

INTROGEN THERAPEUTICS INC

Form 10-K

March 17, 2008

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**UNITED STATES SECURITIES AND EXCHANGE COMMISSION  
Washington, D.C. 20549**

**Form 10-K**

(Mark One)

**ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES  
EXCHANGE ACT OF 1934**

**For the fiscal year ended December 31, 2007.**

**or**

**TRANSITION REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES  
EXCHANGE ACT OF 1934**

**For the transition period from            to            .  
Commission file number: 000-21291**

**Introgen Therapeutics, Inc.**

*(Exact name of registrant as specified in its charter)*

**Delaware**

*(State or other jurisdiction of  
incorporation or organization)*

**74-2704230**

*(I.R.S. Employer  
Identification Number)*

**301 Congress Avenue,  
Suite 1850 Austin, Texas**

*(Address of principal executive offices)*

**78701**

*(Zip Code)*

**Registrant's telephone number, including area code:  
(512) 708-9310**

**Securities registered pursuant to Section 12(b) of the Act:  
Common Stock, \$0.001 par value per share**

**Securities registered pursuant to Section 12(g) of the Act:**

Indicate by check mark if the Registrant is a well-known seasoned issuer, as defined in Rule 405 of the Securities Act. Yes  No

Indicate by check mark if the Registrant is not required to file reports pursuant to Section 13 or Section 15(d) of the Act. Yes  No

Indicate by check mark whether the Registrant (1) has filed all reports required to be filed by Section 13 or 15(d) of the Securities Exchange Act of 1934 during the preceding 12 months (or for such shorter period that the Registrant was required to file such reports), and (2) has been subject to such filing requirements for the past 90 days. Yes  No

Indicate by check mark if disclosure of delinquent filers pursuant to Item 405 of Regulation S-K is not contained herein, and will not be contained, to the best of the Registrant's knowledge, in definitive proxy or information statements incorporated by reference in Part III of this Form 10-K or any amendment to this Form 10-K.

Indicate by check mark whether the registrant is a large accelerated filer, an accelerated filer, a non-accelerated filer, or a smaller reporting company. See the definitions of large accelerated filer, accelerated filer and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

Accelerated filer

Non-accelerated filer

Large accelerated  
filer

Smaller reporting  
company

(Do not check if a smaller reporting company)

Indicate by check mark whether the Registrant is a shell company (as defined in Rule 12b-2 of the Exchange Act). Yes  No

The aggregate market value of the voting stock (common stock) held by non-affiliates of the Registrant, as of the last day of the Registrant's second fiscal quarter, was approximately \$89.1 million based upon the last sale price reported on the Nasdaq Global Market for June 30, 2007. For purposes of this disclosure, shares of common stock held by persons holding more than 5% of the outstanding shares of the Registrant's common stock and shares held by executive officers and directors of the Registrant have been excluded because such persons may be deemed to be affiliates. This determination is not necessarily conclusive.

As of March 11, 2008, the Registrant had 44,004,099 shares of common stock, \$0.001 par value per share, issued and outstanding.

#### **DOCUMENTS INCORPORATED BY REFERENCE**

Certain information required by Items 10, 11, 12, 13 and 14 of Part III of Form 10-K is incorporated by reference to the Registrant's proxy statement for the 2008 Annual Meeting of Stockholders, which will be filed with the Securities and Exchange Commission within 120 days after the close of the Registrant's fiscal year ended December 31, 2007.

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**PART I**

**Item 1. Business**

*This Annual Report on Form 10-K contains forward-looking statements within the meaning of Section 27A of the Securities Act of 1933, as amended (Securities Act) and Section 21E of the Securities Exchange Act of 1934, as amended (Exchange Act). These statements address our future operations, financial condition, business strategies and other prospective items as well as the statements below under Item 1A. Risk Factors, and include, among other subjects, matters concerning our expectations regarding:*

Our expectations regarding various regulatory applications, procedures and approvals relating to our product candidates, including but not limited to our expectations regarding the timing of such applications, procedures and approvals;

The growth of our operations, business and revenues and the growth rate of our costs and expenses;

Future increases in our research and development, sales and marketing and general and administrative expenses;

The sufficiency of our existing cash, cash equivalents, marketable securities and cash generated from operations;

Better efficacy of our product candidates through the use of biomarkers ;

Application of our research and development expertise to other diseases that result from cellular dysfunction and uncontrolled cell growth; and

Access to additional working capital.

