marketed therapies;

the ability to recruit and manage clinical centers and associated trials;

the proximity of patients to clinical sites; and

the patient eligibility criteria for the study.

We are subject to the risk that patients enrolled in our and our collaborator s clinical studies for our product candidates may discontinue their participation at any time during the study as a result of a number of factors, including, withdrawing their consent or experiencing adverse clinical events which may or may not be related to our product candidates under evaluation. We are subject to the risk that if a large number of patients in any one of our studies discontinue their participation in the study, the results from that study may not be positive or may not support an NDA for regulatory approval of our product candidates.

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

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

therapies.

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

Our commercial success will depend in part on obtaining patent protection for our products and other technologies and successfully defending these patents against third-party challenges. Our patent position, like that of other biotechnology and pharmaceutical companies, is highly uncertain. One uncertainty is the United States Patent and Trademark Office, or PTO, or the courts, may deny or significantly narrow claims made under patents issued to us or patent applications we file. This is particularly true for patent applications or patents that concern

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biotechnology and pharmaceutical technologies, such as ours, since the PTO and the courts often consider these technologies to involve unpredictable sciences. Another uncertainty is any patents that may be issued or licensed to us may not provide any competitive advantage to us because they may not effectively preclude others from developing and marketing products like ours. Also, our patents may be successfully challenged, invalidated or circumvented in the future. In addition, our competitors, many of which have substantial resources and have made significant investments in competing technologies, may seek to apply for and obtain patents that will prevent, limit or interfere with our ability to make, use and sell our potential products either in the United States or in international markets.

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

Through our exclusive license from The University of Texas System for technology developed at M. D. Anderson Cancer Center, we have obtained and are currently seeking further patent protection for adenoviral p53, including ADVEXIN therapy, and its use in cancer therapy. Further, the PTO issued us United States patents for our adenovirus production technology and our purified adenoviral compositions. We also control, through licensing arrangements, United States patents for combination therapy involving the p53 tumor suppressor and conventional chemotherapy or radiation, the use of adenoviral p53 in cancer therapy, adenoviral p53 as a product, the core DNA of adenoviral p53, pharmaceutical compositions of adenoviral p53 and clinical applications of such pharmaceutical compositions, as well as patents covering our mda-7 technology. Our competitors may challenge the validity of one or more of our patents in the courts or through an administrative procedure known as an interference, in which the PTO determines the priority of invention where two or more parties are claiming the same invention. The courts or the PTO may not uphold the validity of our patents, we may not prevail in such interference proceedings regarding our patents and none of our patents may give us a competitive advantage. In this regard, we have been notified by the PTO that an unidentified third party is attempting to provoke an interference with one of our patents directed to adenoviral p53 therapy. We do not at present know the identity of this party and cannot assess the likelihood of an interference actually being declared. Should that party prevail in an interference proceeding, a patent may issue to that party that is infringed by, and therefore potentially preclude our commercialization of, products like ADVEXIN therapy that are used for adenoviral p53 therapy.

Schering-Plough filed with the European Patent Office, or EPO, an opposition against our European patent directed to combination therapy with p53 and conventional chemotherapy and/or radiation. An opposition is an administrative proceeding instituted by a third party and conducted by the EPO to determine whether a patent should be maintained or revoked, in part or in whole, based on evidence brought forth by the party opposing the patent. In February 2006, the Technical Board of Appeals of the EPO held a final oral proceeding concerning Schering-Plough s opposition and determined our patent should be maintained as amended. No further appeal by Schering-Plough is possible.

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

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cannot maintain the confidentiality of our technology and other confidential information in connection with our collaborations, then our ability to receive patent protection or protect our proprietary information will be diminished.

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

The biotechnology and pharmaceutical industry has been characterized by extensive litigation regarding patents and other intellectual property rights, and companies have employed intellectual property litigation to gain a competitive advantage. We are aware of a number of issued patents and patent applications related to recombinant DNA therapy, the treatment of cancer and the use of the p53 and other tumor suppressors. Schering-Plough, including its subsidiary Canji, controls various United States applications and a European patent and applications, some of which are directed to therapy using p53, and others to adenoviruses containing p53, or adenoviral p53, and to methods for carrying out therapy using adenoviral p53. Adenoviral p53 technology underlies our ADVEXIN therapy product candidate. Furthermore, we are aware of a United States patent directed to replication-deficient recombinant adenoviral vectors apparently controlled by Transgene SA (Transgene). While we believe the claims of the Transgene adenoviral vector patent are invalid or not infringed by our products, Transgene could assert a claim against us.

