INTROGEN THERAPEUTICS INC
Form 424B3
March 05, 2004

Table of Contents

The information in this preliminary prospectus supplement is not complete and may be changed. This preliminary prospectus supplement is not an offer to sell these securities, and we are not soliciting offers to buy these securities, in any jurisdiction where such offer or sale is not permitted.

Filed Pursuant to Rule 424(b)(3)
Registration No. 333-107799

PRELIMINARY PROSPECTUS SUPPLEMENT | Subject to completion | March 5, 2004

(To Prospectus dated August 25, 2003)

5,500,000 Shares

Common Stock

We are offering all of the 5,500,000 shares of our common stock offered by this prospectus supplement.

Our common stock is quoted on the Nasdaq National Market under the symbol INGN. On March 3, 2004, the last reported sale price of our common stock on the Nasdaq National Market was $9.43 per share.

Investing in our common stock involves a high degree of risk. Before buying any shares, you should carefully read the discussion of material risks of investing in our common stock under the heading Risk factors beginning on page S-10 of this prospectus supplement.

Neither the Securities and Exchange Commission nor any state securities commission has approved or disapproved of these securities or determined if this prospectus supplement or the accompanying prospectus is truthful or complete. Any representation to the contrary is a criminal offense.

	Per share	Total
Public offering price	$	$
Underwriting discounts and commissions	$	$
Proceeds, before expenses, to us	$	$

The underwriters may also purchase from us up to an additional 825,000 shares of common stock from us at the public offering price, less the underwriting discounts and commissions, to cover over-allotments, if any, within 30 days of the date of this prospectus supplement.

The underwriters are offering shares of common stock as described in Underwriting. Delivery of the shares will be made on or about March , 2004.

Sole Book-Running Manager

UBS Investment Bank

SG Cowen

Leerink Swann & Co.

You should rely only on the information contained or incorporated by reference in this prospectus supplement and the accompanying prospectus. We have not and the underwriters have not authorized anyone to provide information different from that contained or incorporated by reference in this prospectus supplement or the accompanying prospectus. Neither the delivery of this prospectus supplement nor the sale of common stock means that information contained or incorporated by reference in this prospectus supplement or the accompanying prospectus is correct after the date of this prospectus supplement. These documents are not an offer to sell or a solicitation of an offer to buy these shares of common stock in any circumstance under which the offer or solicitation is unlawful.

TABLE OF CONTENTS

Table of Contents

(This page intentionally left blank)

Table of Contents

Prospectus supplement summary

This summary does not contain all of the information that you should consider before investing in our common stock. You should read this entire prospectus supplement and the accompanying prospectus carefully, including Risk factors, the financial statements and other information incorporated by reference in this prospectus supplement and the accompanying prospectus, before making an investment decision.

Unless the context requires otherwise, the words Introgen, we, company, us and our refer to Introgen Therapeutics, Inc.

BUSINESS OVERVIEW

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

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

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

We have also completed or are currently conducting numerous Phase 1 and Phase 2 clinical trials of ADVEXIN therapy by itself and in combination with chemotherapy or radiation therapy in a variety of cancers. These trials include a completed Phase 2 clinical trial of ADVEXIN administered as a complement with radiation therapy in non-small cell lung cancer; a Phase 2 clinical trial of ADVEXIN therapy combined with systemic chemotherapy for the treatment of breast cancer; a Phase 1/early Phase 2 clinical trial of ADVEXIN therapy for the treatment of advanced unresectable squamous cell esophageal cancer; a Phase 1 clinical trial of ADVEXIN therapy in prostate cancer; Phase 1 clinical trials of ADVEXIN therapy in bronchoalveolar cancer; and a Phase 1/early Phase 2 clinical trial in which ADVEXIN therapy is being administered to prevent precancerous oral lesions that have a high risk of developing into cancer.

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

We are developing our second product candidate, INGN 241, for the treatment of solid tumors and in melanoma, a deadly form of skin cancer. INGN 241 combines the mda-7 gene with our adenoviral gene delivery system to kill tumor cells, including metastatic tumor cells, through multiple mechanisms.

Table of Contents

A Phase 1/early Phase 2 trial indicated that in patients with various solid tumors, INGN 241 is well tolerated, displays minimal toxicity and is biologically active.

ADVEXIN Therapy (p53)

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

Our lead product candidate, ADVEXIN therapy, combines the p53 gene with a non-replicating, non-integrating adenoviral gene delivery system that we have developed and extensively tested. The p53 gene is one of the most potent members of a group of naturally occurring tumor suppressor genes, which act to kill cancer cells, arrest cancer cell growth and protect cells from becoming cancerous. The p53 gene works through multiple mechanisms of action including apoptosis, or programmed cell death, cancer cell growth arrest, and reducing the blood supply to tumors through a process known as anti-angiogenesis. Molecular pathways normally controlled by the p53 gene are abnormal in the vast majority of cancers. Patients may receive multiple doses of ADVEXIN therapy, and some patients have received ongoing ADVEXIN treatments for several years. Physicians typically inject ADVEXIN therapy directly into the tumor. Since the protein produced by the p53 gene is known to be important in controlling growth of most types of solid tumors, we believe that ADVEXIN therapy could be applicable to a broad range of cancers.