*The words believe, expect, anticipate and other similar expressions generally identify forward-looking statements. These forward-looking statements are based on our current expectations and entail various risks and uncertainties. Given these risks and uncertainties, readers are cautioned not to place undue reliance on such forward-looking statements. We undertake no obligation to revise or publicly release the results of any revision to these forward-looking statements. These forward-looking statements are subject to certain risks and uncertainties that could cause our actual results to differ materially from those reflected in the forward-looking statements. Factors that could cause or contribute to such differences include, but are not limited to, those discussed in this Annual Report on Form 10-K, and in particular, the risks discussed under the heading Risk Factors in Part I, Item 1A of this Annual Report on Form 10-K and those discussed in other documents we file with the Securities and Exchange Commission (SEC). Investors should carefully review the information contained in Item 1A. Risk Factors and elsewhere in, or incorporated by reference into, this Annual Report on Form 10-K.*

**Access to Company Information**

Our Internet website address is [www.introgen.com](http://www.introgen.com). Our Annual Report on Form 10-K, Quarterly Reports on Form 10-Q, Current Reports on Form 8-K and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Exchange Act are available free of charge through our website as soon as reasonably practicable after we electronically file such material with, or furnish it to, the SEC. Our website and the information contained therein or connected thereto is not intended to be incorporated into this Annual Report on Form 10-K.

Our Corporate Governance Standards, the charters of our Audit Committee, our Compensation Committee and our Nominating and Corporate Governance Committee, as well as our Corporate Code of Ethics for All Employees and Directors and our Corporate Code of Ethics for Financial Officers (which specifically applies to our Chief Executive Officer, Chief Financial Officer and persons performing similar functions) are available on our website under Investor Relations Corporate Governance.

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### **Overview**

Introgen Therapeutics, Inc. was incorporated in Delaware in 1993. We are a biopharmaceutical company focused on the discovery, development and commercialization of targeted molecular therapies for the treatment of cancer and other diseases. We are developing product candidates to treat a wide range of cancers using tumor suppressors, cytokines and other targeted molecular therapies. These agents are designed to increase production of normal cancer-fighting proteins that act to overpower cancerous cells, stimulate immune activity and enhance conventional cancer therapies.

Our primary approach to the treatment of cancers is to deliver targeted molecular therapies that increase production of normal cancer-fighting proteins to induce apoptosis, restore cell cycle or cell growth control and alter gene regulation, including the regulation of angiogenic and immune factors to reduce cancer growth. Our products work by acting as templates for the transient *in vivo* production of proteins that have pharmacological properties. The resultant proteins engage disease-related molecular targets or receptors to produce specific therapeutic effects.

We believe the use of targeted molecular therapies to induce the production of biopharmaceutical proteins represents a new approach for treating many cancers while avoiding the toxic side effects common to traditional therapies. We have developed significant expertise in developing targeted therapies that may be used to treat disease and in using what we believe are safe and effective delivery systems to transport these agents to the cancer cells. We believe we will be able to treat a number of cancers in a way that kills cancer cells without harming normal cells.

Our lead product candidate, ADVEXIN® therapy, combines the p53 tumor suppressor with a non-replicating, non-integrating, adenoviral delivery system we have developed and extensively tested. The p53 molecule is one of the most potent members of a group of naturally-occurring tumor suppressors, which act to kill cancer cells, arrest cancer growth and protect cells from becoming cancerous. We are developing other product candidates for the treatment of cancer using other molecules and delivery systems, such as the mda-7 and FUS1 tumor suppressors.

We believe our research and development expertise gained from our targeted molecular therapies for cancer is also applicable to other diseases that, like cancer, result from cellular dysfunction and uncontrolled cell growth. As a result, we are conducting research in collaboration with medical institutions to understand the safety and effectiveness of our targeted molecular therapy product candidates in the treatment of other diseases.

We typically license the technologies on which our products are based from third parties. These licenses generally grant us exclusive rights for pre-clinical and clinical development, manufacturing, marketing and commercialization of product candidates based on those technologies.

