

INTROGEN THERAPEUTICS INC

Form S-3/A

August 22, 2003

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As filed with the Securities and Exchange Commission on August 22, 2003
Registration No. 333-107799

SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

**Amendment No. 1 to
Form S-3
REGISTRATION STATEMENT
under the Securities Act of 1933**

INTROGEN THERAPEUTICS, INC.

(Exact name of Registrant as specified in its charter)

Delaware
(State or other jurisdiction of
incorporation or organization)

74-2704230
(I.R.S. Employer
Identification Number)

301 Congress Avenue, Suite 1850

**Austin, Texas 78701
(512) 708-9310**

(Address, including zip code, and telephone number, including area code, of Registrant's principal executive offices)

**David G. Nance, Chief Executive Officer
Introgen Therapeutics, Inc.
301 Congress Avenue, Suite 1850
Austin, Texas 78701
(512) 708-9310**

(Name, address, including zip code, and telephone number, including area code, of agent for service)

Copies to:

**Christopher J. Ozburn, Esq.
Wilson Sonsini Goodrich & Rosati
8911 Capital of Texas Highway
Westech 360, Suite 3350
Austin, Texas 78759-7247
(512) 338-5400**

Approximate date of commencement of proposed sale to the public: From time to time after the effective date of this Registration Statement.

If any of the securities being registered on this Form are being offered pursuant to dividend or interest reinvestment plans, please check the following box.

If any of the securities being registered on this Form are to be offered on a delayed or continuous basis pursuant to Rule 415 under the Securities Act of 1933, other than securities offered only in connection with dividend or interest reinvestment plans, check the following box.

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If this Form is filed to register additional securities for an offering pursuant to Rule 462(b) under the Securities Act, please check the following box and list the Securities Act registration number of the earlier effective registration statement for the same offering.

If this Form is a post-effective amendment filed pursuant to Rule 462(c) under the Securities Act, check the following box and list the Securities Act registration number of the earlier effective registration statement for the same offering.

CALCULATION OF REGISTRATION FEE

Title of Each Class of Securities to be Registered	Proposed Maximum Aggregate Offering Price	Amount of Registration Fee(1)
Common Stock	\$100,000,000	\$8,090

- (1) Estimated solely for purposes of calculating the registration fee in accordance with Rule 457(o) under the Securities Act of 1933, as amended. This Registration Statement registers an indeterminate number of shares of common stock that the Registrant may sell from time to time. The aggregate offering price for all the shares of common stock that the Registrant may sell from time to time pursuant to this Registration Statement will not exceed \$100,000,000. The aggregate amount of common stock registered hereunder is limited to that which is permissible under Rule 415(a)(4) under the Securities Act of 1933, as amended, to the extent applicable.

The Registrant hereby amends this Registration Statement on such date or dates as may be necessary to delay its effective date until the Registrant shall file a further amendment which specifically states that this Registration Statement shall thereafter become effective in accordance with Section 8(a) of the Securities Act of 1933 or until the Registration Statement shall become effective on such date as the Commission, acting pursuant to said Section 8(a), may determine.

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The information in this prospectus is not complete and may be changed. We may not sell the securities until the Registration Statement filed with the Securities and Exchange Commission is effective. This prospectus is not an offer to sell these securities and is not soliciting an offer to buy these securities in any state where the offer or sale is not permitted.

SUBJECT TO COMPLETION, DATED AUGUST 22, 2003

PROSPECTUS

\$100,000,000

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

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

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

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

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

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

The date of this prospectus is _____, 2003

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

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SUMMARY

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

The Offering

Securities offered by Introgen Therapeutics, Inc.:

Up to \$100,000,000 of common stock in one or more offerings. A prospectus supplement, which we will provide each time we offer common stock, will describe the specific amounts, prices and terms of the common stock.

We may sell the common stock to or through underwriters, dealers or agents or directly to purchasers. We, as well as any agents acting on our behalf, reserve the sole right to accept and to reject in whole or in part any proposed purchase of common stock. Each prospectus supplement will set forth the names of any underwriters, dealers or agents involved in the sale of common stock described in that prospectus supplement and any applicable fee, commission or discount arrangements with them.

Use of proceeds:

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

Risk factors:

See *Risk Factors* for a discussion of the factors you should carefully consider before deciding to invest in shares of our common stock.

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RISK FACTORS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

higher than expected costs to obtain regulatory approvals;

higher than expected costs to pursue our intellectual property strategy;

higher than expected costs to further develop our manufacturing capability;

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

slower than expected progress in reducing our operating costs.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

they are more effective than alternative treatments;

their side effects are acceptable to patients and doctors;

we produce and sell them at a profit; and

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

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

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

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

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

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

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

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

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

The 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

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

Our stock price may fluctuate substantially.

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

the announcement of new products or services by us or our competitors;

quarterly variations in our or our competitors' results of operations;

failure to achieve operating results projected by securities analysts;

changes in earnings estimates or recommendations by securities analysts;

developments in our industry; and

general market conditions and other factors, including factors unrelated to our operating performance or the operating performance of our competitors.

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

results of our pre-clinical and clinical trials;

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

developments concerning proprietary rights, including patent and litigation matters;

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

regulatory developments; and

quarterly fluctuations in our revenues and other financial results.

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

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

potential exposure to unknown liabilities of acquired companies;

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

diversion of management time and attention and other resources;

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

the incurrence of amortization expenses; and

possible dilution to our stockholders.

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

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

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THE COMPANY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Background

Gene Function and Genomics

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

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

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

Gene Therapy and Gene-Induced Protein Therapy Products

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

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

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

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

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Cancer, a Genetic Disease

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

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

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

Tumor Suppressor Genes

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

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

Current Treatment of Cancer

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

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

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

The Introgen Approach

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

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

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

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The Introgen Strategy

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

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

Develop Our Portfolio of Gene-Induced Protein Therapy and Other Drug Products. Utilizing our significant research, clinical, and regulatory expertise, we are evaluating development of additional gene-induced protein therapy, such as FUS-1, and other drug products for various cancers. We have established an efficient process for evaluating new drug candidates and rapidly advancing them from pre-clinical to clinical development. We have identified and licensed multiple technologies, which we intend to combine with our adenoviral and non-viral vector systems and which we believe are attractive development targets for the treatment of various cancers. We are also evaluating the development of mebendazole (INGN 601), our first small molecule product candidate.

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

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

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

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

Product Development Programs

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

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

* Aventis Pharma provides funding for this trial.

** Conducted in conjunction with the National Cancer Institute.

Indications for ADVEXIN® Therapy (p53)

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

We have completed or are conducting a number of Phase 1, Phase 2 and Phase 3 clinical trials to establish the safety and evaluate the efficacy of ADVEXIN therapy both alone and in combination with radiation therapy, chemotherapy and/or surgery. We evaluated efficacy by measuring tumors during each trial to analyze whether tumors had regressed, remained stable or progressed during treatment. We supplemented

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

Head and Neck Cancer

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

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

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