Head and neck cancer

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

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

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

Clinicial trial 302 is a Phase 3 clinical trial that compares the efficacy of ADVEXIN therapy when it is used in combination with a standard chemotherapy treatment to that of standard chemotherapy treatment used alone in patients with recurrent disease. Clinical trial 302 is planned to enroll

Table of Contents

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

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

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

As in all of our previous clinical trials, ADVEXIN therapy was well tolerated without the significant side effects common to conventional cancer treatments.

Non-small cell lung cancer

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

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

Table of Contents

the injected tumor in patients with inoperable NSC lung cancer, and to evaluate the tolerability of the combination treatment.

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

Breast cancer

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

Other cancers

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

Together with the National Cancer Institute, or NCI, we are conducting Phase 1 clinical trials using ADVEXIN therapy for the treatment of ovarian, bladder, brain and bronchoalveolar cancers. We and the NCI are also conducting a Phase 1/early Phase 2 clinical trial in which ADVEXIN therapy is administered in the form of an oral rinse or mouthwash. This trial is the first to investigate the effect of ADVEXIN therapy on non-malignant, oral lesions that are at high risk for developing into cancer. In addition, we are conducting a Phase 1/early Phase 2 study of ADVEXIN therapy for the treatment of advanced unresectable squamous cell esophageal cancer. The study protocol was developed and is sponsored by investigators at Chiba University in Japan.

INGN 241 (mda-7)

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

cells, even if other tumor suppressor genes, including p53 or p16, are not functioning properly, it appears that mda-7 functions via a novel mechanism of tumor suppression.

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

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

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.

INGN 225 (p53 vaccine)

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

Table of Contents

PRODUCT DEVELOPMENT PROGRAMS

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

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

* *Conducted in conjunction with the National Cancer Institute.*

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

OUR STRATEGY

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

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

Develop our portfolio of gene-induced protein therapy and other drug products. Utilizing our significant research, clinical, and regulatory expertise, we are evaluating development of additional gene-induced protein therapies, such as FUS-1, and other drug products for various cancers. We have established an efficient process for evaluating new drug candidates and advancing them from pre-clinical to clinical development. We have identified and licensed multiple technologies, which we intend to combine with our adenoviral and non-viral gene delivery systems and which we believe are attractive development targets for the treatment of various cancers. We are also evaluating the development of mebendazole (INGN 601), our first small molecule product candidate. We intend to evaluate additional opportunities to in-license or acquire new technologies.

Establish targeted sales and marketing capabilities. Because the oncology market is characterized by a concentration of specialists in relatively few major cancer centers, it can be effectively

Table of Contents

addressed by a small, focused sales force. We believe we can address this market by building a direct sales force as part of the ADVEXIN therapy commercialization process and by pursuing marketing and distribution agreements with corporate partners for ADVEXIN therapy as well as additional products.

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

Table of Contents

The offering

Common stock we are offering	5,500,000 shares
Common stock outstanding immediately following this offering	32,083,274 shares
Nasdaq National Market symbol	INGN
Use of proceeds	We expect to use the net proceeds from the sale of common stock offered by this prospectus supplement to fund regulatory activities relating to our lead product candidate, ADVEXIN therapy, to fund ongoing and planned clinical trials, to continue pre-clinical research and development, and for other 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. See Use of proceeds.

The number of shares of common stock to be outstanding after the offering is based on 26,583,274 shares outstanding as of March 2, 2004 and excludes:

- 4,756,401 shares of common stock underlying options outstanding as of December 31, 2003 at a weighted average exercise price of $2.91 per share;
- 400,000 shares of common stock available for issuance upon the exercise of outstanding warrants as of December 31, 2003 at an exercise price of $7.89 per share;
- 2,343,721 shares of common stock available for issuance upon the conversion of 100,000 shares of Series A non-voting convertible preferred stock as of December 31, 2003; and
- 1,484,113 shares of common stock available for issuance or future grant pursuant to our 2000 Stock Option Plan (includes an increase of 1,326,976 shares on January 1, 2004 pursuant to an automatic reload under the 2000 Stock Option Plan).

Unless we specifically state otherwise, all information contained in this prospectus supplement and the accompanying prospectus assumes that the underwriters do not exercise their over-allotment option to purchase up to an additional 825,000 shares of common stock.