Our product research and development efforts include pre-clinical activities as well as the conduct of Phase 1, 2 and 3 clinical trials. We rely on third parties to treat patients in their facilities under these clinical trials. We produce ADVEXIN therapy and other product candidates in manufacturing facilities we own and operate using production methods we developed. We hold a number of patents or patents pending on certain product candidates and manufacturing processes used to produce certain product candidates.

We have not yet generated any significant revenue from unaffiliated third parties nor is there any assurance of future product revenue. We earn minimal revenue from contract services activities, grants and interest income, as well as rent from the lease of a portion of our facilities to The University of Texas M. D. Anderson Cancer Center. Our ability to generate revenue from the commercial sale of our products in the near future is uncertain. We may never generate revenue from the commercial sale of our products.

Our principal executive offices are located at 301 Congress Avenue, Suite 1850, Austin, Texas 78701. Our telephone number is (512) 708-9310. Our Internet website address is [www.introgen.com](http://www.introgen.com).

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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 molecules, 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 by a particular gene is known as gene expression or activity. Many of the proteins inside a cell participate 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 provide precision in their action that results in 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, referred to as the human genome, and in 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 the human genome, 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. This approach is described as Personalized Medicine.

***Delivery Systems***

Targeted molecular therapies are often combined with a delivery system, referred to as a vector, which enables the therapeutic molecule to enter the target cell. The vector must be able to deliver a sufficient dose of the therapeutic molecule to cause a beneficial effect. Among the delivery systems currently in use are modified versions of viruses such as adenoviruses. Viruses are often used as delivery systems because they have the ability to efficiently infect cells and carry therapeutic molecules into the cells. These viruses can be modified by deleting pieces of the viral genome that are necessary for viral reproduction and replacing the deleted pieces with a therapeutic molecule. The resulting viral vector retains the ability of the virus to efficiently deliver the therapeutic molecule into cells, while losing the ability to reproduce itself and spread to other cells.

While viruses are an efficient means of introducing therapeutic molecules into cells, synthetic substances have been developed, such as nanoparticles, which are nanoscale structures that have no viral components. These synthetic or nanoparticle systems can also deliver therapeutic molecules to host cells, including systemic routes of administration. These systems can mimic the characteristics of viral vector systems. We use both viral and synthetic nanoparticle systems in our clinical trials to deliver therapeutic molecules.

***An Overview of Cancer***

Cancer is a leading cause of death in the United States, where approximately 1.4 million people are newly diagnosed with cancer and approximately 566,000 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 National Institutes of Health (NIH) estimates the annual direct cost of treating cancer patients in the United States is approximately \$89.0 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 cause 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.

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The failure of any of these protective pathways can lead to the development of cancer. Cancer is one of the more suitable initial applications for targeted therapies because molecular targets that will lead to the destruction of the cancer cell are understood. The introduction of normal tumor suppressors, such as p53 and mda-7, into cancer cells leads to the destruction of those cancer cells and is a promising approach to treating cancer.

### ***Tumor Suppressors***

Tumor suppressors are one class of molecules that play a crucial role in preventing cancer and its spread. This class includes the p53, mda-7, BAK and FUS-1 tumor suppressors, among others.

The best known and most studied of the tumor suppressors is the p53 molecule. The p53 molecule is one of the most potent members of a group of naturally occurring tumor suppressors, which act to kill cancer cells, arrest cancer cell growth and protect cells from becoming cancerous. The p53 tumor suppressor is involved in multiple cellular processes, including control of cell division, DNA repair, cell differentiation, genome integrity and 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 tumor suppressor is capable of such wide-ranging effects because it orchestrates the activity of a host of 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, can be 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 and disability for 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, and often require additional and costly medications to ameliorate such side effects. Further, certain chemotherapies may not effectively treat tumors that have developed mechanisms to evade the action of the drugs, a phenomenon known as multi-drug resistance.

Due to the various limitations of most conventional cancer therapies, 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 conventional therapies are not likely to provide them with clinical benefit.

Given that established cancer therapies often prove to be incomplete, ineffective and/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 reduce the toxicity and improve upon marginal benefits common to current cancer treatments. Targeted molecular therapy applications are designed to address the cellular dysfunction that causes cancer, compared with small molecule drugs or immunotherapeutic agents, which may act indirectly.



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### **The Introgen Approach**

Our primary approach for the treatment of cancers is to deliver targeted molecular therapies that increase production of normal cancer-fighting proteins. The resultant proteins engage disease-related molecular targets or receptors to produce specific therapeutic effects. We believe we are able to treat a number of cancers in a way that kills cancer cells without harming normal cells.

