INTROGEN THERAPEUTICS INC
Form 424B3
December 02, 2003

Table of Contents

Filed Pursuant to Rule 424(b)(3)
Registration No. 333-107028

PROSPECTUS SUPPLEMENT

2,000,000 Shares of Common Stock
400,000 Shares of Common Stock Issuable upon Exercise of Warrants

The selling stockholders named on page 17 of the prospectus will use the prospectus and this prospectus supplement to resell all or a portion of the following securities:

Up to 2,000,000 shares of our common stock; and

Up to 400,000 shares of our common stock issuable upon exercise of warrants to purchase common stock held by the selling stockholders.

We will not receive any proceeds from the sale of our common stock sold by the selling stockholders, except that we may receive the exercise price from the exercise of warrants for the underlying common stock to the extent the selling stockholders do not utilize the cashless exercise provisions contained in the warrants.

Our common stock is traded on the Nasdaq National Market under the symbol INGN. On November 25, 2003, the last reported sale price for the common stock on the Nasdaq National Market was $7.60 per share.

You are urged to carefully read the Risk Factors section beginning on page S-5 of this prospectus supplement, 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 the prospectus or this prospectus supplement. Any representation to the contrary is a criminal offense.

The date of this prospectus supplement is December 2, 2003

TABLE OF CONTENTS

Table of Contents

TABLE OF CONTENTS

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

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

Table of Contents

PROSPECTUS SUPPLEMENT SUMMARY

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

Introgen 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 formulating genes to act as templates for the in vivo production of proteins that simulate pharmacologic agents. 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 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 United States Food and Drug Administration (FDA) to market the product being tested. Our earlier Phase 2 clinical trials of ADVEXIN therapy in squamous cell cancer of the head and neck demonstrated that treatment with ADVEXIN therapy provided a survival advantage to patients with recurrent squamous cell cancer of the head and neck who had been treated previously with surgery, radiation, or chemotherapy.

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 have conducted and continue to conduct 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 are conducting a Phase 1 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 such cancer prevention treatments approved by the FDA for head and neck malignancies.

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 cells known as dendritic cells. 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. ADVEXIN therapy applied in this manner will be evaluated for its utility to suppress cancer progression in patients with solid cancers. We are currently enrolling and treating patients with small-cell lung cancer in a Phase I clinical trial using INGN 225 after treatment with standard chemotherapy. This clinical trial is being performed in collaboration with Moffitt Cancer Center.

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.

In addition to our ADVEXIN therapy development programs, we are developing other gene-induced therapeutic protein agents for evaluation in the treatment of 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 gene delivery system, is undergoing safety 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 various solid tumors, INGN 241 is well tolerated, produces the desired pharmacologic protein that is in turn biologically active, displays minimal toxicity 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. 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 classification of mda-7 as interleukin-24, or IL-24. Pre-clinical studies also suggest INGN 241 can be effectively combined with radiation therapy and may be useful in enhancing the effects of such therapy. The results of another study recently published in the *Journal of Thoracic and Cardiovascular Surgery* indicate INGN 241 rapidly causes programmed cell death in lung cancer cells containing either normal or mutated p53, indicating that INGN 241 works in a different and possibly complementarily manner to ADVEXIN therapy. This study further showed that INGN 241 kills cancer cells in a manner different from common chemotherapeutics, which could be an advantage in developing therapies to treat cancer patients whose tumors are resistant to chemotherapies.

Preclinical studies have shown that gene delivery of the FUS-1 gene, 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 non-viral delivery system licensed from the NCI has been formulated incorporating FUS-1 and is called INGN 401. 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 thereby causes rapid disruption of tumor cells in which the adenovirus replicates. Preclinical testing indicates that INGN 007 can eradicate human tumors in animal models. We anticipate pursuing clinical confirmation of this therapeutic candidate. We are also evaluating whether this replicating viral construct could form the basis of a self-amplifying delivery system, which could complement our existing replication-disabled, adenoviral gene delivery system 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 The University of Texas 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 current Good Manufacturing Practices requirements, commonly known as CGMP requirements. We have produced ADVEXIN therapy in this facility for use in our Phase 1, 2 and 3 clinical trials. The design 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

Table of Contents

market launch of ADVEXIN therapy. 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. 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 trial.

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

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 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.

We have completed two 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, 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 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 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.

Despite the FDA s designation of ADVEXIN therapy as a Fast Track Drug 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. 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.

Table of Contents

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 September 30, 2003, we had an accumulated deficit of approximately $87.6 million. We expect to incur substantial additional operating expenses and losses over the next several years as our research, development, pre-clinical testing and clinical trial activities increase. We have no products that have generated any commercial revenue. Presently, we earn minimal revenue from contract services activities, grants, interest income and rent from the lease of a portion of our facilities to 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 for multiple disease indications is expensive. We expect that we will fund our operations over the approximately the next 15 to 18 months with our current working capital, which we accumulated 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; and

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

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 that conduct clinical trials work for us. Our success

Table of Contents

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 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.