Table of Contents

Summary consolidated financial data

The summary consolidated financial data presented below is derived from the audited consolidated financial statements of Introgen Therapeutics, Inc. and our subsidiaries incorporated by reference in this prospectus supplement and the accompanying prospectus, except for the year ended December 31, 2001, which is unaudited. The unaudited consolidated financial statement data includes, in our opinion, all adjustments (consisting only of normal recurring adjustments) that are necessary for a fair presentation of our results of operations for this period. The summary consolidated financial data set forth below is qualified in its entirety by, and should be read in conjunction with, the consolidated financial statements and notes thereto and Management s discussion and analysis of financial condition and results of operations incorporated by reference in this prospectus supplement and the accompanying prospectus. The as adjusted balance sheet data gives effect to the issuance and sale by us of 5,500,000 shares of our common stock in this offering at an assumed public offering price of $9.43 per share, after deducting the underwriting discounts and commissions and estimated offering expenses payable by us.

	Year ended December 31,		
Consolidated statement of operations data:	**2001**	**2002**	**2003**
(in thousands, except per share amounts)	**(unaudited)**		
Contract services, grants and other revenue	$ 591	$ 1,173	$ 304
Operating costs and expenses:			
Research and development	19,923	21,512	14,973
General and administrative	6,361	6,722	6,102
Total operating costs and expenses	26,284	28,234	21,075
Loss from operations	(25,693)	(27,061)	(20,771)
Interest income (expense), net	423	(207)	393
Other income	871	1,140	1,052
Net loss	$(24,399)	$(26,128)	$(19,326)
Net loss per share, basic and diluted	$ (1.14)	$ (1.22)	$ (0.84)
Shares used in computing basic and diluted net loss per share	21,440	21,471	22,902

	December 31, 2003	
Consolidated balance sheet data:	**Actual**	**As adjusted**
(in thousands)		
Cash and cash equivalents	$ 36,397	$ 84,750
Working capital	31,091	79,444
Total assets	44,483	92,836
Long-term debt and capital lease obligations, net of current portion	6,714	6,714
Accumulated deficit	(92,969)	(92,969)
Stockholders equity	31,285	79,638

Table of Contents

Risk factors

Investing in our common stock involves a high degree of risk. In addition to the other information included or incorporated by reference in this prospectus supplement and the accompanying prospectus, you should carefully consider the risks described below before purchasing our common stock. If any of the following risks actually occur, our business, financial condition and results of operations could materially suffer. As a result, the trading price of our common stock could decline, and you might lose all or part of your investment.

RISKS RELATED TO OUR BUSINESS

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

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

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

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

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

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

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

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

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

Despite the FDA s designation of ADVEXIN therapy as a Fast Track product, we may encounter delays in the regulatory approval process due to additional information requirements from the FDA, unintentional omissions in our Biologics License Application for ADVEXIN therapy, or other delays in the FDA s review process. We may encounter delays or rejections in the regulatory approval process because of additional government regulation from future legislation or administrative action or changes in FDA policy during the period of product development, clinical trials and FDA regulatory review.

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

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

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

For marketing drugs and biologics outside the United States, the requirements governing the conduct of clinical trials, product licensing, pricing and reimbursement vary greatly from country to country

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

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

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

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

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

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

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

- an acceleration of the number, size or complexity of our clinical trials;
- slower than expected progress in developing ADVEXIN therapy, INGN 241 or other product candidates;
- higher than expected costs to obtain regulatory approvals;
- higher than expected costs to pursue our intellectual property strategy;

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

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

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

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

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

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

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

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

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

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

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

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

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

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

To effectively market our products, we will need to develop sales, marketing and distribution capabilities. In order to develop or otherwise obtain these capabilities, we may have to enter into marketing, distribution or other similar arrangements with third parties in order to sell, market and

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

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

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

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

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

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

To date, the FDA has not approved any gene therapy product or gene-induced product for sale in the United States. The commercial success of our products will depend in part on public acceptance of the use of gene therapy products or gene-induced products, which are a new type of disease treatment for the prevention or treatment of human diseases. Public attitudes may be influenced by claims that gene

therapy products or gene-induced products are unsafe, and these treatment methodologies may not gain the acceptance of the public or the medical community. Negative public reaction to gene therapy products or gene-induced products could also result in greater government regulation and stricter clinical trial oversight.

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

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

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

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

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

Through our exclusive license from The University of Texas System for technology developed at M. D. Anderson Cancer Center, we have obtained and are currently seeking further patent protection for adenoviral p53, including ADVEXIN therapy, and its use in cancer therapy. Further, the PTO issued us a United States patent for our adenovirus production technology. We also control, through licensing arrangements, four issued United States patents for combination therapy involving the p53 gene and conventional chemotherapy or radiation, one issued United States patent covering the use of adenoviral p53 in cancer therapy, one issued United States patent covering adenoviral p53 as a product and an issued United States patent covering the core DNA of adenoviral p53. We have recently been notified by the PTO that additional applications relating to our adenoviral p53, purified adenoviral composition and mda-7 technology have been allowed. We cannot assure you these allowed

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

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

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

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

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

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

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

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

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

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

Regardless of merit or outcome, our involvement in any litigation, interference or other administrative proceedings could cause us to incur substantial expense and could significantly divert the efforts of our technical and management personnel. An adverse determination may subject us to the loss of our

proprietary position or to significant liabilities, or require us to seek licenses that may include substantial cost and ongoing royalties. Licenses may not be available from third parties, or may not be obtainable on satisfactory terms. An adverse determination or a failure to obtain necessary licenses may restrict or prevent us from manufacturing and selling our products, if any. These outcomes could materially harm our business, financial condition and results of operations.