Most cancers are amenable to local treatment, such as surgery and radiation, which are administered far more often than systemic cancer treatments. Our locally delivered product candidates, such as ADVEXIN therapy and INGN 241 therapy, deposit therapeutic molecules directly into a patient's cancerous tumor by hypodermic syringe. We have systemic formulations for intravenous use in those cases for which a systemic therapy may be indicated and have applied ADVEXIN therapy using a nanoparticle formulation system to deliver our tumor suppressors.

We initially focused on advanced cancers lacking effective treatments and in which local tumor growth control, where the tumor stops growing or shrinks, is likely to lead to measurable benefit. We have expanded our focus to include earlier stage cancers and pre-malignancies. We believe our clinical trials have shown our therapies can be used alone and in combination with conventional treatments such as surgery, radiation therapy and chemotherapy.

### **The Introgen Strategy**

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

*Develop and Commercialize ADVEXIN Therapy, INGN 241, INGN 225 and INGN 401 for Multiple Cancer Indications.* We plan to continue our development programs to commercialize several of our product candidates in multiple cancer indications, including:

ADVEXIN therapy, using the p53 tumor suppressor;

INGN 241, using the mda-7 tumor suppressor (also known as interleukin 24 or IL-24);

INGN 225, using the p53 tumor suppressor as a highly specific cancer immunotherapy; and

INGN 401 systemic nanoparticle therapy, using the FUS-1 tumor suppressor.

*Develop Our Portfolio of Targeted Molecular Therapies and Other Drug Products.* Utilizing our research, clinical, regulatory and manufacturing expertise, we are evaluating development of additional molecular therapies for various cancers, including:

INGN 234, an oral rinse or mouthwash formulation containing the p53 tumor suppressor;

INGN 402 and 403, using nanoparticle formulations for systemic delivery of the p53 and mda-7 tumor suppressors; and

INGN 007, a replication-competent viral therapy.

*Develop a Systemic Nanoparticle Administration Platform.* Early pre-clinical and clinical studies with these new nanoparticle drugs have demonstrated a good safety profile and promising anti-cancer activity. In addition to FUS-1, we incorporate the p53 tumor suppressor and the mda-7 tumor suppressor in these nanoparticle formulations. We also have in-licensed technologies for systemic nanoparticle delivery of DNA, siRNA, proteins, peptides and polypeptides.

*Develop the Topical Use of Tumor Suppressors.* We plan to continue developing topical product candidates for the treatment or prevention of oral and dermal cancers, specifically INGN 234 referred to above. We believe these treatments are a logical extension of our loco-regional delivery of cancer therapies and

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represent attractive product candidates since pre-malignant and malignant cells can be exposed to natural, biological tumor suppressors and DNA repairing agents.

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

*Expand Our Market Focus to Non-Cancer Indications.* We plan to leverage our scientific, research and process competencies in molecular therapy and vector development to pursue targeted molecular therapies for a variety of other diseases and conditions. While our primary emphasis at this time is on cancer, 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.

We have an established process for evaluating new drug candidates and advancing them from pre-clinical to clinical development. We have identified and licensed multiple technologies, which we intend to combine with our adenoviral and non-viral vector systems and which we believe are attractive development targets for the treatment of various cancers. We intend to evaluate additional opportunities to in-license or acquire new technologies.

### **Product Development Overview**

#### *ADVEXIN Therapy (p53)*

#### *ADVEXIN Therapy Overview and Regulatory Status*

ADVEXIN therapy is our lead product candidate. It combines the p53 tumor suppressor with a non-replicating, non-integrating adenoviral delivery system we have developed and extensively tested. The p53 molecule is one of the most potent members of a group of naturally-occurring tumor suppressors, which act to kill cancer cells, arrest cancer cell growth and protect cells from becoming cancerous.

ADVEXIN therapy for head and neck cancer has been designated an Orphan Drug under the Orphan Drug Act. This designation may give us up to seven years of marketing exclusivity for ADVEXIN therapy for this indication if approved by the U.S. Food and Drug Administration (FDA).

