INTROGEN THERAPEUTICS INC
Form 424B2
December 08, 2004

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Filed Pursuant to Rule 424(b)(2)
Registration No. 333-107799

PROSPECTUS SUPPLEMENT
(To Prospectus dated August 25, 2003)

2,475,640 Shares

Common Stock

We are offering 2,475,640 shares of our common stock to four investors. In connection with this offering, we will pay fees and issue warrants to purchase approximately 205,700 shares of our common stock at an exercise price of $6.65 per share to a placement agent. See Plan of Distribution beginning on page S-2 of this prospectus supplement for more information regarding this arrangement.

Our common stock is quoted on the Nasdaq National Market under the symbol INGN. On December 6, 2004, the closing price of our common stock as quoted on the Nasdaq National Market was $7.47 per share.

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

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

	Per Share	Maximum Offering
Public offering price	$ 6.65	$16,463,006
Placement agent fee	$0.3325	$ 823,150
Proceeds, before expenses, to us	$6.3175	$15,639,856

We estimate the total expenses of this offering, excluding the placement agent fee, will be approximately $375,000. Because there is no minimum offering amount required as a condition to closing in this offering, the actual public offering amount, placement agent fee and net proceeds to us, if any, in this offering are not presently determinable and may be substantially less than the maximum offering amounts set forth above.

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Prospectus Supplement **Page**

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

This prospectus supplement is not a prospectus for the purposes of, and has not been prepared in accordance with, the Public Offers of Securities Regulations 1995 of the United Kingdom. Furthermore, in the United Kingdom it is directed only at persons with professional experience in matters relating to investments of the type described herein, as such persons are described in Article 19 of the Financial Services and Markets Act 2000 (Financial Promotion) Order 2001 as amended (FPO), and at high net worth companies, unincorporated associations, etc. as described in article 49(2) of the FPO. The shares of common stock being offered for sale as set forth in this prospectus supplement are only available in the United Kingdom to such persons and no other class of person should rely on this prospectus supplement or act upon it.

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GENERAL INFORMATION

This prospectus supplement is part of a registration statement that we filed with the SEC using a shelf registration process. Under this registration statement, we registered the offering of up to $100 million of our common stock from time to time in one or more offerings. In December 2003, we completed an offering of approximately $20 million of our common stock, leaving approximately $80 million available for future offerings. This prospectus supplement provides specific information about the offering of 2,475,640 shares of our common stock under the shelf registration statement. You should read carefully this prospectus supplement, the related prospectus, and the information that we incorporate by reference into those documents. In the event that there are any differences or inconsistencies between this prospectus supplement, the related prospectus, and the information incorporated by reference herein and therein, you should only rely on the information contained in the document with the latest date. Please refer to the information and documents listed and described under the heading Where You Can Find More Information in the prospectus.

You should rely only on the information provided or incorporated by reference in this prospectus supplement and the related prospectus. We have not authorized anyone else to provide you with different information. You should not assume that the information in this prospectus supplement is accurate as of any date other than the date on the front page hereof.

MARKET FOR OUR COMMON STOCK

On December 6, 2004, the last reported sale price of our common stock on the Nasdaq National Market was $7.47 per share. Our common stock is traded on the Nasdaq National Market under the symbol INGN.

As of December 6, 2004 and before the issuance of the 2,475,640 shares of our common stock pursuant to this prospectus supplement, we had approximately 27,158,596 shares of common stock outstanding.

USE OF PROCEEDS

The net proceeds to us from this offering, before expenses, will be approximately $15,639,856. The net proceeds from the sale of common stock offered by this prospectus supplement will be used for general corporate purposes and working capital requirements. We may also use a portion of the net proceeds to fund possible investments in and acquisitions of complementary businesses, partnerships, minority investments, products or technologies. Currently, there are no commitments or agreements regarding such acquisitions or investments that are material. Pending their ultimate use, we intend to invest the net proceeds in money market funds, commercial paper and governmental and non-governmental debt securities with maturities of up to five years.

PLAN OF DISTRIBUTION

We are offering the shares of our common stock through a placement agent. Subject to the terms and conditions contained in the placement agent agreement dated December 6, 2004, Mulier Capital Limited has agreed to act as the placement agent for the sale of up to 4,000,000 shares of our common stock. The placement agent is not purchasing or selling any shares by this prospectus supplement or the related prospectus, nor is it required to arrange the purchase or sale of any specific number or dollar amount of the shares of common stock being offered.

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

in connection with the decision to purchase shares of our common stock, has relied only upon the prospectus and our reports on Forms 10-K, 10-Q and 8-K filed by us with the Securities and Exchange Commission (SEC); and

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has not engaged in any short selling or short sales against the box in our securities, established or increased any put equivalent position as defined in Rule 16(a)-1(h) under the Securities Exchange Act of 1934, as amended, with respect to our securities, or engaged in any purchase or sale, or made any offer to purchase or offer to sell, derivative securities relating to our securities, whether or not issued by us, such as exchange traded options to purchase or sell our securities (puts and calls), within the past 90 trading days.