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

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

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

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

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

Table of Contents

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

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

- they are more effective than alternative treatments;
- their side effects are acceptable to patients and doctors;
- insurers and other third-party healthcare payers will provide adequate reimbursement for them;
- we produce and sell them at a profit; and
- we market ADVEXIN therapy, INGN 241, INGN 225 and other product candidates effectively.

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

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

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

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

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

Table of Contents

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

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

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

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

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

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

Table of Contents

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

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

- decreased demand for our product candidates;
- injury to our reputation and significant media attention;
- withdrawal of clinical trial volunteers;
- substantial delay in FDA approval;
- costs of litigation; and
- substantial monetary awards to plaintiffs.

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

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

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

Our stock price may fluctuate substantially.

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

- progress and results of our pre-clinical and clinical trials;
- announcement of technological innovations by us or our competitors;
- developments concerning proprietary rights, including patent and litigation matters;
- publicity regarding actual or potential results with respect to products under development by us or by our competitors;
- regulatory developments;
- the announcement of new products by us or our competitors;
- quarterly variations in our or our competitors results of operations;
- failure to achieve operating results projected by securities analysts;

changes in earnings estimates or recommendations by securities analysts;

developments in our industry; and

general market conditions and other factors.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

RISKS RELATED TO THE OFFERING

Market volatility may affect our stock price, and the value of your investment in our common stock may be subject to sudden decreases.

The trading price for our common stock has been, and we expect it to continue to be, volatile. The price at which our common stock trades depends on number of factors, including the following, many of which are beyond our control:

- our historical and anticipated operating results, including fluctuations in our financial and operating results;
- pre-clinical and clinical trial results;
- market perception of the prospects for biotechnology companies as an industry sector;
- general market and economic conditions;
- changes in government regulations affecting product approvals, reimbursement or other aspects of our or our competitors businesses;
- FDA review of our product development activities;

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

developments concerning our key personnel and intellectual property rights;

announcements regarding significant collaborations or strategic alliances; and

publicity regarding actual or potential performance of products under development by us or our competitors.

In addition, the stock market has from time to time experienced extreme price and volume fluctuations. These broad market fluctuations may lower the market price of our common stock and affect the volume of trading in our stock. The high and low sale prices per share of our common stock on the Nasdaq National Market were $9.43 and $2.01, respectively, from January 1, 2003 through March 3, 2004. During this period, the average daily trading volume of our common stock on the Nasdaq National Market was approximately 300,000 shares. During periods of stock market price volatility, share prices of many biotechnology companies have often fluctuated in a manner not necessarily related to their individual operating performance. Accordingly, our common stock may be subject to greater price volatility than the stock market as a whole.

Anti-takeover provisions in our charter documents and under Delaware law could make an acquisition of us, which may be beneficial to our stockholders, more difficult.

Provisions of our certificate of incorporation and bylaws will make it more difficult for a third party to acquire us on terms not approved by our board of directors and may have the effect of deterring hostile takeover attempts. For example, our certificate of incorporation authorizes our board of directors to issue up to 5,000,000 shares of preferred stock, of which 100,000 shares have been designated as Series A Non-Voting Convertible Preferred Stock, and to fix the price, rights, preferences, privileges and restrictions, including voting rights, of those shares without any further vote or action by the stockholders.

In connection with the restructuring of the Aventis collaboration and pursuant to a stock purchase agreement with Aventis executed on June 30, 2001, we issued and sold to Aventis 100,000 shares of Series A Non-Voting Convertible Preferred Stock, $0.001 par value per share. The shares of Series A Non-Voting Convertible Preferred Stock are not subject to repurchase or redemption, and are convertible at any time, at our option or the option of Aventis, into 2,343,721 shares of our common stock. Under a voting agreement, Aventis must vote these shares of common stock in the same manner as the shares voted by a majority of the other stockholders on any corporate action put to a vote of our stockholders. This voting requirement terminates at the earliest of the tenth anniversary of the voting agreement, registration of these shares with the Securities and Exchange Commission or the sale of these shares to an Aventis non-affiliate, as defined in the voting agreement. A registration rights agreement grants the holder of a majority of the common stock issuable upon conversion of the Series A Non-Voting Convertible Preferred Stock three demand registrations and three piggyback registrations.

