INTROGEN THERAPEUTICS INC
Form 424B5
November 08, 2006

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Filed Pursuant to Rule 424(b)(5)
Registration No. 333-107799

PROSPECTUS SUPPLEMENT
(To Prospectus dated August 25, 2003)

1,326,086 Shares
Common Stock

We are selling 1,326,086 shares of our common stock to two funds of a single investor group. In connection with this offering, we will pay fees and issue warrants to purchase approximately 73,199 shares of our common stock at an exercise price of $5.03 per share to a placement agent. See Plan of Distribution beginning on page S-37 of this prospectus supplement for more information regarding this arrangement.

Our common stock is quoted on the Nasdaq Global Market under the symbol INGN. On November 6, 2006, the closing price of our common stock as quoted on the Nasdaq Global Market was $5.03 per share.

Before you invest, you should carefully read this prospectus supplement, the related prospectus dated August 25, 2003, and all of the information incorporated by reference herein and therein. Our business, and an investment in our common stock, involves significant risks. These risks are discussed in this prospectus supplement under Risk Factors and the documents incorporated by reference into the prospectus and this prospectus supplement.

NEITHER THE SECURITIES AND EXCHANGE COMMISSION NOR ANY STATE SECURITIES COMMISSION HAS APPROVED OR DISAPPROVED OF THESE SECURITIES OR PASSED UPON THE ADEQUACY OR ACCURACY OF THIS PROSPECTUS SUPPLEMENT OR THE ACCOMPANYING PROSPECTUS. ANY REPRESENTATION TO THE CONTRARY IS A CRIMINAL OFFENSE.

	Per Share	Aggregate Offering
Public offering price	$4.60	$6,099,995.60
Placement agent fee	$0.23	$ 304,999.78
Proceeds, before expenses, to us	$4.37	$5,794,995.82

We estimate the total expenses of this offering, excluding the placement agent fee, will be approximately $150,000.00.

November 7, 2006

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Prospectus Supplement

The purpose of this prospectus supplement is to provide supplemental information regarding Introgen Therapeutics, Inc. in connection with the offering. You should read this prospectus supplement, along with the accompanying prospectus, carefully before you invest. Both documents contain important information you should consider when making your investment decision. This prospectus supplement may add, update or change information contained in the accompanying prospectus.

You should rely only on information contained in this prospectus supplement, the related prospectus and the documents we incorporate by reference into this prospectus supplement and the related prospectus. We have not authorized anyone to provide you with information that is different. We are offering the common stock only in jurisdictions where such offers are permitted. The information contained in this prospectus supplement and the related prospectus is accurate only as of its respective date, regardless of the time of delivery of this prospectus supplement.

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GENERAL INFORMATION

This prospectus supplement is part of a registration statement that we filed with the SEC using a shelf registration process. Under this registration statement, we registered the offering of up to $100 million of our common stock from time to time in one or more offerings. In December 2003, we completed an offering of approximately $20 million of our common stock, leaving approximately $80 million available for future offerings. In December 2004, we completed offerings of approximately $24.3 million of our common stock, leaving approximately $55.7 million available for future offerings. In November 2005, we completed an offering of approximately $20 million of our common stock, leaving approximately $35.7 million available for future offerings. This prospectus supplement provides specific information about the offering of 1,326,086 shares of our common stock under the shelf registration statement. You should read carefully this prospectus supplement, the related prospectus and the information that we incorporate by reference into those documents. In the event there are any differences or inconsistencies between this prospectus supplement, the related prospectus and the information incorporated by reference herein and therein, you should only rely on the information contained in the document with the latest date. Please refer to the information and documents listed and described under the heading Where You Can Find More Information in the prospectus.

SUMMARY

This summary presents a brief overview of Introgen Therapeutics, Inc. and the key aspects of the offering and may not contain all of the information that may be important to you or that you should consider before investing in our common stock. You should read carefully the entire prospectus supplement, especially the risks of investing in our common stock discussed under Risk Factors, the related prospectus and the information that we incorporate by reference into this prospectus supplement and the related prospectus. You should also review our consolidated financial statements, the notes to those financial statements and the other financial information incorporated by reference into this prospectus supplement and the related prospectus. All references to Introgen, the Company, the Registrant, we, us or our mean Introgen Therapeutics, Inc.

Product Development 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 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.

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, such as 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, and INGN 007, a replication-competent viral therapy. We have established an efficient process for evaluating new drug candidates and advancing them from pre-clinical to clinical development. We have identified and licensed multiple technologies, which we intend to combine with our adenoviral and non-viral vector systems and which we believe are attractive development targets for the treatment of various cancers. We are also evaluating the development of mebendazole (INGN 601), our first small molecule product candidate. We intend to evaluate additional opportunities to in-license or acquire new technologies.

Develop a Nanoparticle Systemic Administration Platform. Early 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. 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 has been studied in a variety of cancers including phase 2 trials for non-small lung cancer, breast cancer and esophageal cancers .

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 (EC) Circumstances 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 seven years, 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.

We submitted a SOPA Request to the FDA Division of Cell and Gene Therapy proposing a rolling BLA for ADVEXIN therapy for the treatment of recurrent head and neck cancer, based primarily on data from our Phase 2 clinical trials. We have 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 suggestions by the FDA that we consider proposing to them an interim efficacy analysis of one or both of the ongoing Phase 3 clinical trials. As with the acceleration of the interim safety analysis, we believe that the interim efficacy results 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 has requested that we submit a proposal for the Phase 3 interim efficacy analyses, which we anticipate providing to the FDA by December 31, 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.

With respect to the activities described above, we anticipate that the FDA will agree with our interim efficacy analysis plans for our Phase 3 head and neck cancer studies before the end of 2006. We also anticipate achieving the following additional regulatory milestones during 2007:

Completion and submission to the FDA of the Phase 3 interim efficacy analysis data for head and neck cancer;

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Conditional Approval approach for head and neck cancer application agreed to by the EMEA;

Completion of Exceptional Circumstance Approval Application filing for Li-Fraumeni Syndrome with the EMEA; and

Completion of the necessary filings for head and neck cancer at the FDA and EMEA to support review and advisory committee review meetings, if required, by those agencies.

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 identification of predictive indicators of ADVEXIN therapy activity complies with recent FDA biomarker initiatives to accelerate the approval of oncology products 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 months compared to only 3 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 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.

The targeted molecular therapy provided by ADVEXIN therapy is evidenced by its use to successfully treat a Li-Fraumeni Syndrome (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 Li-Fraumeni Syndrome (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 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.

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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 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

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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 licenced 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.

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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.

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 potently 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 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.

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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.

We have completed enrollment of a Phase 1/early Phase 2 clinical trial using INGN 241 to evaluate safety, mechanism of action and efficacy in approximately 25 patients with solid tumors. This trial has indicated that in patients with solid tumors, INGN 241 was well tolerated, was biologically active and displayed minimal toxicity associated with its use. We have initiated later stage clinical trials using INGN 241 in patients with metastatic melanoma and recurrent head and neck cancer. We are studying INGN 241 in combination with radiation therapy for solid tumors in a phase 3 clinical trial.

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.

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 to the mda-7 tumor suppressor for our therapeutic applications 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.

INGN 225 (p53 molecular immunotherapy)

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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 solid tumors.

We are conducting 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.

Interim results from the Phase 1/2 trial in patients with extensive small cell lung cancer who were previously treated with chemotherapy indicate that greater than 60% of the evaluable patients in the study treated with INGN 225 had objective responses to subsequent chemotherapy. Historically, the expected objective response rate in similar patients to further chemotherapy is between approximately 5% and 30%. Similar patients with this type of lung cancer 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. These findings were published in *Clinical Cancer Research*.

We believe the data indicate INGN 225 may sensitize tumors to the effects of platinum and taxane chemotherapies. Of particular interest, 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/early Phase 2 clinical trial in which p53 is being administered in an oral mouthwash formulation to prevent precancerous oral lesions from developing into cancerous lesions. We are conducting pre-clinical work on other topical administrations of tumor 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 2. Management s Discussion and Analysis of Financial Condition and Results of Operations 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

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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.

INGN 401 has demonstrated synergistic activity with Gefitinib, a novel class of anti-cancer agents that decrease tumor growth by inhibiting growth factor receptors that promote tumor proliferation. While Gefitinib 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. We are working with M. D. Anderson Cancer Center to further evaluate other 3p21.3 family molecules as clinically relevant therapeutics.

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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).

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, which we plan to exploit 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 have in-licensed and are developing a non-viral, nanoparticle delivery platform as a complementary delivery technology for certain types of cancers, or clinical indications, particularly those that require systemic administration. We are 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

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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 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

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common stock purchase agreement, Colgate-Palmolive purchased 3,610,760 shares of our common stock at a purchase price of $5.539 per share for a total of approximately $20.0 million. These shares are subject to trading and transfer restrictions for one year from the date of purchase. Under the common stock purchase agreement, Colgate-Palmolive also 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. Excluded from the alliance agreement is our current portfolio of cancer product candidates, including ADVEXIN therapy, INGN 241, INGN 225 and INGN 401.

Under the alliance agreement, 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 research and development activities. In addition, 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 zero and $150,000 in the three month periods ended September 30, 2006 and September 30, 2005, respectively, and $150,000 and $450,000 in the nine month periods ended September 30, 2006 and September 30, 2005, respectively. We are not obligated to make any additional such purchases at this time. We record these purchases as research and development expense. We are no longer required to make periodic purchases of their Series A Preferred Stock under this agreement. We may be required to make additional stock purchases in the event VirRx reaches certain specified milestones. For additional discussion of our agreements with VirRx, see Business-Business and Collaborative Agreements-VirRx, Inc. in, and Note 9 to our consolidated financial statements included in, our Annual Report on Form 10-K for the year ended December 31, 2005, filed with the SEC on March 16, 2006.

SR Pharma plc

In July 2005, we purchased approximately 8.3% of the issued share capital of SR Pharma for approximately $3.0 million. As of September 30, 2006, the shares we purchased had a quoted market value of $2.4 million. SR Pharma is a European biotechnology company publicly traded on the Alternative Investment Market of the 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.

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

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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.

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

Adenoviral p53 Compositions and Therapies

In developing our patent portfolio, we have focused our efforts in part on seeking protection for our potential products and how they will be used in the clinical trials. Arising out of our work with M. D. Anderson Cancer Center, we currently have an exclusive license to a number of United States and corresponding international 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 also exclusively licensed from Aventis patent applications directed to adenoviral p53 and its clinical applications. We also have an exclusive license to a United States patent application and corresponding international applications directed to the use of the p53 tumor suppressor in the treatment of cancer patients whose tumors express a normal p53 protein.