The European Medicines Agency (EMA) Committee for Orphan Medicinal Products granted ADVEXIN therapy an Orphan Medicinal Product Designation in Europe for the treatment of Li-Fraumeni Syndrome. This designation has been ratified by the European Commission. The Orphan Medicinal Product Designation in Europe confers a number of regulatory benefits to ADVEXIN therapy, including access to protocol assistance, reduced regulatory fees and a ten-year period of marketing exclusivity from the date of marketing authorization by the European Commission. Li-Fraumeni Syndrome is an inherited cancer characterized by inherited mutations in the p53 tumor suppressor.

We have submitted, and the EMA has accepted for review, a Marketing Authorization Application for ADVEXIN therapy under the EMA's Exceptional Circumstances Approval rules for breakthrough therapies. The application is for the use of ADVEXIN therapy for the treatment of Li-Fraumeni Syndrome (LFS). Under these rules, approval, if granted by the EMA, will be based on clinical results from the use of ADVEXIN therapy in LFS and also from results of other trials with ADVEXIN therapy in a wide variety of non-inherited solid tumors that share the p53 biomarker abnormality, which characterizes LFS.

The EMA's Exceptional Circumstances Approval provisions are designed to facilitate access to needed treatments for certain Orphan Medicinal Products. A Marketing Authorization Application filed with the EMA under these provisions can be reviewed on an expedited basis. This Exceptional Circumstance registration approach is designed by EMA to be more streamlined than EMA's Conditional Approval procedures, which are similar to the FDA's Accelerated Approval regulations.

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An audit and inspection of Introgen's facilities and production processes was performed by a European Union Qualified Person (QP) during 2007. This inspection resulted in the QP concluding that ADVEXIN therapy has been manufactured at this site in accordance with the standards of Good Manufacturing Practices in place in the EU for Investigation Medicinal Products (IMPs). This inspection covered all aspects of ADVEXIN therapy manufacture, including production and purification, aseptic filling, labeling, and testing of raw materials, intermediates, and final product, and all quality systems in place for these aspects. This certification was obtained in preparation for the EMEA's inspection we anticipate upon review of the ADVEXIN therapy Marketing Authorization Application.

Most of our regulatory activities involving the EMEA are conducted by Gendux Molecular Limited, a wholly-owned subsidiary of ours based in Ireland.

We plan to analyze data from two Phase 3 clinical trials of ADVEXIN therapy in patients with advanced recurrent squamous cell carcinoma of the head and neck (recurrent head and neck cancer). These trials involve administration of ADVEXIN therapy, both independently and in combination with chemotherapy, in recurrent head and neck cancer.

We received Fast Track designation for ADVEXIN therapy from the FDA under its protocol assessment program as a result of the FDA's agreement with the design of our two Phase 3 clinical trials of ADVEXIN therapy. Under this Fast Track designation, the FDA will take actions to expedite the evaluation and review of the Biologics License Application (BLA) for ADVEXIN therapy. A BLA is the application for approval to market and sell ADVEXIN therapy in the United States. We plan to pursue with the FDA an Accelerated Approval of ADVEXIN therapy, which is one alternative provided under a Fast Track designation.

We reviewed historically successful FDA registration strategies for numerous cancer drugs, noting that during the past decade, approximately 14 cancer drugs were initially approved based upon submissions of Phase 2 clinical data. A number of the Phase 2 trials supporting these approvals employed single-arm studies involving relatively small patient populations. Virtually all of those drugs relied on surrogate endpoints for approval and a substantial number of the products were for orphan drug indications.

We conducted a series of meetings with the FDA to develop and implement the filing strategy for the BLA for ADVEXIN therapy. As a result of these meetings, we are developing and pursuing an initial rolling BLA filing strategy based on data from our Phase 2 and Phase 3 clinical trials of ADVEXIN therapy for treatment of recurrent head and neck cancer. The FDA has concurred that preliminary evaluation of this data suggests a level of efficacy consistent with the standard for the initiation of a rolling BLA. This submission process is also known as Submission Of a Partial Application or SOPA.

The FDA has concluded that ADVEXIN therapy continues to show promise with respect to an unmet medical need since there are limited treatment alternatives in the United States for recurrent head and neck cancer. The FDA has concluded that the clinical development program for ADVEXIN therapy for recurrent head and neck cancer continues to meet the criteria for Fast Track designation. By using new clinical data and new analyses of those data, we hope to more specifically target recurrent head and neck cancer in patients using indicators known as biomarkers, as discussed further below under ADVEXIN Therapy as a Targeted Molecular Therapy. We believe this Personalized Medicine approach will improve efficacy by identifying the patients most likely to benefit from ADVEXIN therapy.