The rights of the holders of our common stock will be subject to, and may be harmed by, the rights of the holders of any preferred stock that may be issued in the future. The issuance of preferred stock could reduce the voting power of the holders of our common stock and the likelihood that common stockholders will receive payments upon liquidation.

In addition, our certificate of incorporation divides our board of directors into three classes having staggered terms. This may delay any attempt to replace our board of directors. These and other impediments to a third-party acquisition or change of control could limit the price investors are willing to pay in the future for shares of our common stock.

We are also subject to provisions of Delaware law that could have the effect of delaying, deferring or preventing a change in control of our company. One of these provisions prevents us from engaging in a business combination with any interested stockholder for a period of three years from the date the person becomes an interested stockholder, unless specified conditions are satisfied.

If registration rights that we have previously granted are exercised, then our stock price may be negatively affected.

We have granted registration rights in connection with the issuance of our securities to a number of our stockholders and warrant holders. In the aggregate, as of December 31, 2003, these registration rights covered approximately 8,665,940 shares of our common stock which were then outstanding. If these registration rights, or similar registration rights that may apply to securities we may issue in the future, are exercised by the holders, it could result in additional sales of our common stock in the market, which may have an adverse effect on our stock price. We currently have in effect a registration statement relating to up to 2,400,000 shares held by various stockholders pursuant to which these stockholders may freely resell these 2,000,000 shares, as well as an additional 400,000 shares upon the exercise of warrants, into the public market at any time or from time to time.

Our issuance of shares pursuant to future collaborations or other agreements or under our shelf registration statement will dilute the equity ownership of our existing stockholders.

We may enter into certain other agreements involving our issuance of additional shares of common stock. In connection with any such collaboration or any other similar agreement that we may enter into in the future, we may issue additional shares of common stock or other equity securities, and the value of the securities issued may be substantial.

In addition, we may sell up to an additional $30.0 million of our common stock under our outstanding shelf registration statement. Future sales under our shelf registration statement will depend primarily on the market price of our common stock, the interest in our company by institutional investors and our cash needs. In addition, we may register additional shares with the SEC for sale in the future.

We do not intend to pay cash dividends on our common stock in the foreseeable future.

We do not anticipate paying cash dividends on our common stock in the foreseeable future. Any payment of cash dividends will depend upon our financial condition, results of operations, capital requirements and other factors and will be at the discretion of our board of directors. Furthermore, we may become subject to contractual restrictions or prohibitions on the payment of dividends.

Table of Contents

Forward-looking statements

Certain statements in this prospectus supplement and the accompanying 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, and Section 21E of the Securities and Exchange Act of 1934, as amended, 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 this prospectus supplement and the accompanying 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.

We have not authorized any person to give any information or to make any representation other than those contained in this prospectus supplement and the accompanying prospectus in connection with this offering. You should not rely on such information or representation. Neither the delivery of this prospectus supplement, or the accompanying prospectus, or any sale made pursuant thereto shall create any implication that the information contained in this prospectus supplement or the accompanying prospectus is correct as of any time subsequent to the date hereof. Neither this prospectus supplement or the accompanying prospectus constitutes an offer to sell nor solicitation of an offer to buy any security other than the common stock covered by this prospectus supplement or the accompanying prospectus.

Table of Contents

Use of proceeds

We estimate that the net proceeds to us from this offering will be approximately $48.2 million, or $55.5 million if the underwriters over-allotment option is exercised in full, assuming a public offering price of $9.43 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

Unless otherwise indicated in the prospectus supplement, we intend to use the net proceeds from the sale of common stock offered by this prospectus supplement to fund regulatory activities relating to our lead product candidate, ADVEXIN therapy, to fund ongoing and planned clinical trials, to continue pre-clinical research and development, and for other 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 in amount. The amounts and timing of the expenditures will depend on numerous factors, such as the timing and progress of our clinical trials and research and development efforts, technological advances and the competitive environment for our drug candidates. As of the date of this prospectus supplement, we cannot specify with certainty all of the particular uses for the net proceeds to us from this offering. Accordingly, we will retain broad discretion over the use of these proceeds.

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.

Table of Contents

Capitalization

The following table shows our cash and cash equivalents and capitalization as of December 31, 2003:

- on an actual basis; and
- as adjusted to give effect to the sale by us of 5,500,000 shares of our common stock in this offering at an assumed public offering price of $9.43 per share, after deducting underwriting discounts and commissions and estimated offering expenses payable by us.

This table should be read with Management s discussion and analysis of financial condition and results of operations and our financial statements and the related notes incorporated by reference in this prospectus supplement and the accompanying prospectus.