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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®); 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. Additionally, in order 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®. Furthermore, 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. In this regard, we own three issued United States patents as well as a number of pending United States applications and corresponding international applications directed to highly purified adenoviral compositions, commercial-scale processes for producing adenoviral-based compositions having a high level of purity, as well as to 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 also 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 the clinical application 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 include various applications and patents relating to p53, combination therapy with 2-methoxyestradiol, anti-proliferative factor technologies, retroviral delivery systems, stimulation of anti-p53, screening and product assurance technologies, as well as second-generation p53 molecules. We have exclusively licensed a number of United States and international applications directed to

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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 recently issued that is directed to adenoviruses that exhibit tissue specific replication. We also have exclusive rights in an issued United States patent and corresponding international applications directed to a low toxicity analogue of IL-24, also called F42K.

Benzimidazole Small Molecule Cancer Therapy Program

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

Trade Secrets

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

Our principal executive offices are located at 301 Congress Avenue, Suite 1850, Austin, Texas 78701 and our telephone number is (512) 708-9310. Our website is located at www.introgen.com. The information contained on our website is not a part of this prospectus supplement or the related prospectus.

The Offering

Common stock offered by Introgen Therapeutics, Inc.:	1,326,086
Use of proceeds:	We will use the proceeds from the sale of our common stock for general corporate purposes and working capital requirements.
Risk factors:	See Risk Factors for a discussion of the factors you should carefully consider before deciding to invest in shares of our common stock.

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RISK FACTORS

An investment in our common stock involves a high degree of risk. In addition to the other information contained in this prospectus supplement, you should carefully consider the following risks and uncertainties before purchasing our common stock. Our business, financial condition and operating results could be materially adversely affected by these risks and uncertainties. In that case, the trading price of our common stock could decline and you could lose all or part of your investment. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties may also impair our business operations.

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.

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.

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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.

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.

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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 September 30, 2006, we had an accumulated deficit of approximately $165.1 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.

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

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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 9 to 12 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

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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 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.

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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 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.

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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 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 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 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.

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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 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

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acceptable terms. There are a limited number of contract manufacturers who currently have the capability to produce ADVEXIN therapy, INGN 241 or our other product candidates, and the inability of any of these contract manufacturers to deliver our required quantities of product candidates timely and at commercially reasonable prices would negatively affect our operations.

Before we can begin commercially manufacturing ADVEXIN therapy, INGN 241 or any other product candidate, we must obtain regulatory approval of our manufacturing 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;

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;

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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 our Annual Report on Form 10-K for the year ended December 31, 2005, filed with the SEC on March 16, 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.

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.

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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, SFAS 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 123R has had a significant impact on our results of operations for the three and nine months ended September 30, 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 for the remainder of 2006 and subsequent periods.

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 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 three months ended March 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, 2005, filed with the SEC on March 16, 2006.

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.

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MARKET FOR OUR COMMON STOCK

On November 6, 2006, the last reported sale price of our common stock on the Nasdaq Global Market was $5.03 per share. Our common stock is traded on the Nasdaq Global Market under the symbol INGN.

As of November 1, 2006 and before the issuance of the 1,326,086 shares of our common stock pursuant to this prospectus supplement, we had approximately 37,256,728 shares of common stock outstanding.

USE OF PROCEEDS

The net proceeds to us from this offering, before expenses, will be approximately $5.8 million. The net proceeds from the sale of common stock offered by this prospectus supplement will be used for general corporate purposes and working capital requirements. We may also use a portion of the net proceeds to fund possible investments in and acquisitions of complementary businesses, partnerships, minority investments, products or technologies. Currently, there are no commitments or agreements regarding such acquisitions or investments that are material. Pending their ultimate use, we intend to invest the net proceeds in money market funds, commercial paper and governmental and non-governmental debt securities with maturities of up to five years.

PLAN OF DISTRIBUTION

We are offering the shares of our common stock through a placement agent. Subject to the terms and conditions contained in the placement agent agreement dated November 7, 2006, Mulier Capital Limited has agreed to act as the placement agent for the sale of up to 1,326,086 shares of our common stock. The placement agent is not purchasing or selling any shares of our common stock by this prospectus supplement, or the accompanying prospectus, nor is it required to arrange the purchase or sale of any specific number or dollar amount of shares being sold by this prospectus supplement, and the accompanying prospectus, but has agreed to use its best efforts to arrange for the sale of all such shares being offered.

The placement agent agreement provides that the obligations of the placement agent and the investors are subject to certain conditions precedent, including the absence of any material adverse change in our business and the receipt of certain opinions, letters and certificates from our counsel, our independent auditors and us.

Additionally, the sale of our common stock to the investors is being made on terms we negotiated with the investors. The subscription agreements between the investors and us contain representations that each investor, among other things:

- in connection with such investor s decision to purchase shares of our common stock, has relied only upon the accompanying prospectus, any free writing prospectuses (as that term is defined in Rule 405 under the Securities Act of 1933, as amended) relating to this offering and our reports on Forms 10-K, 10-Q and 8-K filed by us with the SEC; and

- has not within the past ninety trading days engaged in any short selling or short sales against the box in our securities, established or increased any put equivalent position as defined in Rule 16(a)-1(h) under the Securities Exchange Act of 1934, as amended (Exchange Act), with respect

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to our securities, or engaged in any purchase or sale, or made any offer to purchase or offer to sell, derivative securities relating to our securities, whether or not issued by us, such as exchange traded options to purchase or sell our securities.

Confirmations and final prospectus supplements will be distributed to all investors who agree to purchase shares of our common stock, informing such investors of the closing date as to such shares. We currently anticipate that the closing of the sale of 1,326,086 shares of our common stock will take place on or about November 7, 2006. Investors will also be informed of the date and manner in which they must transmit the purchase price for their shares.

On the scheduled closing date, the following will occur:

we will receive funds in the amount of the aggregate purchase price; and

the placement agent will be paid its fee and will be issued the stock purchase warrants.

We will pay the placement agent a commission equal to 5.0% of the gross proceeds of the sale of shares of our common stock in the offering and will issue to the placement agent warrants to purchase approximately 73,199 shares of our common stock at an exercise price of $5.03 per share.

The placement agent agreement with Mulier Capital Limited will be included as an exhibit to the Company s Current Report on Form 8-K that will be filed with the SEC in connection with the consummation of this offering.

The following table shows the per share and aggregate public offering price, placement agent fee, and proceeds before expenses to us:

	Per Share	Aggregate Offering
Public offering price	$4.60	$6,099,995.60
Placement agent fee	$0.23	$ 304,999.78
Proceeds, before expenses, to us	$4.37	$5,794,995.82

The following table shows the aggregate number of shares that may be exercisable by the placement agent pursuant to a warrant to be issued to the placement agent in connection with the offering:

Aggregate Offering Amount	Shares Exercisable Pursuant to Warrant
$6,099,995.60	73,199

We estimate the total expenses of this offering, excluding the placement agent fee, will be approximately $150,000.00.

The transfer agent for our common stock is Computershare Trust Company, N.A.

Our common stock is traded on the Nasdaq Global Market under the symbol INGN. It is a component of the Nasdaq Biotechnology Index, which includes pharmaceutical and biotechnology companies as classified by the FTSE Global Classification System.

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The investors may be considered underwriters under applicable securities laws. Resales of common stock by the investors and persons receiving shares from the investors in the United States, its territories and possessions must be made in compliance with applicable United States securities laws.

DISCLOSURE REGARDING FORWARD-LOOKING STATEMENTS

Please see the information in the prospectus and the materials incorporated by reference into the prospectus and this prospectus supplement about the risks and uncertainties associated with forward-looking statements contained in these documents.

LEGAL MATTERS

The validity of the common stock being offered hereby is being passed upon for us by Wilson Sonsini Goodrich & Rosati, Professional Corporation, Austin, Texas.

EXPERTS

Ernst & Young LLP, independent registered public accounting firm, has audited our consolidated financial statements included in our Annual Report on Form 10-K for the year ended December 31, 2005, and management s assessment of the effectiveness of our internal control over financial reporting as of December 31, 2005, as set forth in its reports, which are incorporated by reference in this prospectus supplement. Our financial statements and management s assessment are incorporated by reference in reliance on Ernst & Young LLP s reports, given on its authority as experts in accounting and auditing.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference the information we file with them, which means that we can disclose important information to you by referring you to documents that we have previously filed with the SEC or documents that we will file with the SEC in the future. The information incorporated by reference is considered to be part of this prospectus supplement, and later information that we file with the SEC will automatically update and supersede this information. We incorporate by reference into this prospectus supplement any filings made by us with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus supplement until the termination of this offering, as well as the following documents:

our Annual Report on Form 10-K for the fiscal year ended December 31, 2005, filed with the SEC on March 16, 2006, as amended by our Form 10-K/A filed with the SEC on November 6, 2006;

those portions of our Definitive Proxy Statement, filed with the SEC on April 13, 2006, that are deemed filed with the SEC;

our Quarterly Report on Form 10-Q for the quarter ended March 31, 2006, filed with the SEC on May 10, 2006;

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our Quarterly Report on Form 10-Q for the quarter ended June 30, 2006, filed with the SEC on August 9, 2006;

our Quarterly Report on Form 10-Q for the quarter ended September 30, 2006, filed with the SEC on November 6, 2006;

our Current Report on Form 8-K filed with the SEC on February 24, 2006;

our Current Report on Form 8-K filed with the SEC on March 15, 2006;

our Current Report on Form 8-K filed with the SEC on May 10, 2006;

our Current Report on Form 8-K filed with the SEC on May 30, 2006;

our Current Report on Form 8-K filed with the SEC on August 9, 2006; and

the description of our common stock contained in our Registration Statement on Form 8-A, filed with the SEC on September 8, 2000, and any further amendment or report filed hereafter for the purpose of updating such description.

You may request a copy of any of these filings, at no cost to you, by writing or telephoning us at the following address and telephone number: Introgen Therapeutics, Inc., 301 Congress Avenue, Suite 1850, Austin, Texas 78701; telephone number (512) 708-9310.

Additionally, we make these filings available, free of charge, on our website at www.introgen.com as soon as reasonably practicable after we electronically file such materials with, or furnish them to, the SEC. The information on the website listed above, other than these filings, is not, and should not be, considered part of this prospectus supplement, or the accompanying prospectus, and is not incorporated by reference to this document or the accompanying prospectus.

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PROSPECTUS

$100,000,000

By this prospectus, we may offer shares of our common stock from time to time. We will provide specific terms of the common stock in supplements to this prospectus. You should read this prospectus and any supplement carefully before you purchase any of our common stock.