One of the foregoing patent applications directed to p53 therapy, which we understand is owned by The Johns Hopkins University (Johns Hopkins) and controlled by Schering-Plough, was involved in a PTO interference proceeding with a patent owned by Canji. This Johns Hopkins application was the United States counterpart to the European patent recently revoked in its entirety by the EPO (see below). Priority of invention in that interference was awarded by the PTO to the Johns Hopkins inventors, leading to the issuance of a United States patent, and the Canji patent has been found unpatentable. While it is our belief that the claims of the Johns Hopkins patent are invalid and not infringed by our ADVEXIN therapy, Schering-Plough or Johns Hopkins may assert that our ADVEXIN therapy, which uses p53 therapy, infringes the claims of such patent. While we believe we would have both an invalidity and non-infringement defense against such an assertion, in the United States an issued patent enjoys a presumption of validity, which can be overcome only through clear and convincing evidence. We cannot assure such a defense would prevail.

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

We have recently been involved in patent opposition proceedings before the EPO, in which we have sought to have the EPO revoke three different European patents owned or controlled by Canji/Schering-Plough. These European patents relate to the use of p53, or the use of tumor suppressors, in the preparation of therapeutic products. In one opposition involving a Canji European patent directed to the use of a recombinant tumor suppressor, the EPO revoked the European patent in its entirety in a final, non-appealable decision. In the second opposition, involving a patent that is directed to therapeutic and other applications of the p53 and that is owned by Johns Hopkins and, we understand,

controlled by Schering-Plough, the EPO recently revoked the patent in its entirety. The patent owner appealed this decision and the final hearing before the EPO Technical Board of Appeals was held in June 2005, at which time the Technical Board of Appeals confirmed the final revocation of all claims of this patent relevant to

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clinical therapeutic applications of p53. In a third case involving the use of p53, the European patent at issue was initially upheld, but finally revoked in a hearing held in late April 2004.

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

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

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

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

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

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

We compete with pharmaceutical and biotechnology companies, including Canji and Genvec, which are pursuing forms of treatment similar to ours for the diseases ADVEXIN therapy and our other product candidates target. We are aware that Canji, with its parent Schering-Plough, has in the past been involved in research and/or development of adenoviral p53 products and has numerous patents and patent applications relating to adenoviral p53 therapy. We understand Schering-Plough has stopped its adenoviral p53 clinical trials, and it is unknown whether these parties are continuing their adenoviral p53 research and/or development efforts. We are also aware that a Chinese pharmaceutical company, SiBiono GeneTech, has recently announced it has received regulatory approval from the Chinese drug regulatory agency to market an adenoviral p53 product only in China. We control an issued Chinese patent covering adenoviral p53, and a number of pending Chinese applications directed to p53 therapy and adenoviral production. We understand enforcement of patents in China is unpredictable and we do not know if monetary damages could be recovered from SiBiono GeneTech if its product infringes our patent or patent applications. Patent enforcement and respect of international patent standards, rules and laws have not historically been a key characteristic of the Chinese government and patent system. Further, geopolitical developments, including trade and tariff disputes between the

government of China and the United States Department of Commerce could add additional uncertainty to any effort to enforce patents, recover damages, if any, or engage in the sales and marketing of patented or non-patented products in China. We are aware that ImClone and Bristol Myers Squibb have obtained marketing approval for a monoclonal antibody product (Erbitux) for the treatment of certain kinds of recurrent head and neck cancer. We also may face competition from companies that may develop internally or acquire competing technology from universities and other research institutions. As these companies

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develop or acquire their technologies, they may develop competitive positions that may prevent or limit our product commercialization efforts.

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

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

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

they are more effective than alternative treatments;

their side effects are acceptable to patients and doctors;

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

we produce and sell them at a profit; and

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

We must achieve significant market share and obtain high per-patient prices for our products to achieve profitability.