	As of December 31, 2003	
	Actual	As adjusted
	(in thousands, except per share data)	
Cash and cash equivalents	$ 36,397	$ 84,750
Long term debt and capital lease obligation, net of current portion	6,714	6,714
Stockholders equity:		
Series A non-voting, convertible preferred stock, $0.001 par value per share; 100 shares authorized, issued and outstanding, actual and as adjusted	1	1
Common stock, $0.001 par value per share; 50,000 shares authorized; 26,539 shares issued and outstanding, actual; 32,040 shares issued and outstanding, as adjusted	27	32
Additional paid-in capital	124,270	172,618
Deferred compensation	(44)	(44)
Accumulated deficit	(92,969)	(92,969)
Total stockholders equity	$ 31,285	$ 79,638
Total capitalization	37,999	86,352

The number of shares of common stock outstanding is based on the number of shares outstanding as of December 31, 2003 and excludes:

- 4,756,401 shares of common stock underlying options outstanding as of December 31, 2003 at a weighted average exercise price of $2.91 per share;
- 400,000 shares of common stock available for issuance upon the exercise of outstanding warrants at an exercise price of $7.89 per share;
- 2,343,721 shares of common stock available for issuance upon the conversion of 100,000 shares of Series A non-voting convertible preferred stock; and
- 1,484,113 shares of common stock available for issuance or future grant pursuant to our 2000 Stock Option Plan (includes an increase of 1,326,976 shares on January 1, 2004 pursuant to an automatic reload under the 2000 Stock Option Plan).

Table of Contents

Dilution

If you invest in our common stock, your interest will be diluted to the extent of the difference between the public offering price per share you pay in this offering and the net tangible book value per share of our common stock immediately after this offering.

Our net tangible book value at December 31, 2003 was approximately $31.3 million, or $1.18 per share of common stock. Net tangible book value per share is equal to our total tangible assets minus total liabilities, all divided by the number of shares of common stock outstanding as of December 31, 2003. After giving effect to the sale by us of the 5,500,000 shares of common stock we are offering and deducting underwriting discounts and commissions and our estimated offering expenses, our as adjusted net tangible book value would have been approximately $79.6 million, or $2.49 per share of common stock. This represents an immediate increase in net tangible book value of $1.31 per share to existing stockholders and an immediate dilution of $6.94 per share to new investors. The following table illustrates this calculation on a per share basis:

Assumed public offering price per share		$9.43
Net tangible book value per share as of December 31, 2003	$1.18	
Increase per share attributable to the offering	1.31	
As adjusted net tangible book value per share after this offering		$2.49
Dilution per share to new investors		$6.94

If the underwriters exercise their over-allotment option in full, the as adjusted net tangible book value as of December 31, 2003 would have been $2.65 per share, representing an increase to existing stockholders of $1.47 per share, and there will be an immediate dilution of $6.78 per share to new investors.

The foregoing table does not take into effect further dilution to new investors that could occur upon the exercise of outstanding options having a per share exercise price less than the offering price per share in this offering. As of December 31, 2003, there were:

4,756,401 shares of common stock underlying options outstanding at a weighted average exercise price of $2.91 per share;

400,000 shares of common stock available for issuance upon the exercise of outstanding warrants at an exercise price of $7.89 per share;

2,343,721 shares of common stock reserved for issuance upon the conversion of 100,000 shares of Series A non-voting convertible preferred stock; and

1,484,113 shares of common stock available for issuance or future grant pursuant to our 2000 Stock Option Plan (includes an increase of 1,326,976 shares on January 1, 2004 pursuant to an automatic reload under the 2000 Stock Option Plan).

Table of Contents

Price range of common stock

Our common stock is quoted on the Nasdaq National Market under the symbol INGN. The following table sets forth, for the periods indicated, the high and low reported sale prices of our common stock as reported on the Nasdaq National Market:

	High	Low
Year ended December 31, 2002		
First quarter	$ 5.59	$3.56
Second quarter	4.97	1.80
Third quarter	2.80	1.35
Fourth quarter	2.58	1.48
Year ended December 31, 2003		
First quarter	$ 3.36	$1.97
Second quarter	10.16	1.98
Third quarter	11.24	5.26
Fourth quarter	10.20	6.95
Year ending December 31, 2004		
First quarter (through March 2, 2004)	$10.37	$8.07

As of March 3, 2004, there were 156 holders of record of our common stock. On March 3, 2004, the last sale price reported on the Nasdaq National Market for our common stock was $9.43 per share.

Dividend policy

We have never paid our stockholders dividends, and we do not anticipate paying any cash dividends in the foreseeable future as we intend to retain any earnings for use in our business. The payment of any future cash dividends on our common stock will depend upon our earnings and financial needs and will be subject to applicable legal and contractual restrictions.

Table of Contents

Underwriting

We are offering the shares of our common stock described in this prospectus supplement through the underwriters named below. UBS Securities LLC, SG Cowen Securities Corporation and Leerink Swann & Co. are the representatives of the underwriters. UBS Securities LLC is the sole book-running manager of this offering.