Our common stock is traded on the Nasdaq National Market under the symbol INGN. On August 20, 2003, the last reported sale price for the common stock on the Nasdaq National Market was $7.00 per share.

This prospectus may not be used to offer and sell securities unless accompanied by a prospectus supplement.

You are urged to carefully read the Risk Factors section beginning on page 2 of this prospectus, which describes the specific risks and certain other information associated with an investment in our common stock.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or passed upon the adequacy or accuracy of this prospectus. Any representation to the contrary is a criminal offense.

We may offer the common stock in amounts at prices and on terms determined at the time of offering. We may sell the common stock directly to you, through agents we select, or through underwriters and dealers we select. If we use agents, underwriters or dealers to sell the securities, we will name them and describe their compensation in a prospectus supplement.

The date of this prospectus is August 25, 2003

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No person has been authorized to give any information or make any representations in connection with this offering other than those contained or incorporated by reference in this prospectus and any accompanying prospectus supplement in connection with the offering described herein and therein, and, if given or made, such information or representations must not be relied upon as having been authorized by us. Neither this prospectus nor any prospectus supplement shall constitute an offer to sell or a solicitation of an offer to buy offered securities in any jurisdiction in which it is unlawful for such person to make such an offering or solicitation. Neither the delivery of this prospectus or any prospectus supplement nor any sale made hereunder shall under any circumstances imply that the information contained or incorporated by reference herein or in any prospectus supplement is correct as of any date subsequent to the date hereof or of such prospectus supplement.

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SUMMARY

This prospectus is part of a registration statement that we filed with the Commission, using a shelf registration process. Under this shelf process, we may, from time to time, sell the securities described in this prospectus in one or more offerings up to a total dollar amount of $100,000,000. This prospectus provides you with a general description of the securities we may offer. Each time we sell securities, we will provide a prospectus supplement that will contain specific information about the terms of that offering. This prospectus does not contain all of the information included in the registration statement. For a more complete understanding of the offering of the securities, you should refer to the registration statement, including its exhibits. The prospectus supplement may also add, update or change information contained in this prospectus. You should read both this prospectus and any prospectus supplement, including the risk factors, together with the additional information described under the heading Where You Can Find Information. All references to Introgen, the Company, the Registrant, we, us or our mean Introgen Therapeutics, Inc.

The Offering

Securities offered by Introgen Therapeutics, Inc.:	Up to $100,000,000 of common stock in one or more offerings. A prospectus supplement, which we will provide each time we offer common stock, will describe the specific amounts, prices and terms of the common stock. We may sell the common stock to or through underwriters, dealers or agents or directly to purchasers. We, as well as any agents acting on our behalf, reserve the sole right to accept and to reject in whole or in part any proposed purchase of common stock. Each prospectus supplement will set forth the names of any underwriters, dealers or agents involved in the sale of common stock described in that prospectus supplement and any applicable fee, commission or discount arrangements with them.
Use of proceeds:	Unless otherwise indicated in the prospectus supplement, the net proceeds from the sale of common stock offered by this prospectus will be used for general corporate purposes and working capital requirements. We may also use a portion of the net proceeds to fund possible investments in and acquisitions of complementary businesses, partnerships, minority investments, products or technologies. Currently, there are no commitments or agreements regarding such acquisitions or investments that are material. Pending their ultimate use, we intend to invest the net proceeds in money market funds, commercial paper and governmental and non-governmental debt securities with maturities of up to five years.
Risk factors:	See Risk Factors for a discussion of the factors you should carefully consider before deciding to invest in shares of our common stock.

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RISK FACTORS

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

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

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

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

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

the failure of the product candidate to be more effective than current therapies;

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

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

the death of patients during a clinical trial, even though the product candidate may not have caused those deaths;

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

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

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

We may encounter delays or rejections in the regulatory approval process because of additional government regulation from future legislation or administrative action or changes in FDA policy during the period of product development, clinical trials and FDA regulatory review. Failure to comply with applicable FDA or other applicable regulatory requirements may result in criminal prosecution, civil penalties, recall or seizure of products, total or partial suspension of production or injunction, as well as other regulatory action against our product candidates or us.

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

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

We have generated operating losses since we began operations in June 1993. As of March 31, 2003, we had an accumulated deficit of approximately $79.1 million. We expect to incur substantial additional operating expenses and losses over the next several years as our research, development, pre-clinical testing and clinical trial activities increase. We have no products that have generated any commercial revenue. Presently, we earn minimal revenue from contract services activities, grants, interest income and rent from the lease of a portion of our facilities to The University of Texas M. D. Anderson Cancer Center. Prior to December 31, 2000, we earned revenue from Aventis Pharmaceuticals, Inc. under collaborative agreements for research and development and sales of ADVEXIN therapy for use in Aventis clinical trials, which are revenues we no longer receive. We do not expect to generate revenues from the commercial sale of products in the foreseeable future, and we may never generate revenues from the commercial sale of products.

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

Developing a new drug and conducting clinical trials for multiple disease indications is expensive. We expect that we will fund our operations over the approximately the next 18 to 24 months with our current working capital, resulting primarily from the net proceeds from our initial public offering in October 2000, the sale of Series A Non-Voting Convertible Preferred Stock to Aventis in June 2001, net proceeds from the sale of common stock and warrants to purchase common stock in a private placement to selected institutional investors in June 2003, income from contract services and research grants, debt financing of equipment acquisitions, the lease of a portion of our facilities to M. D. Anderson Cancer Center and interest on invested funds. We may need to raise additional capital sooner, however, due to a number of factors, including:

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

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

higher than expected costs to obtain regulatory approvals;

higher than expected costs to pursue our intellectual property strategy;

higher than expected costs to further develop our manufacturing capability;

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

slower than expected progress in reducing our operating costs.

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

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

Our strategy for the research, development and commercialization of our product candidates may require us to enter into contractual arrangements with corporate collaborators, academic institutions and others. We have entered into sponsored research and/or collaborative arrangements with several entities, including M. D. Anderson Cancer Center, the National Cancer Institute, Chiba University in Japan, VirRx and Corixa Corporation, as well as numerous other institutions who conduct clinical trials work for us. Our success depends upon our collaborative partners performing their responsibilities under these arrangements. We cannot control the amount and timing of resources our collaborative partners devote to our research and

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testing programs or product candidates, which can vary because of factors unrelated to such programs or product candidates. These relationships may in some cases be terminated at the discretion of our collaborative partners with only limited notice to us. We may not be able to maintain our existing arrangements, enter into new arrangements or negotiate current or new arrangements on acceptable terms, if at all. Some of our collaborative partners may also be researching competing technologies independently from us to treat the diseases targeted by our collaborative programs.

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

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

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

Serious unwanted side effects attributable to treatment, which physicians classify as treatment-related adverse events, occurring in the field of gene therapy may result in greater governmental regulation and negative public perception of our product candidates, as well as potential regulatory delays relating to the testing or approval of our product candidates. The FDA recently placed a clinical hold on gene therapy clinical trials using retroviral vectors to transduce hematopoietic stem cells after two participants in such a trial for the X-linked form of severe combined immune deficiency disease (X-SCID) being conducted in Europe developed what appeared to be a leukemia-like illness. This clinical hold requires a case-by-case review of the use of retroviral vectors in these European trials. We do not use retroviral vectors in our ongoing clinical trials and are not developing products using the production process used in those clinical trials. We have received no communications from the FDA to indicate this clinical hold will affect our clinical trials, and we anticipate no future negative effects on our clinical trials from this event. In accordance with our pharmacovigilance procedures, we monitor every patient in our clinical trials for safety and report all side effects to the FDA and the National Institutes of Health according to applicable regulations. We have witnessed no adverse effects in our clinical trials that even remotely resemble what occurred in the X-SCID trial. Due to the fundamental differences between retroviral vectors and the adenoviral vector employed in ADVEXIN therapy, we believe the likelihood of our encountering an event such as that experienced in the X-SCID trial is remote.

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

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

To date no governmental authority has approved any gene therapy product or gene-induced product for sale in the United States or internationally. The commercial success of our products will depend in part on

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public acceptance of the use of gene therapy products or gene-induced products, which are a new type of disease treatment for the prevention or treatment of human diseases. Public attitudes may be influenced by claims that gene therapy products or gene-induced products are unsafe, and these treatment methodologies may not gain the acceptance of the public or the medical community. Negative public reaction to gene therapy product or gene-induced products could also result in greater government regulation and stricter clinical trial oversight.

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

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

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

Through our exclusive license from The University of Texas System for technology developed at M. D. Anderson Cancer Center, we have obtained and are currently seeking further patent protection for adenoviral p53, including ADVEXIN therapy, and its use in cancer therapy. Further, the PTO issued us a United States patent for our adenovirus production technology. We also control, through licensing arrangements, four issued United States patents for combination therapy involving the p53 gene and conventional chemotherapy or radiation, one issued United States patent covering the use of adenoviral p53 in cancer therapy, one issued United States patent covering adenoviral p53 as a product and an issued United States patent covering the core DNA of adenoviral p53. Our competitors may challenge the validity of one or more of our patents in the courts or through an administrative procedure known as an interference. The courts or the PTO may not uphold the validity of our patents, we may not prevail in such interference proceedings regarding our patents and none of our patents may give us a competitive advantage.

We have been notified by the European Patent Office, or EPO, that Schering-Plough has filed an opposition against our European patent directed to combination therapy with p53 and conventional chemotherapy and/or radiation. An opposition is an administrative proceeding instituted by a third party and conducted by the EPO to determine whether a patent should be maintained or revoked in part or in whole, based on evidence brought forth by the party opposing the patent. The EPO will hold an initial oral proceeding in October 2003 to determine whether the patent should be maintained. Resolution of this opposition will require that we expend time, effort and money. If the party opposing the patent ultimately prevails in having our European patent revoked in whole or in part then the scope of our protection for our product in Europe will

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be reduced. We would not expect, however, such a result to have a significant impact on our commercialization efforts in Europe.

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

The biotechnology and pharmaceutical industry has been characterized by extensive litigation regarding patents and other intellectual property rights, and companies have employed intellectual property litigation to gain a competitive advantage. We are aware of a number of issued patents and patent applications that relate to gene therapy, the treatment of cancer and the use of the p53 and other tumor suppressor genes. Schering-Plough Corporation, including its subsidiary Canji, Inc., controls various United States patent applications and a European patent and applications, some of which are directed to therapy using the p53 gene, and others to adenoviruses that contain the p53 gene, or adenoviral p53, and to methods for carrying out therapy using adenoviral p53. In addition, Canji controls an issued United States patent and its international counterparts, including a European patent, involving a method of treating mammalian cancer cells lacking normal p53 protein by introducing a p53 gene into the cancer cell.