ADVEXIN therapy, our lead product candidate will, if approved, initially be targeted for the treatment of recurrent head and neck cancer, a disease with an annual incidence of approximately 40,000 patients in the United States. As a result, our per-patient prices must be sufficiently high in order to recover our development costs and achieve profitability. Until additional disease targets with larger potential markets are approved, we believe we will need to market worldwide to achieve significant market penetration. If we are unable to obtain sufficient market share for our drug products at a high enough price, or obtain expanded approvals for larger markets, we may not achieve profitability or be able to independently continue our product development efforts.

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

To complete our clinical trials and commercialize our product candidates, if approved, we will need access to, or development of, facilities to manufacture a sufficient supply of our product candidates. We have used manufacturing facilities we constructed in Houston, Texas to manufacture ADVEXIN therapy, INGN 241 and other product candidates for currently planned clinical trials. We anticipate our facilities are suitable for the initial commercial launch of ADVEXIN therapy. We have no experience manufacturing ADVEXIN therapy, INGN 241 or any other product candidates in the volumes necessary to support commercial sales. If we are unable to manufacture our product candidates in clinical or, when necessary, commercial quantities, then we will need to rely on third-party

manufacturers to produce our products for clinical and commercial purposes. These third-party manufacturers must receive FDA approval before they can produce clinical material or commercial product. Our products may be in competition with other products for access to these facilities and may be subject to delays in manufacture if third parties give other products greater priority than ours. In addition, we may not be able to enter into any necessary third-party manufacturing arrangements on acceptable terms. There are a limited number of contract manufacturers who currently have the capability to produce ADVEXIN therapy, INGN 241 or our other

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product candidates, and the inability of any of these contract manufacturers to deliver our required quantities of product candidates timely and at commercially reasonable prices would negatively affect our operations.

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

Our current manufacturing facilities have not yet been subject to a Pre-Approval Inspection by the FDA or other global regulatory authorities. Failure to pass Pre-Approval Inspections may significantly delay approval of our products. If we fail to comply with these requirements, we would be subject to possible regulatory action and may be limited in the jurisdictions in which we are permitted to sell our products. Further, the FDA and foreign regulatory authorities have the authority to perform unannounced periodic inspections of our manufacturing facilities to ensure compliance with CGMP and foreign regulatory requirements. Our facilities in Houston, Texas are our only manufacturing facilities. If these facilities were to incur significant damage or destruction, then our ability to manufacture ADVEXIN therapy, INGN 241 or any other product candidates would be significantly hampered, and our pre-clinical testing, clinical trials and commercialization efforts would be delayed.

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

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

We rely on a limited number of suppliers for some of our manufacturing materials. Any problems experienced by such suppliers could negatively affect our operations.

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

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

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

decreased demand for our product candidates;

injury to our reputation and significant media attention;

withdrawal of clinical trial volunteers;

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substantial delay in FDA or foreign regulatory authority approval;

costs of litigation; and

substantial monetary awards to plaintiffs.

We currently maintain product liability insurance with coverage of $5.0 million per occurrence with a $10.0 million annual aggregate limit. This coverage may not be sufficient to protect us fully against product liability claims. We intend to expand our product liability insurance coverage beyond clinical trials to include the sale of commercial products if we obtain marketing approval for any of our product candidates. Our inability to obtain sufficient product liability insurance at an acceptable cost to protect against product liability claims could prevent or limit the commercialization of our products.

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

Our business involves the use of a broad range of hazardous chemicals and materials. Environmental laws impose stringent civil and criminal penalties for improper handling, disposal and storage of these materials. In addition, in the event of an improper or unauthorized release of, or exposure of individuals to, hazardous materials, we could be subject to civil damages due to personal injury or property damage caused by the release or exposure. A failure to comply with environmental laws could result in fines and the revocation of environmental permits, which could prevent us from conducting our business.

Our stock price may fluctuate substantially.

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

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

announcement of technological innovations by us or our competitors;

developments concerning proprietary rights, including patent and litigation matters;

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

regulatory developments;

the announcement of new products by us or our competitors;

quarterly variations in our or our competitors results of operations;

failure to achieve operating results projected by securities analysts;

changes in earnings estimates or recommendations by securities analysts;

developments in our industry; and

general market conditions and other factors.