We have entered into an underwriting agreement with the representatives. Subject to the terms and conditions of the underwriting agreement, each of the underwriters has severally agreed to purchase the number of shares of common stock listed next to its name in the following table:

Underwriters	Number of shares
UBS Securities LLC	
SG Cowen Securities Corporation	
Leerink Swann & Co.	
Total	5,500,000

The underwriting agreement provides that the underwriters must buy all of the shares if they buy any of them. However, the underwriters are not required to take or pay for the shares covered by the underwriters over-allotment option described below.

Our common stock is offered subject to a number of conditions, including:

- receipt and acceptance of our common stock by the underwriters; and
- the underwriters right to reject orders in whole or in part.

In connection with this offering, certain of the underwriters and securities dealers may distribute prospectus supplements and the accompanying prospectuses electronically.

Sales of shares made outside of the United States may be made by affiliates of the underwriters.

OVER-ALLOTMENT OPTION

We have granted the underwriters an option to buy up to an aggregate of 825,000 additional shares of our common stock. The underwriters may exercise this option solely for the purpose of covering over-allotments, if any, made in connection with this offering. The underwriters have 30 days from the date of this prospectus supplement to exercise this option. If the underwriters exercise the option, they will each purchase additional shares approximately in proportion to the amounts specified in the table above.

COMMISSIONS AND DISCOUNTS

Shares sold by the underwriters to the public will initially be offered at the initial offering price set forth on the cover of this prospectus supplement. Any shares sold by the underwriters to securities dealers may be sold at a discount of up to $ per share from the initial offering price. Any of these securities dealers may resell any shares purchased from the underwriters to other brokers or dealers at a discount of up to $ per share from the initial public offering price. If all the shares are not sold at the initial offering price, the representatives may change the offering price and the other selling terms. Upon execution of the underwriting agreement, the underwriters will be obligated to purchase the shares at the prices and upon the terms stated therein, and, as a result, will thereafter bear any risk associated with changing the offering price to the public or other selling terms.

Table of Contents

Underwriting

The following table shows the per share and total underwriting discounts and commissions we will pay to the underwriters assuming both no exercise and full exercise of the underwriters option to purchase up to an additional 825,000 shares.

Paid by the Company	No exercise	Full exercise
Per share	$	$
Total	$	$

We estimate that the total expenses of the offering payable by us, not including underwriting discounts and commissions, will be approximately $400,000.

NO SALES OF SIMILAR SECURITIES

We and our executive officers and directors have entered into lock-up agreements with the underwriters. Under these agreements, we and each of these persons generally may not, without the prior written approval of UBS Securities LLC, subject to certain permitted exceptions, offer, sell, contract to sell or otherwise dispose of or hedge our common stock or securities convertible into or exercisable or exchangeable for our common stock. These restrictions will be in effect for a period of 90 days after the date of this prospectus supplement. At any time and without public notice, UBS Securities LLC may, in its sole discretion, release all or some of the securities from these lock-up agreements.

INDEMNIFICATION AND CONTRIBUTION

We have agreed to indemnify the underwriters against certain liabilities, including liabilities under the Securities Act. If we are unable to provide this indemnification, we will contribute to payments the underwriters may be required to make in respect of these liabilities.

NASDAQ NATIONAL MARKET QUOTATION

Our common stock is quoted on the Nasdaq National Market under the symbol INGN.

PRICE STABILIZATION, SHORT POSITIONS, PASSIVE MARKET MAKING

In connection with this offering, the underwriters may engage in activities that stabilize, maintain or otherwise affect the price of our common stock including:

- stabilizing transactions;
- short sales;
- purchases to cover positions created by short sales;
- imposition of penalty bids; and
- syndicate covering transactions.

Stabilizing transactions consist of bids or purchases made for the purpose of preventing or retarding a decline in the market price of our common stock while this offering is in progress. These transactions may also include making short sales of our common stock, which involves the sale by the underwriters of a greater number of shares than they are required to purchase in this offering, and purchasing shares of common stock on the open market to cover positions created by short sales. Short sales may be covered short sales, which are short positions in an amount not greater than the underwriters over allotment option referred to above, or may be naked short sales, which are short positions in excess of that amount.

Table of Contents

Underwriting

The underwriters may close out any covered short position by either exercising their over-allotment option, in whole or in part, or by purchasing shares in the open market. In making this determination, the underwriters will consider, among other things, the price of shares available for purchase in the open market as compared to the price at which they may purchase shares through the over-allotment option. The underwriters must close out any naked short position by purchasing shares in the open market. A naked short position is more likely to be created if the underwriters are concerned there may be downward pressure on the price of shares in the open market after pricing that could adversely affect investors who purchase in this offering.