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

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

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

We compete with pharmaceutical and biotechnology companies, including Canji, Inc. and Genvec, Inc., which are pursuing other forms of treatment for the diseases ADVEXIN therapy and our other product candidates target. We also may face competition from companies that may develop internally or acquire competing technology from universities and other research institutions. As these companies develop their

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

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

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

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

they are more effective than alternative treatments;

their side effects are acceptable to patients and doctors;

we produce and sell them at a profit; and

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

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

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

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

Our current manufacturing facilities have not yet been subject to an FDA or other regulatory inspection. Failure to pass a pre-approval inspection may significantly delay FDA approval of our products. If we fail to comply with these requirements, we would be subject to possible regulatory action and may be limited in the jurisdictions in which we are permitted to sell our products. Further, the FDA and foreign regulatory

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authorities have the authority to perform unannounced periodic inspections of our manufacturing facility to ensure compliance with CGMP and foreign regulatory requirements. Our facility in Houston, Texas is our only manufacturing facility. If this facility were to incur significant damage or destruction, then our ability to manufacture ADVEXIN therapy or any other product candidates would be significantly hampered and we would incur delays in our pre-clinical testing, clinical trials and commercialization efforts.

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

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

We rely on third-party suppliers for some of the materials used in the manufacturing of ADVEXIN therapy, INGN 241 and our other product candidates. Some of these materials are available from only one supplier or vendor. Any significant problem that one of our sole source suppliers experiences could result in a delay or interruption in the supply of materials to us until that supplier cures the problem or until we locate an alternative source of supply. Any delay or interruption would likely lead to a delay or interruption in our manufacturing operations, which could negatively affect our operations.

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

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

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

decreased demand for our product candidates;

injury to our reputation and significant media attention;

withdrawal of clinical trial volunteers;

substantial delay in FDA approval;

costs of litigation; and

substantial monetary awards to plaintiffs.

We currently maintain product liability insurance with coverage of $5.0 million per occurrence with a $15.0 million annual aggregate limit. This coverage may not be sufficient to protect us fully against product liability claims. We intend to expand our product liability insurance coverage 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

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

Our stock price may fluctuate substantially.

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

- the announcement of new products or services by us or our competitors;
- quarterly variations in our or our competitors results of operations;
- failure to achieve operating results projected by securities analysts;
- changes in earnings estimates or recommendations by securities analysts;
- developments in our industry; and
- general market conditions and other factors, including factors unrelated to our operating performance or the operating performance of our competitors.

In addition, stock prices for many companies in the technology and emerging growth sectors have experienced wide fluctuations that have often been unrelated to the operating performance of such companies. Many factors may have a significant adverse effect on the market price of our common stock, including:

- results of our pre-clinical and clinical trials;
- announcement of technological innovations or new commercial products by us or our competitors;
- developments concerning proprietary rights, including patent and litigation matters;
- publicity regarding actual or potential results with respect to products under development by us or by our competitors;
- regulatory developments; and
- quarterly fluctuations in our revenues and other financial results.

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

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

- potential exposure to unknown liabilities of acquired companies;
- the difficulty and expense of assimilating the operations and personnel of acquired businesses;
- diversion of management time and attention and other resources;
- loss of key employees and customers as a result of changes in management;
- the incurrence of amortization expenses; and

possible dilution to our stockholders.

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

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

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THE COMPANY

Introgen Therapeutics, Inc. was incorporated in Delaware on June 17, 1993. We are a leading developer of biopharmaceutical products using non-integrating gene agents designed to induce therapeutic protein expression for the treatment of cancer and other diseases. Our drug discovery and development programs have resulted in innovative approaches by which physicians may use genes to initiate therapeutic protein production. Genes provide instructions for the manufacture of proteins in a cell. In the Introgen approach, genes are used as the means of introducing into the target cancer cells the necessary amounts of normal cancer fighting proteins that act to overpower the cancer cell. Thus, rather than acting to repair or replace aberrant or missing genes and thereby creating a permanent, long-term change to the patient s genome, our products work in a different manner by targeting genes formulated to act as pharmacologic agents to engage molecular targets. The resultant proteins engage their normal molecular targets or receptors to produce a specific therapeutic effect. Our lead product candidate, ADVEXIN therapy, combines the p53 gene with an adenoviral gene delivery system that we have developed and extensively tested. The p53 gene is one of the most potent members of a group of naturally occurring tumor suppressor genes, which act to kill cancer cells, arrest cancer cell growth and protect cells from becoming cancerous.

We are conducting pivotal Phase 3 clinical trials of ADVEXIN therapy, both by itself and in combination with chemotherapy, in advanced squamous cell cancer of the head and neck. Pivotal Phase 3 clinical trials are efficacy trials, which are usually followed by the filing of an application with the FDA to market the product being tested.

We have completed a Phase 2 clinical trial of ADVEXIN therapy administered as a complement with radiation therapy in non-small cell lung cancer. Phase 2 trials are efficacy trials. This Phase 2 trial showed that approximately 60 percent of patients primary tumors regressed or disappeared after the combination therapy, as assessed by both biopsies and by CT scans three months after treatment. Moreover, ADVEXIN therapy administration did not appear to increase the side effects caused by radiation treatment. These data were published in the January 2003 issue of the journal *Clinical Cancer Research*. We are reviewing future development plans for this indication.

We are conducting a Phase 2 clinical trial of ADVEXIN therapy combined with systemic chemotherapy for the treatment of breast cancer. Interim results of this trial were published in June 2003 at the annual meeting of the American Society of Clinical Oncology. These results indicated that in patients with locally advanced breast cancer, ADVEXIN therapy can be safely combined with a two-drug standard chemotherapy regimen and that 90 percent of the patients had objective responses to the therapy.

We are conducting a Phase 1-2 clinical trial of ADVEXIN therapy for the treatment of advanced unresectable squamous cell esophageal cancer. The study protocol was developed and is sponsored by investigators at Chiba University in Japan. Preliminary results from this trial indicate ADVEXIN therapy can be safely administered and that a positive biological effect resulted from the expression of the p53 protein. These results were published in June 2003 at the meeting of the American Society of Clinical Oncology. Of the first eight patients evaluated to date, one patient was observed to have minor tumor regression following ADVEXIN therapy injections.

We are conducting Phase 1 clinical trials, or safety trials, of ADVEXIN therapy in other types of cancer. In a Phase 1 trial for the treatment of bronchoalveolar cancer, a form of non-small cell lung cancer, in which ADVEXIN therapy is administered directly into the airway leading to the diseased lung, we noted the therapy was well-tolerated in all 26 patients treated, that there was an improved ability to breathe in 20 percent of the patients who were able to be evaluated and that the disease stabilized and did not continue to grow in a majority of those patients. This trial was conducted under our Cooperative Research and Development Agreement with the National Cancer Institute (NCI).

We and the NCI will conduct a Phase 1-2 clinical trial in which ADVEXIN therapy will be administered in the form of an oral rinse or mouthwash. This trial will be the first to investigate the cancer prevention effect of ADVEXIN therapy on oral lesions that have a high risk of developing into cancer. Currently, there are no treatments for such cancer prevention approved by the FDA.

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As a supplement to our gene-induced therapeutic protein programs, we are developing INGN 225 using ADVEXIN therapy to create a highly specific therapeutic cancer vaccine that stimulates a patient s particular immune cell known as a dendritic cell. Recently published research in *Current Opinion in Drug Discovery & Development* concluded that ADVEXIN therapy can be used with a patient s isolated dendritic cells as an antigen delivery and immune enhancing therapeutic strategy. Preclinical testing has shown that the immune system can recognize and kill tumors after treatment with ADVEXIN therapy stimulated dendritic cells. We believe ADVEXIN therapy applied in this manner could have broad utility as a prophylaxis for cancer progression in patients with solid cancers. A Phase 1 trial has been initiated to treat patients with small-cell lung cancer using INGN 225 after treatment with standard chemotherapy.

To date, clinical investigators at clinical sites in North America, Europe and Japan have treated hundreds of patients with ADVEXIN therapy, establishing a large safety database. We hold the worldwide rights for pre-clinical and clinical development, manufacturing, marketing and commercialization of ADVEXIN therapy. ADVEXIN therapy for head and neck cancer is designated as an orphan drug under the Orphan Drug Act, which gives us seven years of marketing exclusivity for ADVEXIN therapy if approved by the FDA.

We are developing additional gene-induced therapeutic protein agents that we believe may be effective in treating certain cancers. These additional therapeutic protein agents include those based on several genes, including the mda-7, FUS-1 and BAK genes, as well as additional vector technologies for delivering the gene-based products efficiently into target cells.

Our INGN 241 product candidate, which combines the mda-7 gene with our adenoviral vector system, is undergoing safety and efficacy testing in a Phase 1-2 clinical trial, with one of the objectives also being to determine if this technology displays anti-tumor activity. This trial has demonstrated that in patients with solid tumors, INGN 241 is well tolerated, is biologically active, displays minimal toxicity associated with its use and can lead to tumor regression. Preclinical studies have demonstrated that INGN 241 works to kill tumor cells directly and simultaneously stimulates the immune system, known as cytokine activity, to kill metastatic tumor cells through multiple mechanisms in a variety of cancers. These studies have shown that the mda-7 protein produced by INGN 241 may play an important role in controlling the growth of tumors, which resulted in the designation of mda-7 as interleukin-24, or IL-24. Preclinical studies also suggest INGN 241 can be effectively combined with radiation therapy and may be useful in enhancing the effects of such therapy.

Preclinical studies have shown that gene delivery of FUS-1, our INGN 401 product candidate, which we exclusively license from The University of Texas M. D. Anderson Cancer Center, using either adenoviral or non-viral gene transfer, significantly inhibits the growth of tumors and greatly reduces the metastatic spread of lung cancer in animals. A Phase 1 trial is ongoing for INGN 401 in patients with advanced non-small cell lung cancer who have previously been treated with chemotherapy.

We are investigating other vector technologies for delivering gene-based products into targeted cells. Through our strategic collaboration with VirRx, Inc., we are developing INGN 007, a replication-competent viral therapy that over-expresses an adenoviral gene and causes rapid disruption of tumor cells in which the adenovirus replicates. Preclinical testing indicates that INGN 007 over-expresses a gene that allows the vector to saturate the entire tumor and to eradicate cancer in animal models. We anticipate pursuing clinical confirmation as to whether this self-amplifying delivery system can complement our existing adenoviral gene delivery system, which is replication disabled, in selected therapeutic scenarios.