Serious unwanted and unexpected 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. 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. No ongoing or active clinical study of any product candidate of ours has ever been placed on hold by the FDA. 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

Table of Contents

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 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, 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 potential that an interference will actually be declared.

Table of Contents

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 held an initial oral proceeding on October 20, 2003 and determined that our patent should be maintained as amended. Schering-Plough will have an opportunity to 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. 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.

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.

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 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. 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

Table of Contents

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 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 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 forms of treatment for the diseases ADVEXIN therapy and our other product candidates target. We are aware that Canji, with its parent Schering-Plough Corporation, has in the past been involved in research and/or development of adenoviral p53 products. 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 only in China. We control an issued Chinese patent covering adenoviral p53, and a number of pending Chinese applications directed to p53 therapy and adenoviral production. We 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. 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.

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 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 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, INGN 241 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 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 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

Table of Contents

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;
- 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.

Table of Contents

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 supplement or the accompanying prospectus.

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 supplement, and later information that we file with the SEC will automatically update and supersede this information. We incorporate by reference into this prospectus supplement any filings made by us with the SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of the 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;

a 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;

a current report on Form 8-K, filed with the SEC on June 18, 2003;

a current report on Form 8-K, filed with the SEC on June 19, 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.

Table of Contents

PROSPECTUS

2,000,000 Shares of Common Stock
400,000 Shares of Common Stock Issuable upon Exercise of Warrants

The selling stockholders named on page 17 of this prospectus will use this prospectus to resell all or a portion of the following securities:

Up to 2,000,000 shares of our common stock; and

Up to 400,000 shares of our common stock issuable upon exercise of warrants to purchase common stock held by the selling stockholders.

We will not receive any proceeds from the sale of our common stock sold by the selling stockholders, except that we may receive the exercise price from the exercise of warrants for the underlying common stock to the extent the selling stockholders do not utilize the cashless exercise provisions contained in the warrants.

Our common stock is traded on the Nasdaq National Market under the symbol INGN. On August 7, 2003, the last reported sale price for the common stock on the Nasdaq National Market was $5.75 per share.

You are urged to carefully read the Risk Factors section beginning on page 6 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.

The date of this prospectus is August 7, 2003

Table of Contents

TABLE OF CONTENTS

Table of Contents

SUMMARY

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

Introgen 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 United States Food and Drug Administration (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 injection.

Table of Contents

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 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, doctors 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 gene delivery system, is undergoing safety 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. 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 classification of mda-7 as interleukin-24, or IL-24.

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

Table of Contents

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 with 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 The University of Texas 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, and we are pursuing similar proceedings with respect to an additional European patent. 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 current Good Manufacturing Practices requirements, commonly known as 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

Table of Contents

market launch of ADVEXIN therapy. 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 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 Offering

Securities offered by Introgen Therapeutics, Inc.:	None
Common stock offered by selling stockholders:	2,400,000 (including up to 400,000 shares issuable upon exercise of warrants to purchase common stock held by the selling stockholders)
Use of proceeds:	We will not receive any proceeds from the sale of our common stock or warrants sold by the selling stockholders, except that we may receive the exercise price from the exercise of the warrants for the underlying common stock, but only to the extent the selling stockholders do not utilize the cashless exercise provisions contained in the warrants.
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

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

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 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 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;

Table of Contents

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 M. D. Anderson Cancer Center. Prior to December 31, 2000, we earned revenue from Aventis Pharmaceuticals Products 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 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;

Table of Contents

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

Table of Contents

and negative public perception of our product candidates, as well as potential regulatory delays relating to the testing or approval of our product candidates. The FDA recently placed a clinical hold on gene therapy clinical trials using retroviral vectors to transduce hematopoietic stem cells after two participants in such a trial for the X-linked form of severe combined immune deficiency disease (X-SCID), being conducted in Europe, developed what appeared to be a leukemia-like illness. This clinical hold requires a case-by-case review of the use of retroviral vectors in these trials. We do not use retroviral vectors in our ongoing clinical trials and are not developing products using the production process used in those European 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 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 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. Implementation of any additional review and reporting procedures or other regulatory measures could increase the costs of or prolong our product development efforts or clinical trials. 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 gene therapy products and gene-induced products 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.

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

Table of Contents

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 the issuance of our European patent directed to combination therapy with p53 and conventional chemotherapy and/or radiation. An opposition is an administrative proceeding instituted by a third party and conducted by the EPO to determine whether a patent should be maintained or revoked in part or in whole, based on evidence brought forth by the party opposing the patent. 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

Table of Contents

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

Table of Contents

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 or our other product candidates. The commercial success of our product candidates will depend on whether:

they are more effective than alternative treatments;

their side effects are acceptable to patients and doctors;

we produce and sell them at a profit; and

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

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

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

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

Table of Contents

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;

costs of litigation; and

substantial monetary awards to plaintiffs.

Table of Contents

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

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

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

Our stock price may fluctuate substantially.

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

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

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

- results of our pre-clinical and clinical trials;
- announcement of technological innovations or new commercial products by us or our competitors;
- 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.

Table of Contents

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.