Confirmations will be distributed to the investors informing such investors of the closing date as to such shares. We currently anticipate that the closing of the sale of 2,475,640 shares of common stock will take place on or about December 8, 2004.

On the scheduled closing date, the following will occur:

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

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

We will pay the placement agent a commission equal to 5.0% of the gross proceeds of the sale of shares of common stock in the offering and will issue to the placement agent warrants to purchase approximately 205,700 shares of our common stock at an exercise price of $6.65 per share.

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

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

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

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

DISCLOSURE REGARDING FORWARD-LOOKING STATEMENTS

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

LEGAL MATTERS

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

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

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SEC under Sections 13(a), 13(c), 14 or 15(d) of the Exchange Act after the date of this prospectus supplement until the termination of this offering, as well as the following documents:

- our Annual Report on Form 10-K for the fiscal year ended December 31, 2003, filed with the SEC on March 5, 2004;
- our Definitive Proxy Statement, filed with the SEC on May 24, 2004;
- our Quarterly Report on Form 10-Q for the quarter ended September 30, 2004, filed with the SEC on November 15, 2004;
- our Quarterly Report on Form 10-Q for the quarter ended June 30, 2004, filed with the SEC on August 16, 2004;
- our Quarterly Report on Form 10-Q for the quarter ended March 31, 2004, filed with the SEC on May 14, 2004; and
- The description of our common stock contained in our Registration Statement on Form 8-A, filed with the SEC on September 8, 2000 and incorporated by reference from Description of Capital Stock set forth in our Registration Statement on Form S-1, originally filed with the SEC on February 17, 2000 (File No. 333-30582) and all amendments thereto.

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

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

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PROSPECTUS

$100,000,000

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

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

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

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

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

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

The date of this prospectus is August 25, 2003

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

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SUMMARY

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

The Offering

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

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RISK FACTORS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

higher than expected costs to obtain regulatory approvals;

higher than expected costs to pursue our intellectual property strategy;

higher than expected costs to further develop our manufacturing capability;

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

slower than expected progress in reducing our operating costs.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

they are more effective than alternative treatments;

their side effects are acceptable to patients and doctors;

we produce and sell them at a profit; and

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

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

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

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

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

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

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

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

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

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

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

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

decreased demand for our product candidates;

injury to our reputation and significant media attention;

withdrawal of clinical trial volunteers;

substantial delay in FDA approval;

costs of litigation; and

substantial monetary awards to plaintiffs.

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

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

Our business involves the use of a broad range of hazardous chemicals and materials. Environmental laws impose stringent civil and criminal penalties for improper handling, disposal and storage of these materials. In addition, in the event of an improper or unauthorized release

of, or exposure of individuals to, hazardous

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

Our stock price may fluctuate substantially.

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

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

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

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

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

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

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

possible dilution to our stockholders.

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

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

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THE COMPANY

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Background

Gene Function and Genomics

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

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

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

Gene Therapy and Gene-Induced Protein Therapy Products

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

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

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

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

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Cancer, a Genetic Disease

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

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

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

Tumor Suppressor Genes

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

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

Current Treatment of Cancer

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

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

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

The Introgen Approach

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

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

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

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The Introgen Strategy

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

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

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

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

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

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

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

Product Development Programs

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

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

* Aventis Pharma provides funding for this trial.

** Conducted in conjunction with the National Cancer Institute.

Indications for ADVEXIN® Therapy (p53)

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

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

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

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

Head and Neck Cancer

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

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

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

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

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

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

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

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

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

Non-Small Cell Lung Cancer

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

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

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

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

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

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

Breast Cancer

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

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Prostate Cancer

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

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

Other Cancers

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

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

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

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

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

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

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

Indications for INGN-241 (mda-7)

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

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

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

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

Indications for INGN 401 (FUS-1)

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

Research and Development Programs

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

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

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

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

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

Introgen Enabling Technologies

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

Viral Delivery Systems

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

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

Non-Viral Delivery Systems

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

Additional Enabling Technologies

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

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

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

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

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

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

Manufacturing and Process Development

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

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

Business and Collaborative Arrangements

VirRx, Inc.

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

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Aventis Pharma AG

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

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

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

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

Gendux, Inc. and Gendux AB

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

Academic and Other Collaborations

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

The University of Texas M. D. Anderson Cancer Center

Many of our core technologies were developed by scientists at The University of Texas M. D. Anderson Cancer Center in Houston, Texas, one of the largest academic cancer centers in the world. We sponsor research conducted at M. D. Anderson Cancer Center to further the development of technologies that have potential commercial viability. Through these sponsored research agreements, we have access to M. D. Anderson Cancer Center s resources and expertise for the development of our technology. In addition, we have the right to include certain patentable inventions arising from these sponsored research agreements under our exclusive license with M. D. Anderson Cancer Center.