We believe our research and development expertise gained from our gene-induced protein therapies for cancer is also applicable to other diseases that, like cancer, result from cellular dysfunction and uncontrolled cell growth. As a result, we are conducting research in collaboration with medical institutions to understand the safety and effectiveness of our gene-induced protein therapy product candidates in the treatment of diseases such as rheumatoid arthritis. In addition, we have developed a variety of technologies, which we refer to as enabling technologies, for administering gene-based products to patients and enhancing the effects of these products. We also have specialized manufacturing expertise and a manufacturing facility to support our continued product development and commercialization efforts.

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

We place substantial emphasis on developing and maintaining a strong intellectual property program. We own or exclusively control numerous patents and pending patent applications in the United States and elsewhere that cover ADVEXIN therapy and INGN 241 (mda-7) therapy in particular, adenoviral p53 and adenoviral mda-7 in general, clinical applications of adenoviral and other forms of p53 and mda-7, and adenoviral production. Certain of our patents are licensed from The University of Texas System, Columbia University and Aventis Pharmaceuticals, Inc. The patents directed to clinical applications of p53 broadly cover the use of p53 in combination with standard chemotherapy and clinical therapy with adenoviral p53 in general. Our adenoviral production patent position is of particular potential commercial importance in that it covers most methods currently in use by us and others for commercial scale adenoviral production and purification processes. We have recently been successful in having certain European patents held by our competitors revoked by the European Patent Office, subject to appeal by the patent holders. In addition to our p53 and mda-7 intellectual property position, we also own or have exclusively licensed rights in a number of other patents and applications directed to the clinical application of various other tumor suppressor genes.

We own and operate a manufacturing facility that we believe complies with the FDA s CGMP requirements. We have produced ADVEXIN therapy in this facility for use in our Phase 1, 2 and 3 clinical trials. The designs of the facility and the processes operated in the facility have been reviewed with the FDA. Our work to validate our manufacturing processes in accordance with FDA regulations is ongoing. We plan to use this facility for our market launch of ADVEXIN therapy. We have produced over 20 batches of ADVEXIN therapy clinical material, including all clinical material used in our Phase 2 and Phase 3 clinical trials. In addition, we have entered into agreements with third parties under which we have provided process development and manufacturing services related to products they are developing. We have also produced INGN 241 in a separate facility for use in our Phase 1-2 clinical trials.

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

Background

Gene Function and Genomics

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

In recent years, scientists have made significant progress toward understanding the nature of the complete set of human genes, the human genome, and evaluating the role that genes and the proteins they express play in both normal and disease states. Academic and governmental initiatives have sequenced a large number of the genes that comprise the human genome. As new genes are discovered and decoded within this sequence,

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scientists are identifying and understanding their functions and interactions within these pathways. These discoveries provide opportunities to develop targeted therapeutic applications for individual genes and the proteins they express, including treatment and prevention of disease.

Gene Therapy and Gene-Induced Protein Therapy Products

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

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

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

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

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Cancer, a Genetic Disease

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

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

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

Tumor Suppressor Genes

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

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

Current Treatment of Cancer

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

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Due to the various limitations of most cancer therapies currently utilized, the treatment of cancer remains complex. Physicians refer to the first treatment regimen for a newly-diagnosed cancer, usually surgery if possible, or radiation therapy, as primary treatment. If the primary treatment is not successful, the cancer will re-grow or continue to grow, which is referred to as recurrent disease. In most cases, recurrent cancer is not curable, with secondary treatment regimens, usually chemotherapy, only providing marginal benefits for a limited period of time. Physicians consider recurrent cancer that has proven resistant to a secondary treatment to be refractory. Most new cancer treatments are tested initially in patients with either recurrent or refractory disease because the effects of the new therapy are more quickly apparent.

Given that established cancer therapies often prove to be incomplete, ineffective or toxic to the patient, there is a need for 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 improve the toxicity and marginal benefits common to current cancer treatments. Gene-induced protein therapy applications directly address the cellular dysfunction that causes cancer, compared with small molecule drugs or immunotherapeutic agents, which may act indirectly.

The Introgen Approach

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

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

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

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The Introgen Strategy

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

Develop and Commercialize ADVEXIN therapy and INGN 241 for Multiple Cancer Indications. We plan to continue developing ADVEXIN therapy using the p53 gene and our INGN 241 product using the mda-7 gene in multiple cancer indications. Using ADVEXIN therapy, we are conducting pivotal Phase 3 clinical trials in head and neck cancer, are designing a follow-on clinical trial with respect to our recently completed Phase 2 clinical trial in non-small cell lung cancer and are conducting a Phase 2 clinical trial for breast cancer and a Phase 1-2 study for esophageal cancer. We have completed enrollment in a Phase 1 clinical trial of ADVEXIN therapy delivered intravenously. We have used ADVEXIN therapy to create INGN 225, a highly specific therapeutic cancer vaccine, for which we have initiated a Phase 1 clinical trial in small-cell lung cancer. In cooperation with the National Cancer Institute, or NCI, we have concluded several clinical trials and are presently conducting additional Phase 1 clinical trials using ADVEXIN therapy, including a trial in which ADVEXIN therapy is administered as an oral rinse or mouthwash to treat pre-malignant lesions and a trial in which ADVEXIN therapy is used to create a highly specific therapeutic cancer vaccine. Using INGN 241, we are conducting testing in a Phase 1-2 clinical trial for multiple tumor types.

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

Expand Our Delivery System Technologies. We believe no single gene delivery system will be applicable to all clinical needs. At present, we have a broad portfolio of delivery technologies under development. We are leveraging the experience gained with our existing adenoviral vector systems to develop next generation vectors for both viral and non-viral delivery systems. Through our strategic collaboration with VirRx, Inc., we are developing INGN 007, a replication-competent viral therapy in which viruses bind directly to cancer cells, replicate in those cells, and cause those cancer cells to die. To further augment our portfolio, we will continue to examine new licensing opportunities and develop collaborations in the area of novel delivery and targeting technologies.

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

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

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

Product Development Programs

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

Product (Gene)	Cancer Indication	Development Status
ADVEXIN® Gene Therapy (p53)	Head and Neck	Phase 3
	Non-Small Cell Lung	Phase 2 completed
	Breast	Phase 2*
	Perioperative (and Surgery)	Phase 2
	Esophageal	Phase 1-2
	Prostate	Phase 1 completed
	Intravenous Administration	Phase 1 completed
	Ovarian	Phase 1 completed**
	Bladder	Phase 1 completed**
	Oral Cancer (Mouthwash)	Phase 1-2**
	Therapeutic Cancer Vaccine	Phase 1
	Brain (Glioblastoma)	Phase 1**
	Bronchoalveolar	Phase 1
	Rheumatoid Arthritis	Pre-clinical
INGN 241 (mda-7)	Various (solid tumors)	Phase 1-2
	Pancreatic	Pre-clinical
	Breast	Pre-clinical
INGN 007 (Replication competent viral therapy)	Various (solid tumors)	Research
BAK Program	Various	Research
INGN 401 (FUS-1 Program)	Lung	Phase 1
p16 Program	Pancreatic	Research
INGN 601 (Mebendazole)	Gastro-intestinal	Research

* Aventis Pharma provides funding for this trial.

** Conducted in conjunction with the National Cancer Institute.

Indications for ADVEXIN® Therapy (p53)

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

We have completed or are conducting a number of Phase 1, Phase 2 and Phase 3 clinical trials to establish the safety and evaluate the efficacy of ADVEXIN therapy both alone and in combination with radiation therapy, chemotherapy and/or surgery. We evaluated efficacy by

measuring tumors during each trial to analyze whether tumors had regressed, remained stable or progressed during treatment. We supplemented

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these analyses, where possible, with microscopic tissue analysis, or biopsy, to determine the presence of residual cancer cells within the treated area. We further evaluated efficacy by measuring the survival time of the patients treated in all of these trials.

Head and Neck Cancer

Head and neck cancer, encompassing cancers of the tongue, mouth, vocal cords and tissues surrounding them, has a worldwide incidence of approximately 400,000 new cases per year. In the United States, the annual incidence of squamous cell cancer, a cancer of cells that line the oral cavity, pharynx and larynx, is approximately 37,000 with annual deaths of approximately 11,000. Head and neck cancer is frequently fatal, with most patients dying from local and regional disease, rather than from metastasis to other organs. Primary treatments for head and neck cancer are surgery and radiation therapy. However, these treatments are debilitating and have permanent side effects, including loss of teeth, loss of voice or disfigurement. Moreover, a large number of patients with head and neck cancer experience recurrence. Once the disease recurs, few patients survive despite secondary treatment with conventional therapies, with median patient survival of less than 12 months. Although chemotherapy is often used as a secondary treatment, there are no such drugs available today that have been approved by the FDA for treatment of patients with recurrent head and neck cancer.

We believe ADVEXIN therapy is a viable candidate for treatment of head and neck cancer. Based on clinical results from our Phase 1 and Phase 2 clinical trials, we are currently enrolling patients in and conducting two multi-national pivotal Phase 3 clinical trials that the FDA has reviewed, and if successful, are expected to be useful, along with other data, to support regulatory approval. We intend for our ADVEXIN clinical studies to demonstrate the efficacy of ADVEXIN therapy for treatment of patients with squamous cell carcinoma of the head and neck, regardless of whether the p53 gene is mutant or non-mutated, in whom standard treatment of surgery and radiation therapy have not been effective and who have recurrent or refractory disease. The first Phase 3 trial compares the efficacy of ADVEXIN therapy to a standard chemotherapy treatment in patients with refractory disease. The second Phase 3 trial compares the efficacy of ADVEXIN therapy when it is used in combination with a standard chemotherapy treatment to that of standard chemotherapy treatment used alone in patients with recurrent disease. The Phase 2 clinical trials used ADVEXIN therapy as a monotherapy, or single agent, to determine safety and efficacy. The Phase 1 clinical trials used ADVEXIN therapy in multiple dose levels to determine the safety of the drug in human subjects.

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

We conducted a Phase 2 clinical trial of ADVEXIN therapy in 112 patients with either recurrent or refractory head and neck cancers at 18 clinical centers in the United States and Europe, using the highest dose

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of ADVEXIN therapy tested in the Phase 1 clinical trial discussed below. This trial did not have a treatment control arm and the main purpose of the trial was to evaluate the safety, side effects and efficacy of ADVEXIN therapy administered alone to tumors of various sizes. The primary measure of efficacy was to assess patient response to ADVEXIN therapy by periodically measuring the size of all tumors in the patient compared to their size at the start of treatment. A positive response is defined as the disappearance of the tumor, shrinkage of the tumor or the absence of additional tumor growth beyond 25% of pre-treatment measurements, an accepted indicator of tumor growth control.