We submitted a SOPA Request to the FDA Division of Cellular and Gene Therapies proposing a rolling BLA for ADVEXIN therapy for the treatment of recurrent head and neck cancer. This request was based primarily on data from our Phase 2 clinical trials. We have proposed to the FDA that, since the basis of the proposed rolling BLA is Phase 2 clinical data utilizing surrogate endpoints, the rolling BLA could be evaluated under the provisions of Subpart H for Accelerated Approval. In order to fully explore all of the review and approval possibilities for ADVEXIN therapy, the FDA has requested we submit new data and analyses from the Phase 2 ADVEXIN therapy clinical trials for recurrent head and neck cancer and conduct efficacy analyses on one or both of our Phase 3 trials. Given that we have two Phase 3 clinical trials in recurrent head and neck cancer as discussed further below, we and the FDA are evaluating the most effective use of the data from these Phase 2 and 3 clinical trials in the review and approval of ADVEXIN therapy. Regulatory approval approaches may allow Accelerated Approval on the basis of

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Phase 2 clinical data with subsequent confirmatory data being provided by the Phase 3 clinical studies or, alternatively, a full approval based on data from Phase 2 and certain Phase 3 clinical trials.

In addition to our original Phase 3 protocol determination to assess patient's genomic mutation status and other Personalized Medicine characteristics, we subsequently reached agreement with the FDA that biomarker evaluations as described in its Critical Path Initiative, which permits new product evaluation on the basis of specifically targeted (i.e., by prognostic or biologic parameters) clinical trials and/or patient populations, can be used in the ADVEXIN therapy approval process. This initiative also encouraged sponsors to examine novel approaches to define tumor responses that correlate with clinical benefit. Our phase 3 statistical analysis plan and clinical protocols describe assessments of p53 biomarker profiles based upon p53 protein levels determined by immunohistochemistry and p53 mutational gene sequence evaluations. We have employed several biomarker and response criteria to evaluate ADVEXIN therapy efficacy as described below.

We are currently conducting the efficacy analysis of one of our ADVEXIN therapy Phase 3 studies. This analysis involves comparing ADVEXIN therapy to methotrexate for the treatment of recurrent head and neck cancer. The efficacy assessment of the randomized, controlled clinical trial is based upon analysis of biomarkers and clinical outcomes. The efficacy evaluation of the Phase 3 study will incorporate the biomarker analyses identified in Phase 2 clinical trials of ADVEXIN therapy of recurrent head and neck cancer. The Phase 3 Statistical Analysis Plan was finalized with input from the FDA. We have followed advice from the FDA to accelerate our Phase 3 safety analysis and to perform an efficacy analysis for this study. An independent Data Safety Monitoring Board review in 2006 noted no safety issues with the Phase 3 study. We completed the submission of the Phase 2 data to the FDA in the second quarter of 2007. These data contained information on response rate, survival and biomarker findings associated with the use of ADVEXIN therapy in recurrent head and neck cancer.

During 2008, we plan to:

- Conduct efficacy and biomarker analyses of one or both of our two Phase 3 clinical trials for recurrent head and neck cancer and plan to submit those data to the FDA and EMEA in support of ADVEXIN therapy registration programs;

- Complete filings with the EMEA in support of an Exceptional Circumstance Approval Application for Li-Fraumeni Syndrome cancers.

We have noted a positive correlation between ADVEXIN therapy clinical activity and p53 biomarker pathways in multiple patients with different types of cancer. We are continuing to analyze patient tissue samples for p53 and other biomarker data obtained from previously conducted clinical trials investigating the use of ADVEXIN therapy in various solid cancers. We plan to include relevant data from this research in our submissions to regulatory agencies.

There is no assurance we will be able to achieve these regulatory milestones during the time period we currently anticipate. We may encounter delays in the regulatory process relating to these milestones due to additional information requirements from regulatory authorities, unintentional omissions in our applications, additional government regulation or other delays in the review process. We may update our expectations regarding these regulatory milestones from time to time to reflect new information as it becomes available to us.