The underwriters also may impose a penalty bid. This occurs when a particular underwriter repays to the underwriters a portion of the underwriting discount received by it because the representatives have repurchased shares sold by or for the account of that underwriter in stabilizing or short covering transactions.

As a result of these activities, the price of our common stock may be higher than the price that otherwise might exist in the open market. If these activities are commenced, they may be discontinued by the underwriters at any time. The underwriters may carry out these transactions on the Nasdaq National Market, in the over-the-counter market or otherwise.

In addition, in connection with this offering, certain of the underwriters (and selling group members) may engage in passive market making transactions in the common stock on the Nasdaq National Market prior to the pricing and completion of the offering. Passive market making consists of displaying bids on the Nasdaq National Market no higher than the bid prices of independent market makers and making purchases at prices no higher than these independent bids and effected in response to order flow. Net purchases by a passive market maker on each day are limited to a specified percentage of the passive market maker s average daily trading volume in the common stock during a specified period and must be discontinued when such limit is reached. Passive market making may cause the price of the common stock to be higher than the price that otherwise would exist in the open market in the absence of such transactions. If passive market making is commenced, it may be discontinued at any time.

AFFILIATIONS

Certain of the underwriters and their affiliates have in the past provided, and may from time to time provide, other services to us, including investment banking and financial advisory services, for which they were and will be entitled to receive separate compensation. The underwriters and their affiliates may from time to time in the future engage in transactions with us and perform services for us in the ordinary course of their business.

Table of Contents

Experts

Our consolidated financial statements for the years ended December 31, 2003 and 2002, incorporated by reference in this prospectus supplement and the accompanying prospectus 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 supplement and the accompanying prospectus 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 supplement and the accompanying 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 supplement and the accompanying prospectus. Under these circumstances, Rule 437(a) of the Securities Act of 1933, as amended, permits this prospectus supplement 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 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, 2001 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 supplement and the accompanying prospectus in response to Item 304(a)(1) of Regulation S-K.

Table of Contents

Information incorporated 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 the accompanying prospectus, 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, 2003, filed with the SEC on March 5, 2004;
- our Proxy Statement, filed with the SEC on April 30, 2003, as amended on May 8, 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 and incorporated by reference from Description of Capital Stock set forth in our Registration Statement on Form S-1, originally filed with the SEC on February 17, 2000 (File No. 333-30582) and all amendments thereto.

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

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. Dewey Ballantine LLP, New York, New York, is counsel for the underwriters in connection with this offering.

Table of Contents

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 5 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

Table of Contents

TABLE OF CONTENTS

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.

Table of Contents

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, u our mean Introgen Therapeutics, Inc.

Table of Contents

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.

Table of Contents

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.

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 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 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 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 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.

Table of Contents

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

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

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

- decreased demand for our product candidates;
- injury to our reputation and significant media attention;
- withdrawal of clinical trial volunteers;
- 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 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;

12

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.

Table of Contents

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.

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.

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.

Table of Contents

The company

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, 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

Table of Contents

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.

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.

Table of Contents

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.

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.

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.

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.

Table of Contents

The company

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	Phase 2
	Surgery)	Phase 1-2
	Esophageal	Phase 1 completed
	Prostate	Phase 1 completed
	Intravenous	Phase 1 completed**
	Administration	Phase 1 completed**
	Ovarian	Phase 1-2**
	Bladder	Phase 1
	Oral Cancer	Phase 1**
	(Mouthwash)	Phase 1
	Therapeutic Cancer	Pre-clinical
	Vaccine	
	Brain (Glioblastoma)	
	Bronchoalveolar	
	Rheumatoid Arthritis	
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 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.

Table of Contents

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.

Table of Contents

The company

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 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 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

Table of Contents

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.

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.

Table of Contents

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 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.

Table of Contents

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, 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.

Table of Contents

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.

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.

Table of Contents

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.

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,

Table of Contents

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.

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.

Table of Contents

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 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.

Table of Contents

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.

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.

Table of Contents

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 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.

Table of Contents

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

Table of Contents

will consider, among other things, ethical factors, the safety of human subjects, informed consent and the possible liability of the institution. Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA.

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

Table of Contents

surrogate endpoint that is reasonably likely to predict clinical benefit. Approval of a fast track product may be subject to (1) post-approval trials to validate the surrogate endpoint or confirm the effect on the clinical endpoint and (2) prior review of copies of all promotional material. If a preliminary review of the clinical data suggests efficacy, the FDA may initiate review of sections of an application for a fast track product before the application is complete. This rolling review is available if the applicant provides a schedule for submission of remaining information and pays applicable user fees.

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

International

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

COMPETITION

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

We compete with pharmaceutical and biotechnology companies, including Canji, Inc. 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.

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.

Table of Contents

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 concerning potential 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.

Table of Contents

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.

Table of Contents

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 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.

Table of Contents

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 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.

Table of Contents

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 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.

Table of Contents

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*.

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.

Table of Contents