In order to design Phase 3 clinical trials and to identify the patient characteristics most amenable to ADVEXIN therapy, we conducted a preliminary analysis on the first 88 patients treated and evaluated in our Phase 2 clinical trial. This analysis showed that approximately 25% of the patients that the investigators injected and evaluated had a positive response to treatment. In addition, because a subset of patients had multiple tumors treated, the preliminary analysis also evaluated individual tumor response. The analysis showed that 60% of the individual tumors that the investigators injected and evaluated had a positive response. Tumors with non-mutated p53 genes and those with mutant p53 genes both responded to ADVEXIN therapy. The patients in this Phase 2 clinical trial tolerated ADVEXIN therapy well, without the significant side effects common to conventional cancer treatments. Side effects were consistent with those experienced in the Phase 1 clinical trial discussed below.

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

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

Through a Clinical Trials Agreement with the National Cancer Institute (NCI), Introgen and the NCI will conduct a Phase 1-2 clinical trial in which ADVEXIN therapy will be administered in the form of an oral rinse or mouthwash. This trial will be the first to investigate the effect of ADVEXIN therapy on non-malignant, oral lesions that are at high risk for developing into cancer.

Non-Small Cell Lung Cancer

Lung cancer is the most common cause of cancer-related death in the United States, with an estimated 172,000 new cases diagnosed annually. An estimated 157,000 people die from the disease annually. The five-year survival rate for patients diagnosed with lung cancer is 15%. Non-small cell, or NSC, lung cancer comprises approximately 80% of all lung cancer cases. Surgery can be an effective treatment, but only a minority of patients are eligible because early-stage diagnosis is uncommon. Only approximately 30% of these patients will have a complete surgical resection of their disease. The remaining patients typically undergo a combination of surgery, radiation and chemotherapy. This combination treatment is only effective in a small percentage of cases. Of patients who have unresectable disease, approximately 80% will again have active cancer cells three months after completing a full course of radiation. Due to the ineffective treatment of NSC lung cancer in many patients, a significant, unmet need for better treatments exists. The opportunity for a new beneficial treatment is great, particularly if it can be combined with existing treatments without increasing the toxicity of those treatments.

We have completed a Phase 2 clinical trial of ADVEXIN therapy in combination with radiotherapy as the primary treatment for patients who had newly-diagnosed, inoperable NSC lung cancer and who could not

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tolerate chemotherapy. Radiotherapy is the standard treatment for patients in this condition. All patients in this trial received three ADVEXIN therapy injections into their tumors during a five-to-six week course of radiotherapy. These patients were evaluated for the efficacy, safety and side effects of the treatment to ascertain whether the combination of ADVEXIN therapy with radiation was tolerated. Objectives of this trial were to determine if the addition of ADVEXIN therapy injected directly into the tumor with standard radiotherapy improved the response rate of the injected tumor in patients with inoperable NSC lung cancer, and to evaluate the tolerability of the combination treatment. An evaluation was performed three months after treatment was completed, consisting of a radiograph to assess the size of the treated tumor mass, supplemented by a biopsy to assess for living cancer cells within the tumor at the site of treatment. The patients were then followed without further treatment for clinical evidence of disease progression.

We conducted an analysis of 19 patients that the investigators treated and evaluated in the Phase 2 clinical trial of ADVEXIN therapy. This analysis included both the radiographs and the tumor biopsies that we refer to above. The results of this analysis established an acceptable safety profile and showed evidence of local tumor control and reductions in tumor size. Twelve of the 19 patients that the investigators treated, or 63%, had radiographic evidence of local tumor growth control, including twelve complete or partial responses of the tumor that the investigators injected. Furthermore, the preliminary analysis showed that nine of these twelve patients had no living tumor cells in the biopsy that the investigator took from the site of the injection. Based on the preliminary results of this Phase 2 clinical trial using this therapy with radiation therapy, a larger trial is being evaluated to further test whether ADVEXIN therapy enhances the effectiveness of radiation therapy and chemotherapy when investigators use them together to treat NSC lung cancer. This study was published in the January 2003 issue of *Clinical Cancer Research*.

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

As a supplement to our gene-induced therapeutic protein programs, we are developing INGN 225 using ADVEXIN therapy to create a highly specific therapeutic cancer vaccine that stimulates a patient s particular immune cell known as a dendritic cell. Recently published research in *Current Opinion in Drug Discovery & Development* concluded that ADVEXIN therapy can be used with a patient s isolated dendritic cells as an antigen delivery and immune enhancing therapeutic strategy. Preclinical testing has shown that the immune system can recognize and kill tumors after treatment with ADVEXIN therapy stimulated dendritic cells, which suggests a vaccine consisting of ADVEXIN therapy stimulated dendritic cells (INGN 225) could have broad utility as a prophylaxis for progression of solid tumors. A Phase 1 trial has been initiated to treat patients with small-cell lung cancer using INGN 225 after treatment with standard chemotherapy.

Breast Cancer

Physicians diagnose an estimated 213,000 new cases of breast cancer annually in the United States, and approximately 40,000 of these people are estimated to die from the disease each year. We are conducting, and Aventis Pharma SA, or Aventis, is funding, a Phase 2 clinical trial using ADVEXIN therapy administered in combination with chemotherapy in women who have newly diagnosed, locally advanced breast cancers. Interim results of this trial were published in June 2003 at the annual meeting of the American Society of Clinical Oncology. These results indicated that in patients with locally advanced breast cancer, ADVEXIN therapy can be safely combined with a two-drug standard chemotherapy regimen and that 90 percent of the patients had objective responses to the therapy. Also, the NCI has concluded a Phase 1 clinical trial using ADVEXIN therapy in patients with locally recurrent breast cancer involving the chest wall.

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Prostate Cancer

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

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

Other Cancers

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

Ovarian Cancer. There are an estimated 25,000 new cases of ovarian cancer and 14,000 deaths attributed to ovarian cancer in the United States each year. In approximately 80% of patients with advanced disease, the cancer remains localized within the peritoneal, or abdominal, cavity. This allows ready access to cancer cells for simple intraperitoneal administration, that is, administration of gene therapeutic agents into the abdominal cavity. The NCI has conducted a Phase 1 clinical trial of ADVEXIN therapy in this population.

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

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

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

Esophageal Cancer. Esophageal cancer is a major health problem in Japan. We are conducting a Phase 1-2 study of ADVEXIN therapy for the treatment of advanced unresectable squamous cell esophageal cancer. The study protocol was developed and is sponsored by investigators at Chiba University in Japan. The purpose of the study is to determine the safety and biological and therapeutic activity of ADVEXIN therapy

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in esophageal cancer. Preliminary results demonstrating safety and positive biological effect resulting from the expression of the p53 protein were published in June 2003 at the meeting of the American Society of Clinical Oncology. Of the first eight patients evaluated to date, one patient was observed to have minor tumor regression following ADVEXIN therapy injection.

Indications for INGN-241 (mda-7)

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

Our pre-clinical trials also indicate that in addition to its known activity as a tumor suppressor gene, the proteins produced by the mda-7 gene may also stimulate the body s immune system to protect it against cancer, thereby offering the potential of providing an added advantage in treating various cancers because it may attack cancer using two different mechanisms. For this reason, mda-7 has been classified as interleukin-24, or IL-24. The mda-7 gene and the proteins it produces may work effectively as a radiation sensitizer to make several types of human cancer cells more susceptible to the anti-cancer effect of radiation therapy as indicated in our pre-clinical work. We have also published the results of a pre-clinical trial indicating INGN 241 may suppress the growth in vivo of non-small cell lung cancer through apoptosis, or programmed cell death, in combination with anti-angiogenesis.

We are currently conducting a Phase 1-2 clinical trial using INGN 241 to evaluate safety, mechanism of action and efficacy in approximately 25 patients with solid tumors. This trial has demonstrated that in patients with solid tumors, INGN 241 was well tolerated, was biologically active and displayed minimal toxicity associated with its use.

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

Indications for INGN 401 (FUS-1)

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

Research and Development Programs

In addition to our clinical programs underway with ADVEXIN therapy and INGN 241, we are conducting a number of pre-clinical and research programs involving a variety of therapeutic genes for the treatment of cancer. These programs involve genes that act through diverse mechanisms to inhibit the growth of or kill cancer cells.

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

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a widely known tumor suppressor gene, from M. D. Anderson Cancer Center and have demonstrated that the gene inhibits tumor growth in animal models.

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

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

Introgen Enabling Technologies

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

Viral Delivery Systems

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

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

Non-Viral Delivery Systems

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

Additional Enabling Technologies

Our research activities include a number of additional technologies that expand our capabilities.

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

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

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

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

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

Manufacturing and Process Development

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

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

Business and Collaborative Arrangements

VirRx, Inc.

We are working with VirRx, Inc. (VirRx) to investigate other vector technologies, specifically replication-competent viral therapies, for delivering gene-based products into targeted cells. We have an agreement with VirRx, which began in 2002, to purchase shares of VirRx s Series A Preferred Stock. We purchased $825,000 of this stock for cash through June 30, 2003, which we have recorded as research and development expense. We have agreed to purchase an additional $150,000 of this stock for cash on the first day of each quarter through January 1, 2006. VirRx is required to use the proceeds from these stock sales in accordance with the terms of a collaboration and license agreement between us and VirRx for the development of VirRx s technologies. We may unilaterally terminate this collaboration and license agreement with 90 days prior notice at any time after March 7, 2003, which would also terminate the requirement for us to make any additional stock purchases. Provided the collaboration and license agreement remains in place, we will make additional milestone stock purchases, either for cash or through the issuance of our common stock, upon the completion of Phase 1, Phase 2 and Phase 3 clinical trials involving technologies licensed under this agreement and we will make a $5.0 million cash milestone payment to VirRx, for which we receive no VirRx stock, upon approval by the FDA of a biologics license application involving these technologies. To the extent we have already made cash milestone payments, we may receive a credit of 50% of the Phase 2 clinical trial milestone payments and 25% of the Phase 3 clinical trial milestone payments against this $5.0 million cash milestone payment. The additional milestone stock purchases and cash payment are not anticipated to be required in the near future. We have an option to purchase all outstanding shares of VirRx at any time until March 2007.