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We entered into this license agreement with M. D. Anderson Cancer Center in 1994. It terminates on July 20, 2009. The agreement is also terminable upon our insolvency, either party s breach or upon our notice on a patent-by-patent basis. The technologies we have licensed from M. D. Anderson Cancer Center, under the exclusive license agreement, relate to p53 and the 3p21.3 family of genes. Under the agreement, we have agreed to pay M. D. Anderson Cancer Center royalties on sales of products utilizing these technologies. We are obligated to reimburse any of M. D. Anderson Cancer Center s costs that may be incurred in connection with obtaining patents related to the licensed technologies. Our strategy for product development is designed to take advantage of the significant multidisciplinary resources available at M. D. Anderson Cancer Center. These efforts have resulted in our becoming a significant corporate sponsor of activities at M. D. Anderson Cancer Center in recent years and have yielded to us exclusive patent and licensing rights to numerous technologies.

National Cancer Institute

We have entered into a cooperative research and development agreement, or CRADA, with the NCI. The CRADA has a flexible duration, but is terminable upon the mutual consent of the parties or upon 30 days notice of either party. Under the CRADA, NCI agreed to sponsor and conduct pre-clinical and human clinical trials to evaluate the effectiveness and potential superiority to other treatments of ADVEXIN therapy against a range of designated cancers, including breast cancer, ovarian cancer, bladder cancer and brain cancer. To date, NCI has conducted or is conducting numerous Phase 1 clinical trials for ADVEXIN therapy. NCI provided most of the funding for these activities. We supplied NCI with ADVEXIN therapy product to be administered in these trials. We have exclusive rights to all pre-clinical and clinical data accumulated under the CRADA.

Corixa Corporation

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

Marketing and Sales

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

Patents and Intellectual Property

Our Portfolio

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

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

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

Adenoviral p53 Compositions and Therapies

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

Combination Therapy with the p53 Gene

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

Adenovirus Production, Purification and Formulation

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

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Other Tumor Suppressor Genes

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

Other Therapeutic, Composition and Process Technologies

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

Benzimidazole Small Molecule Cancer Therapy Program

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

Trade Secrets

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

Government Regulation

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

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

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

The Drug Approval Process

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

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

Pre-Clinical Testing

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

Clinical Trials

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

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

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

National Institutes of Health

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

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

Marketing Applications

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

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

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

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

Orphan Drug Act

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

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

Off-Label Use

Physicians may prescribe drugs for uses that are not described in the product s labeling that differ from those tested by us and approved by the FDA. Such off-label uses are common across medical specialties and may constitute the best treatment for many patients in various circumstances. The FDA does not regulate the behavior of physicians in their choice of treatments. The FDA does, however, restrict manufacturers communications on the subject of off-label use. Companies cannot actively promote FDA-approved drugs for off-label uses. However, new regulations, if followed, provide a safe harbor from FDA enforcement action that would allow us to disseminate to physicians articles published in peer-reviewed journals, like the *New England Journal of Medicine,* that discuss off-label uses of approved products. We cannot disseminate articles concerning drugs that have not been approved for any indication.

Fast Track Products

The Food and Drug Administration Modernization Act of 1997, or FDAMA, was enacted, in part, to ensure the timely availability of safe and effective drugs, biologics and medical devices, by expediting the FDA review process for new products. FDAMA established a statutory program for the approval of fast track products. The fast track provisions essentially codify FDA s Accelerated Approval regulations for drugs and biologics. A fast track product is defined as a new drug or biologic intended for the treatment of a serious or life-threatening condition that demonstrates the potential to address unmet medical needs for such a condition. Under the new fast track program, the sponsor of a new drug or biologic may request the FDA to designate the drug or biologic as a fast track product at any time during the clinical development of the product. FDAMA specifies that the FDA must determine if the product qualifies for fast track designation within 60 days of receipt of the sponsor s request. Approval of an NDA for a fast track product can be based on a clinical endpoint or on a surrogate endpoint that is reasonably likely to predict clinical benefit. Approval of a fast track product may be subject to (1) post-approval trials to validate the surrogate endpoint or confirm the effect on the clinical endpoint and (2) prior review of copies of all promotional material. If a preliminary review of the clinical data suggests efficacy, the FDA may initiate review of sections of an application for a fast track product before the application is complete. This rolling review is available if the applicant provides a schedule for submission of remaining information and pays applicable user fees.

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

International

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

Competition

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

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

We expect that competition among products approved for sale will be based, among other things, on product efficacy, safety, reliability, availability, price, patent position and sales, marketing and distribution capabilities. Our competitive position also depends upon our ability to attract and retain qualified personnel, obtain patent protection or otherwise develop proprietary products or processes, and secure sufficient capital resources for the often substantial period between technological conception and commercial sales.

Scientific Advisory Board

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

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

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

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

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

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

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FORWARD-LOOKING STATEMENTS

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

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

USE OF PROCEEDS

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

PLAN OF DISTRIBUTION

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

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

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

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

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

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

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

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

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

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

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

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

LEGAL MATTERS

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

EXPERTS

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

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

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

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

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

INCORPORATION OF CERTAIN INFORMATION BY REFERENCE

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

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

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

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

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

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

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

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

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

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

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

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

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

WHERE YOU CAN FIND MORE INFORMATION

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

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DISCLOSURE OF SEC POSITION ON INDEMNIFICATION

FOR SECURITIES ACT LIABILITIES

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

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