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

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

For planning purposes, we estimate the timing of a variety of clinical, regulatory and other milestones, such as when a certain product candidate will enter clinical development, when a clinical trial will be completed or when an application for regulatory approval will be filed. Some of our estimates are included in this Annual Report on Form 10-K for the year ended December 31, 2006. Our estimates are based on present facts and a variety of assumptions. Many of the underlying assumptions are outside of our control. If milestones are not achieved when we expect them to be, investors could be disappointed, and our stock price may decrease.

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

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

potential exposure to unknown liabilities of acquired companies;

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

diversion of management time and attention and other resources;

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

the incurrence of amortization expense; and

possible dilution to our stockholders.

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

Due to the potential value of our strategic investments, we could be determined to be an investment company, and if such a determination were made, we would become subject to significant regulation that would adversely affect our business.

We may be deemed to be an investment company under the Investment Company Act of 1940 if, among other things, we own investment securities with a value exceeding 40% of the value of our total assets, unless a particular exemption or safe harbor is applicable. We invest certain of our assets in short-term, investment grade securities, some of which may qualify as investment securities under the Investment Company Act. Additionally, from time to time we may make strategic investments in businesses that we do not operate or control, which investments may also qualify as investment securities under the Investment Company Act. Our non-controlling position in SR Pharma, along with investments of our available cash resources in certain types of fixed-income securities, could be considered investment securities under the Investment Company Act. Investment companies are subject to registration under the Investment Company Act and compliance with a variety of restrictions and requirements imposed by the Investment Company Act. If we were to be deemed an investment company we would become subject to these restrictions and requirements, and the consequences of having been an investment company without registering under the Investment Company Act could have a material adverse effect on our business, financial condition and results of operations, as well as restrict our ability to sell and issue securities, borrow funds, engage in various transactions or other activities and make certain investment decisions. In addition, we may incur significant costs to avoid investment company status if an exemption from the Investment Company Act were to be considered unavailable to us at a time when the value of our investment securities exceeds 40% of the value of our total assets. We believe that we are primarily engaged in the research, development and commercialization of biological cancer therapies and that any investment securities are ancillary to our primary business. We believe we are generally otherwise exempted from the definition of an investment company and the registration requirements of the Investment Company Act, but, absent an exemptive order from the SEC, this result cannot be assured. Nevertheless, to address any uncertainty in this regard, we generally invest a significant portion of our portfolio in money market funds and U.S. government securities and

limit the level of investment in corporate bonds and other instruments that could be considered investment securities.

At December 31, 2006, the value of our investment securities exceeded 40% of the value of our total assets due primarily to our non-controlling position in SR Pharma. In addition, certain other exemptions under the Investment Company Act upon which we may normally rely were not available to us. Accordingly, our Board of Directors elected to take advantage of the Rule 3a-2 exemption for transient investment companies as of such date, which allows us to avoid being deemed an investment company for up to one year as long as we have a bona fide intent to be engaged primarily, as soon as is reasonably possible, in a business other than that of investing, reinvesting, holding or trading in securities. In connection with such election, our Board of Directors directed management to

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take appropriate actions to regain compliance with the prima facie provisions of the Investment Company Act, including, among other things, liquidating certain investment securities. Accordingly, among other things, we intend over time to reduce the level of our investment securities by periodic sales or other dispositions of such investment securities. These dispositions may be effected under unfavorable market conditions. The lower rates of return realized after the reinvestment of our investment portfolio, and any required dispositions of non-controlling investments, could adversely affect our future reported results.

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

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

Future changes in financial accounting standards or practices or existing taxation rules or practices may cause adverse unexpected financial reporting fluctuations and affect our reported results of operations.

A change in accounting standards or practices or a change in existing taxation rules or practices can have a significant effect on our reported results and may even affect our reporting of transactions completed before the change is effective. New accounting pronouncements and taxation rules and varying interpretations of accounting pronouncements and taxation practice have occurred and may occur in the future. Changes to existing rules or the questioning of current practices may adversely affect our reported financial results or the way we conduct our business. For example, Statement of Financial Accounting Standards (SFAS) No. 123R, Share-Based Payment, became effective for us on January 1, 2006. This statement requires that employee share-based compensation be measured based on its fair value on the grant date and treated as an expense that is reflected in the financial statements over the related service period. SFAS No. 123R has had a significant impact on our results of operations for the year ended December 31, 2006. Using the Black-Scholes option pricing model to compute share-based compensation expense as we do requires extensive use of accounting judgment and financial estimates. Items requiring estimation include the expected term optionholders will retain their vested stock options before exercising them, the estimated volatility of our common stock price over the expected term of a stock option and the number of stock options that will be forfeited prior to the completion of their vesting requirements. Application of alternative assumptions could result in significantly different share-based compensation amounts being recorded in our financial statements. We anticipate that SFAS No. 123R will continue to have a significant impact on our results of operations.