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Aventis Pharma AG

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

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

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

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

Gendux, Inc. and Gendux AB

Gendux, Inc. is a wholly owned subsidiary of Introgen. Gendux AB, which is based in Stockholm, Sweden, is a wholly-owned subsidiary of Gendux, Inc. We formed Gendux AB to create a European presence with which to extend our technology and product development opportunities and enhance our interactions with European academic and commercial institutions.

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 entered into this license agreement with M. D. Anderson Cancer Center in 1994. It terminates on July 20, 2009. The agreement is also terminable upon our insolvency, either party s breach or upon our notice on a patent-by-patent basis. The technologies we have licensed from M. D. Anderson Cancer Center, under the exclusive license agreement, relate to p53 and the 3p21.3 family of genes. Under the agreement, we have agreed to pay M. D. Anderson Cancer Center royalties on sales of products utilizing these technologies. We are obligated to reimburse any of M. D. Anderson Cancer Center s costs that may be incurred in connection with obtaining patents related to the licensed technologies. Our strategy for product development is designed to take advantage of the significant multidisciplinary resources available at M. D. Anderson Cancer Center. These efforts have resulted in our becoming 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 entered into a cooperative research and development agreement, or CRADA, with the NCI. The CRADA has a flexible duration, but is terminable upon the mutual consent of the parties or upon 30 days notice of either party. Under the CRADA, NCI agreed to sponsor and conduct pre-clinical and human clinical trials to evaluate the effectiveness and potential superiority to other treatments of ADVEXIN therapy against a range of designated cancers, including breast cancer, ovarian cancer, bladder cancer and brain cancer. To date, NCI has conducted or is conducting numerous Phase 1 clinical trials for ADVEXIN therapy. NCI provided most of the funding for these activities. We supplied NCI with ADVEXIN therapy product to be administered in these trials. We have exclusive rights to all pre-clinical and clinical data accumulated under the CRADA.

Corixa Corporation

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

Marketing and Sales

We are focusing our current product development and commercialization efforts on the oncology market. This market is characterized by its concentration of specialists in relatively few major cancer centers, which we believe can be effectively addressed by a small, focused sales force. We will likely address this market by building a direct sales force as part of the ADVEXIN therapy commercialization process and by pursuing marketing and distribution arrangements with corporate partners for ADVEXIN therapy as well as additional products.

Patents and Intellectual Property

Our Portfolio

Our success will depend in part on our ability to develop and maintain proprietary aspects of our technology. To this end, we have an intellectual property program directed at developing proprietary rights in technology that we believe may be important to our success. We also rely on a licensing program to ensure continued strong technology development and technology transfer from companies and research institutions with whom we work. In addition to our intellectual property license with Aventis, we have entered into a number of exclusive license agreements or options with companies and institutions, including M. D. Anderson Cancer Center, Sidney Kimmel Cancer Center, Corixa, the Imperial Cancer Research Fund and LXR

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Biotechnology, Inc., with the LXR rights being subsequently sold to Tanox, Inc. In addition to patents, we rely on trade secrets and proprietary know-how, which we seek to protect, in part, through confidentiality and proprietary information agreements.

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

Adenoviral p53 Compositions and Therapies

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

Combination Therapy with the p53 Gene

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

Adenovirus Production, Purification and Formulation

Another focus of our research has involved the development of procedures for the commercial scale production of our potential adenoviral-based products, including that of ADVEXIN therapy. In this regard, we own an issued United States patent as well as a number of pending United States applications, and corresponding international applications, directed to commercial scale processes for producing adenoviral gene-based compositions having a high level of purity, as well as to storage-stable formulations. These applications include procedures for preparing commercial quantities of recombinant adenoviruses for gene-based products and include procedures applicable to the p53 gene, as well as any of the other of our potential gene-based products. We have also licensed from Aventis a United States application and corresponding international applications directed to processes for the production of purified adenoviruses, which are useful for gene-based applications.

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Other Tumor Suppressor Genes

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

Other Therapeutic, Composition and Process Technologies

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

Benzimidazole Small Molecule Cancer Therapy Program

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

Trade Secrets

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

Government Regulation

The production and marketing of our proposed products and our research and development activities are subject to regulation for safety, effectiveness and quality by numerous governmental authorities in the United States and other countries. In the United States, drugs and research personnel are subject to rigorous FDA and National Institutes of Health, or NIH, regulations. The Federal Food, Drug and Cosmetic Act (the FDC Act), as amended, the regulations promulgated under the FDC Act, and other federal and state statutes and regulations govern, among other things, the testing, manufacture, safety, effectiveness, labeling, storage, record

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keeping, advertising and promotion of our products. Product development and approval within this regulatory framework takes a number of years and involves the expenditure of substantial resources.

The FDA recently placed a clinical hold on gene therapy clinical trials using retroviral vectors to transduce hematopoietic stem cells after two participants in such a trial for the X-linked form of severe combined immune deficiency disease (X-SCID) being conducted in Europe developed what appeared to be a leukemia-like illness. This clinical hold requires a case-by-case review of the use of retroviral vectors in these trials. We do not use retroviral vectors in our ongoing clinical trials and are not developing products using the production process used in those clinical trials. We have received no communications from the FDA to indicate this clinical hold will affect our clinical trials, and we anticipate no future negative effects on us from this event. Our pharmacovigilance department monitors every patient in our clinical trials for safety and reports all side effects to the FDA and the National Institutes of Health according to applicable regulations. We have witnessed no adverse effects in our clinical trials that even remotely resemble what occurred in the X-SCID trial. Due to the fundamental differences between retrovirus vectors and the adenovirus vector employed in ADVEXIN therapy, we believe the likelihood of our encountering an event such as that experienced in the X-SCID trial is remote.

The Drug Approval Process

The steps required before our proposed products may be marketed in the United States include pre-clinical testing, the submission to the FDA of an investigational new drug, or IND, application for clinical trials, clinical trials to establish the safety and effectiveness of the drug, the submission to the FDA of a BLA (for a biologic) or an NDA (for a drug) and the FDA approval of the BLA or NDA prior to any commercial sale of the drug. Our products will be regulated as biologics. In addition to obtaining FDA approval for each product, each domestic manufacturing establishment must be registered with, and approved by, the FDA.

Domestic manufacturing establishments are subject to biennial inspections by the FDA and must comply with CGMP requirements. To supply products for use in the United States, foreign manufacturing establishments, including third party facilities, must comply with CGMP requirements and are subject to periodic inspection by the FDA or by corresponding regulatory agencies in such countries under reciprocal agreements with the FDA.

Pre-Clinical Testing

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

Clinical Trials

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

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safety of human subjects, informed consent and the possible liability of the institution. Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA.

Clinical trials are typically conducted in three sequential phases, but the phases often overlap. In Phase 1, the initial introduction of the drug into healthy volunteers or patients, the drug is tested for safety or adverse effects, dosage tolerance, absorption, distribution, metabolism, excretion and clinical pharmacology. Phase 2 involves clinical trials in a limited patient population to determine the effectiveness of the drug for specific, targeted indications, determine dosage tolerance and optimal dosage and identify possible adverse effects and safety risks. When a compound is found to be effective and to have an acceptable safety profile in Phase 2 evaluations, Phase 3 clinical trials are undertaken to further evaluate clinical effectiveness and to further test for safety within an expanded patient population at geographically dispersed clinical trial sites. Phase 3 clinical trials conducted to seek marketing approval by the FDA are called pivotal trials.

National Institutes of Health

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

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

Marketing Applications

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

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

If the FDA approves the BLA or NDA, the drug becomes available for physicians to prescribe. Periodic reports must be submitted to the FDA, including descriptions of any adverse reactions reported. The FDA may request additional trials, referred to as Phase 4 clinical trials, to evaluate long-term effects. Phase 4

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clinical trials and post-marketing trials may also be conducted to explore new indications and to broaden the application and use of the drug and its acceptance in the medical community.

Orphan Drug Act

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

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

Off-Label Use

Physicians may prescribe drugs for uses that are not described in the product s labeling that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties and may constitute the best treatment for many patients in various circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturers communications on the subject of off-label use. Companies cannot actively promote FDA-approved drugs for off-label uses. However, new regulations, if followed, provide a safe harbor from FDA enforcement action that would allow us to disseminate to physicians articles published in peer-reviewed journals, like the *New England 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 Food and Drug Administration Modernization Act of 1997, or FDAMA, was enacted, in part, to ensure the timely availability of safe and effective drugs, biologics and medical devices, by expediting the FDA review process for new products. FDAMA established a statutory program for the approval of fast track products. The fast track provisions essentially codify FDA s Accelerated Approval regulations for drugs and biologics. A fast track product is defined as a new drug or biologic intended for the treatment of a serious or life-threatening condition that demonstrates the potential to address unmet medical needs for such a condition. Under the new fast track program, the sponsor of a new drug or biologic may request the FDA to designate the drug or biologic as a fast track product at any time during the clinical development of the product. FDAMA specifies that the FDA must determine if the product qualifies for fast track designation within 60 days of receipt of the sponsor s request. Approval of an NDA for a fast track product can be based on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit. Approval of a fast track product may be subject to (1) post-approval trials to validate the surrogate endpoint or confirm the effect on the clinical endpoint and (2) prior review of copies of all promotional material. If a preliminary review of the clinical data suggests efficacy, the FDA may initiate review of sections of an application for a fast track product before the application is complete. This rolling review is available if the applicant provides a schedule for submission of remaining information and pays applicable user fees.

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

International

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

Competition

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

We compete with pharmaceutical and biotechnology companies, including Canji, Inc. and Genvec, Inc., which are pursuing other forms of treatment for the diseases ADVEXIN therapy and our other product candidates target. There are many other companies, both publicly and privately held, including well-known pharmaceutical companies, engaged in developing products for human therapeutic applications. We also compete with universities and other research institutions in the development of products, technologies and processes. In many instances, we compete with other commercial entities in acquiring products or technologies from universities and other research institutions.

We expect that competition among products approved for sale will be based, among other things, on product efficacy, safety, reliability, availability, price, patent position and sales, marketing and distribution capabilities. Our competitive position also depends upon our ability to attract and retain qualified personnel, 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.

Scientific Advisory Board

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

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

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

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

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

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

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FORWARD-LOOKING STATEMENTS

Certain statements in this prospectus and the documents incorporated herein by reference are forward looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (the Securities Act), and Section 21E of the Securities and Exchange Act of 1934, as amended (the Exchange Act), that involve risks and uncertainties. Any statements contained herein (including without limitation statements to the effect that we estimate, expect, anticipate, plan, believe, project, continue, may, or will or statements concernin opportunity or variations thereof or comparable terminology or the negative thereof) that are not statements of historical fact should be construed as forward-looking statements. These statements are not guarantees of future performance and are subject to certain risks, uncertainties and assumptions that are difficult to predict. Actual results could differ materially and adversely from those anticipated in such forward looking statements as a result of certain factors, including those described in the prospectus under Risk Factors. Because of these and other factors that may affect our operating results, past performance should not be considered an indicator of future performance and investors should not use historical results to anticipate results or trends in future periods. We undertake no obligation to revise or publicly release the results of any revision to these forward-looking statements. Readers should carefully review the risk factors described in other documents we file from time to time with the SEC including its quarterly reports on Form 10-Q to be filed during 2003.