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 our quarterly reports on Form 10-Q to be filed during 2003.

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

USE OF PROCEEDS

All proceeds from the sale of common stock in this offering will go to the stockholders selling common stock under this prospectus. We will not receive any proceeds from the sale of common stock sold by the selling stockholders, except that we may receive the exercise price from the exercise of warrants, but only to the extent the selling stockholders do not utilize the cashless exercise provisions contained in the warrants. The proceeds from the exercise of the warrants, if any, will be used for working capital purposes, including, but not limited to, the development of ADVEXIN and INGN 241, two of our biopharmaceutical products using non-integrating gene agents designed to induce therapeutic protein expression for the treatment of cancer.

SELLING STOCKHOLDERS

The following table provides certain information as of June 18, 2003 regarding the beneficial ownership of our common stock and warrants by the stockholders selling common stock under this prospectus prior to and after the offering. Beneficial ownership is determined under the rules of the SEC, and generally includes voting and investment power with respect to securities.

Our registration of the common stock does not necessarily mean that the selling stockholders will sell all or any of these securities. We have assumed for purposes of the table below that the selling stockholders will sell all of the shares (and exercise all of the warrants and sell the shares received thereby) offered for sale.

Table of Contents

Name	Shares Owned Prior to Offering (2)	Shares Being Offered Hereby	Shares Issuable Upon Exercise of Warrants Being Offered Hereby	Shares Owned After Offering (3)	Percentage Owned After Offering (3)
Steelhead Investments Ltd. (1)	1,620,000	1,350,000	270,000		*
Cranshire Capital, L.P.	480,000	400,000	80,000		*
Smithfield Fiduciary, LLC	300,000	250,000	50,000		*

* Represents less than 1% of our common stock.

(1) HBK Investments, L.P. has sole voting and dispositive power over the shares pursuant to an Investment Management Agreement with Steelhead Investments Ltd.

(2) For purposed of this table, ownership means beneficial ownership as determined in accordance with the rules of the SEC.

(3) Assumes that each selling stockholder sells all shares registered under this Registration Statement.

PLAN OF DISTRIBUTION

The selling stockholders and any of their pledgees, assignees and successors-in-interest may, from time to time, sell any or all of their shares of common stock on any stock exchange, market or trading facility on which the shares are traded or in private transactions. These sales may be at fixed or negotiated prices. The selling stockholders may use any one or more of the following methods when selling shares:

ordinary brokerage transactions and transactions in which the broker-dealer solicits purchasers;

block trades in which the broker-dealer will attempt to sell the shares as agent but may position and resell a portion of the block as principal to facilitate the transaction;

purchases by a broker-dealer as principal and resale by the broker-dealer for its account;

an exchange distribution in accordance with the rules of the applicable exchange;

privately negotiated transactions;

short sales;

broker-dealers may agree with the selling stockholders to sell a specified number of such shares at a stipulated price per share;

a combination of any such methods of sale; and

any other method permitted pursuant to applicable law.

The selling stockholders may also sell shares under Rule 144 under the Securities Act, if available, rather than under this prospectus.

The selling stockholders may also engage in short sales against the box, puts and calls and other transactions in our securities or derivatives of our securities and may sell or deliver shares in connection with these trades.

Table of Contents

Broker-dealers engaged by the selling stockholders may arrange for other brokers-dealers to participate in sales. Broker-dealers may receive commissions or discounts from the selling stockholders (or, if any broker-dealer acts as agent for the purchaser of shares, from the purchaser) in amounts to be negotiated. The selling stockholders do not expect these commissions and discounts to exceed what is customary in the types of transactions involved.

The selling stockholders may from time to time pledge or grant a security interest in some or all of the shares of common stock owned by them, and, if they default in the performance of their secured obligations, the pledgees or secured parties may offer and sell the shares of common stock from time to time under this prospectus, or under an amendment to this prospectus under Rule 424(b)(3) or other applicable provision of the Securities Act of 1933 amending the list of selling stockholders to include the pledgee, transferee or other successors in interest as selling stockholders under this prospectus.

The selling stockholders also may transfer the shares of common stock in other circumstances, in which case the transferees, pledgees or other successors in interest will be the selling beneficial owners for purposes of this prospectus.

The selling stockholders and any broker-dealers or agents that are involved in selling the shares may be deemed to be underwriters within the meaning of the Securities Act in connection with such sales. In such event, any commissions received by such broker-dealers or agents and any profit on the resale of the shares purchased by them may be deemed to be underwriting commissions or discounts under the Securities Act.

We are required to pay all fees and expenses incident to the registration of the shares, including fees and disbursements of counsel to the selling stockholders. We have agreed to indemnify the selling stockholders against certain losses, claims, damages and liabilities, including liabilities under the Securities Act.

LEGAL MATTERS

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

EXPERTS

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

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

Table of Contents

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 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.

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;

a 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;

a current report on Form 8-K, filed with the SEC on June 18, 2003;

a current report on Form 8-K, filed with the SEC on June 19, 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.

Table of Contents

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.

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*.

Table of Contents

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 our 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.