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

Section 203 of the Delaware General Corporation Law and our certificate of incorporation and by-laws contain provisions that might enable our management to resist a takeover of our company or discourage a third party from

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attempting to take over our company. These provisions include the inability of stockholders to act by written consent or to call special meetings, the ability of our board of directors to designate the terms of and issue new series of preferred stock without stockholder approval and the fact that our board of directors is divided into three classes serving staggered thee-year terms.

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

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

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

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

In October 2004, we acquired all of the outstanding capital stock of Magnum, a company owned at the time of this acquisition by one of our executive officers. 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 for the acquisition, 50% of the shares were held by an independent escrow agent for a period of approximately one year subsequent to the acquisition date to satisfy the indemnification obligations of the selling shareholder under terms of the purchase agreement. Such shares have since been released from escrow. Magnum s primary asset is the funding it receives under a research grant from the NIH, which supplements our ongoing research and development programs. During the year ended December 31, 2006, we earned $163,000 of revenue under this grant, which completed the funding available to us under this grant. In the event certain of Magnum s technologies result in commercial products, we may be obligated to pay royalties related to the sales of those products to certain third parties.

We have relationships with Jack A. Roth, M.D., and M. D. Anderson Cancer Center, both of whom are affiliated with The Board of Regents of the University of Texas System, one of our stockholders. For more information concerning these relationships, see our Notes to Consolidated Financial Statements beginning on page F-7 of our Annual Report on Form 10-K for the year ended December 31, 2006.

Subsequent to December 31, 2006, we became an owner of 49% of the outstanding stock of Introgen Research Institute (IRI). The other 51% of IRI is owned by our corporate Secretary, who is also an Introgen shareholder. We transferred to IRI an NIH grant originally awarded to us. IRI will be responsible for the remaining research contemplated by that grant and will receive future funding, if any, from the NIH under that grant. We have contractual relationships with IRI under which we may perform research and development services for them in the future.

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

Item 1B. ***Unresolved Staff Comments***

Not applicable.

Item 2. ***Properties***

We conduct our primary operations from facilities in Houston, Texas. These facilities 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 (TMX), 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 leases the land under our primary 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 below under Part II, Item 7. Management s Discussion and Analysis of Financial Condition and Results of Operations Liquidity and Capital Resources 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 our primary 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 primary facilities described above, we lease other space in Houston, Texas in 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, will have a material effect on our business. You can read the discussion of our opposition of the patents under Part I, Item 1A. Risk Factors above.

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 Annual Report on Form 10-K.

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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 Global 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 Global Market.

	High	Low
Fiscal Year Ended December 31, 2005:		
First Fiscal Quarter	$ 8.60	$ 6.35
Second Fiscal Quarter	8.10	6.07
Third Fiscal Quarter	7.40	4.90
Fourth Fiscal Quarter	6.60	4.54
Fiscal Year Ended December 31, 2006:		
First Fiscal Quarter	$ 6.45	$ 4.91
Second Fiscal Quarter	5.62	3.50
Third Fiscal Quarter	4.88	3.78
Fourth Fiscal Quarter	5.20	4.28

At December 31, 2006, there were 43,591,201 shares of our common stock issued and outstanding held by approximately 153 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.

Stock Repurchases

We did not repurchase any shares of capital stock during the fourth quarter of the fiscal year covered by this Annual Report on Form 10-K.

Securities Authorized for Issuance Under Equity Compensation Plans

This information is incorporated by reference to Part III, Item 12 of this Annual Report on Form 10-K.

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Stock Price Performance Graph

COMPARISON OF 5 YEAR CUMULATIVE TOTAL RETURN*
Among Introgen Therapeutics, Inc., The NASDAQ Composite Index
And The S & P Biotechnology Index