We have not authorized any person to give any information or to make any representation other than those contained in this prospectus in connection with this offering. You should not rely on such information or representation. Neither the delivery of this prospectus or any sale made pursuant to this prospectus shall create any implication that the information contained in this prospectus is correct as of any time subsequent to the date hereof. This prospectus does not constitute an offer to sell or solicitation of an offer to buy any security other than the common stock covered by this prospectus.

USE OF PROCEEDS

Unless otherwise indicated in the prospectus supplement, the net proceeds from the sale of common stock offered by this prospectus will be used for general corporate purposes and working capital requirements. We may also use a portion of the net proceeds to fund possible investments in and acquisitions of complimentary businesses, partnerships, minority investments, products or technologies. Currently, there are no commitments or agreements regarding such acquisitions or investments that are material. Pending their ultimate use, we intend to invest the net proceeds in money market funds, commercial paper and governmental and non-governmental debt securities with maturities of up to five years.

PLAN OF DISTRIBUTION

We may sell the common stock from time to time in one or more transactions:

- through one or more underwriters or dealers;
- directly to purchasers;
- through agents; and
- through a combination of any of these methods of sale.

We may distribute the common stock from time to time in one or more transactions:

- at a fixed price or prices, which may be changed from time to time; and
- at negotiated prices.

We will describe the method of distribution of common stock in the applicable prospectus supplement.

Underwriters, dealers or agents may receive compensation in the form of discounts, concessions or commissions from us or our purchasers as their agents in connection with the sale of the securities. These

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underwriters, dealers or agents may be considered to be underwriters under the Securities Act. As a result, discounts, commissions or profits on resale received by underwriters, dealers or agents may be treated as underwriting discounts and commissions. Each prospectus supplement will identify any underwriter, dealer or agent, and describe any compensation received by them from us. Any initial public offering price and any discounts or concessions allowed or reallowed or paid to dealers may be changed from time to time.

Underwriters, dealers and agents may be entitled to indemnification by us against certain civil liabilities, including liabilities under the Securities Act, or to contribution with respect to payments made by the underwriters, dealers or agents, under agreements between us and the underwriters, dealers and agents.

We may grant underwriters who participate in the distribution of common stock option to purchase additional securities to cover over-allotments, if any, in connection with the distribution.

In connection with the offering of common stock, certain persons participation in such offering may engage in transactions that stabilize, maintain or otherwise affect the market prices of such common stock, including stabilizing transactions, syndicate covering transactions and the imposition of penalty bids. Specifically, such persons may overallot in connection with the offering and may bid for and purchase the common stock in the open market.

Underwriters or agents and their associates may be customers of, engage in transactions with or perform services for us in the ordinary course of business.

To the extent required, this prospectus may be amended and supplemented from time to time to describe a specific plan of distribution.

LEGAL MATTERS

The validity of the common stock being offered hereby is being passed upon for us by Wilson Sonsini Goodrich & Rosati, Professional Corporation, Austin, Texas.

EXPERTS

Our consolidated financial statements at December 31, 2002 and for the year ended December 31, 2002, incorporated by reference in this prospectus and registration statement have been audited by Ernst & Young LLP, independent auditors, as set forth in their report thereon (the 2001 and 2000 financial statements were audited by other auditors who have ceased operations and for which Ernst & Young LLP has expressed no opinion or other form of assurance on the 2001 and 2000 financial statements taken as a whole) incorporated by reference herein, and are included in reliance upon such report given on the authority of such firm as experts in accounting and auditing.

Additionally, our audited consolidated financial statements incorporated by reference in this prospectus and elsewhere in the registration statement to the extent and for the periods indicated in their reports have been audited with respect to our and our subsidiaries consolidated balance sheet as of December 31, 2001 and June 30, 2001 and 2000, and the related consolidated statements of operations, stockholders equity and cash flows for the six months ended December 31, 2001 and the years ended June 30, 2001 and 2000, by Arthur Andersen LLP, independent public accountants. These reports are incorporated by reference in this prospectus in reliance upon the authority of these accounting firms as experts in giving these reports.

We have been unable to obtain, after reasonable efforts, the written consent of Arthur Andersen LLP to our naming it as an expert and as having audited the consolidated financial statements for the six months ended December 31, 2001 and the two years ended June 30, 2001 and 2000 and including its audit report in this prospectus. Under these circumstances, Rule 437(a) of the Securities Act of 1933, as amended, permits this registration statement to be filed without the consent of Arthur Andersen LLP. This lack of consent may limit your ability to recover damages from Arthur Andersen LLP under Section 11 of the Securities Act for any untrue statements of material fact contained in the financial statements audited by Arthur Andersen LLP

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or any omissions to state a material fact required to be stated therein or necessary to make the statements therein not misleading.

We changed certifying accountants from Arthur Andersen LLP to Ernst & Young LLP effective March 6, 2002. Arthur Andersen LLP s report on the financial statements for the six months ended December 31, 2002 and the years ended June 30, 2001 and 2000 did not contain an adverse opinion or disclaimer of opinion and was not qualified or modified as to uncertainty, audit scope or accounting principles. The decision to change accountants was approved by our Board of Directors. During each of the two years ended June 30, 2000 and 2001 and for the six-month transition period ended December 31, 2001, and through March 20, 2002, there were no disagreements with Arthur Andersen LLP on any matter of accounting principles or practices, financial statement disclosure, or auditing scope or procedures, which disagreements, if not resolved to the satisfaction of Arthur Andersen LLP, would have caused it to make reference to the subject matter of the disagreement in connection with its report. During each of the two years ended June 30, 2000 and 2001 and for the six-month transition period ended December 31, 2001, and through March 20, 2002, Arthur Andersen LLP did not advise us of any reportable events as described in Item 304(a)(1)(v) of Regulation S-K under the Securities Act of 1933, as amended. We have requested and received from Arthur Andersen LLP the letter required by Item 304(a)(3) of Regulation S-K (and filed the same as Exhibit 16 to our report on Form 8-K filed on March 12, 2002), and we state that Arthur Andersen LLP agrees with the statements made by us in this prospectus in response to Item 304(a)(1) of Regulation S-K.

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

The SEC allows us to incorporate by reference the information we file with them, which means that we can disclose important information to you by referring you to documents that we have previously filed with the SEC or documents that we will file with the SEC in the future. The information incorporated by reference is considered to be part of this prospectus, and later information that we file with the SEC will automatically update and supersede this information. We incorporate by reference into this prospectus any filings made by us with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus until the termination of this offering, as well as the following documents:

our Annual Report on Form 10-K for the fiscal year ended December 31, 2002, filed with the SEC on March 31, 2003;

our Proxy Statement, filed with the SEC on April 30, 2003, as amended on May 8, 2003;

our Current Report on Form 8-K, filed with the SEC on May 13, 2003, as amended on May 13, 2003;

our Quarterly Report on Form 10-Q for the quarter ended March 31, 2003, filed with the SEC on May 15, 2003;

our Current Report on Form 8-K, filed with the SEC on June 18, 2003;

our Current Report on Form 8-K, filed with the SEC on June 19, 2003;

our Current Report on Form 8-K, filed with the SEC on August 12, 2003;

our Quarterly Report on Form 10-Q for the quarter ended June 30, 2003, filed with the SEC on August 14, 2003; and

The description of our common stock contained in our Registration Statement on Form 8-A, filed with the SEC on September 8, 2000.

You may request a copy of any of these filings, at no cost to you, by writing or telephoning us at the following address and telephone number: Introgen Therapeutics, Inc., 301 Congress Avenue, Suite 1850, Austin, Texas 78701; telephone number (512) 708-9310.

Additionally, we make these filings available, free of charge, on *www.introgen.com* as soon as reasonably practicable after we electronically file such materials with, or furnish them to, the SEC. The information on

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the website listed above, other than these filings, is not, and should not be, considered part of this prospectus and is not incorporated by reference to this document.

WHERE YOU CAN FIND MORE INFORMATION

We file annual, quarterly and periodic reports, proxy statements and other information with the SEC. You may inspect these documents without charge at the principal office of the SEC located at 450 Fifth Street, N.W., Washington, D.C. 20549, and you may obtain copies of these documents from the SEC s Public Reference Room at its principal office. Information regarding the operation of the Public Reference Room may be obtained by calling 1-800-SEC-0330. The SEC maintains a web site that contains reports, proxy and information statements and other information regarding registrants that file electronically with the SEC. The address of the SEC s web site is *www.sec.gov*.

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DISCLOSURE OF SEC POSITION ON INDEMNIFICATION

FOR SECURITIES ACT LIABILITIES

We are organized under the laws of the State of Delaware. Our Certificate of Incorporation, as amended, and bylaws, as amended, eliminate the personal liability of its directors to the fullest extent permitted by the Delaware General Corporation Law. In addition, our Certificate of Incorporation, as amended, and bylaws, as amended, provide indemnity for our current or former officers and directors against all liabilities and costs of defending an action or suit in which they were involved by reason of their positions with us. However, we cannot indemnify any person if a court finds that the person did not act in good faith. Our bylaws, as amended, also provide that we may purchase insurance to protect any director, officer, employee or agent against any liability. We have entered into separate indemnification agreements with each of our directors and executive officers, whereby we have agreed, among other things, to indemnify them to the fullest extent permitted by the Delaware General Corporation Law, subject to specified limitations, against certain liabilities actually incurred by them in any proceeding in which they are a party that may arise by reason of their status as directors, officers, employees or agents or may arise by reason of their serving as such at our request for another entity and to advance their expenses incurred as a result of any proceeding against them as to which they could be indemnified. We intend to enter into similar separate indemnification agreements with any directors or officers who may join us in the future. There is no pending litigation or proceeding involving any of our directors, officers, employees or other agents as to which indemnification is being sought nor are we aware of any pending or threatened litigation that may result in claims for indemnification.

Insofar as indemnification for liabilities arising under the Securities Act may be permitted to directors, officers or controlling persons pursuant to the foregoing provisions, we have been informed that in the opinion of the SEC such indemnification is against public policy as expressed in the Securities Act, and is therefore unenforceable.

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