### *ADVEXIN Therapy as a Targeted Molecular Therapy*

We identified a set of predictive indicators, commonly referred to as biomarkers, associated with high response rates and increased survival in Phase 2 clinical trials of ADVEXIN therapy in patients with recurrent head and neck cancer. These trials are discussed in more detail below under Other ADVEXIN Therapy Activities. We believe these biomarkers support the use of ADVEXIN therapy as a targeted molecular therapy.

The FDA, the National Cancer Institute (NCI), and the Centers for Medicare & Medicaid Services are undertaking the Oncology Biomarker Qualification Initiative to expedite the development of novel cancer treatments that reflect the Personalized Medicine approach. These agencies define biomarkers as clinical or biological indicators of disease or therapeutic effects, which can be measured through dynamic imaging tests, laboratory tests

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on blood or tissue samples as well as by clinically defined parameters. This initiative was developed to employ biomarkers as a way of speeding the development and evaluation of new cancer therapies. The identification of predictive indicators of ADVEXIN therapy activity is responsive to these initiatives by predicting the patient populations most likely to benefit from a specific cancer therapy.

We have compiled molecular biomarker data from several of our clinical studies in patients with head and neck, lung, prostate and Li-Fraumeni Syndrome cancers. Some of these studies are described in more detail in the following paragraphs. In the subset of patients with tumor samples available for evaluation, there was a statistically significant correlation between specific p53 biomarkers and tumor response after treatment with ADVEXIN therapy. In 54 cancer patients evaluated, tumor response after ADVEXIN therapy monotherapy was observed in 35 percent of patients with an abnormal p53 biomarker, and all tumor responses occurred in the abnormal p53 biomarker group. The association of tumor response with abnormal p53 biomarkers was statistically significant ( $p = 0.0013$ ).

In an analysis of 112 patients in the Phase 2 trial of recurrent head and neck cancer treated with the ADVEXIN therapy dose proposed for regulatory approval, the percentages of patients with tumor responses defined by reductions in bi-dimensional tumor area on CT scan of 50 percent, 25 percent, 10 percent or stable disease for more than 2 treatment cycles were 6 percent, 7 percent, 12 percent and 22 percent, respectively. Median survival for these responder populations were 41, 17, 15 and 10 months, respectively. There was a statistically significant increase in median survival for each of the responder populations compared to the 6 month median survival of the non-responders (tumor reduction of less than 10% and  $p$  less than 0.0016). Spontaneous tumor remissions generally are not observed in recurrent head and neck cancer.

Specific p53 biomarkers were associated with a statistically significant increase in tumor responses to ADVEXIN therapy in recurrent head and neck cancer. A reduction in tumor size was observed in 38 percent of patients with specific p53 biomarkers compared to none (zero percent) of the patients with p53 protein normal tumors. The increased tumor response associated with the favorable p53 biomarker was statistically significant ( $p = 0.05$ ). In addition, certain p53 biomarkers were predictive for increased survival following ADVEXIN therapy treatment. Median survival of patients with the predictive p53 biomarker was 11.6 months, compared to 3.5 months for patients with other p53 profiles ( $p = 0.0007$ ). These biomarker analyses were conducted with pre-treatment samples from 28 patients on a completely blinded basis by an independent laboratory that was not aware of the clinical results of the study.

The targeted molecular therapy provided by ADVEXIN therapy is evidenced by its use to successfully treat a Li-Fraumeni Syndrome cancer patient on a compassionate use basis under a protocol authorized by the FDA. Li-Fraumeni Syndrome cancer patients have inherited defects in the p53 tumor suppressor that is the target of ADVEXIN therapy. Our treatment of a tumor in a Li-Fraumeni Syndrome patient with ADVEXIN therapy led to improvement of tumor-related symptoms and resulted in a complete response in the treated lesion as determined by positron emission tomography (PET) computerized tomography (CT) scans. PET-CT scans measure the metabolic activity of tumors and are being increasingly utilized in the management of cancer patients because they provide more sensitive assessments of treatment effects compared to conventional CT and magnetic resonance imaging scans.

This Li-Fraumeni Syndrome study defined important biomarkers to guide the administration of ADVEXIN therapy to patients with other cancers who display p53 pathway abnormalities. Our molecular analysis of biopsies of the Li-Fraumeni Syndrome tumor before and after treatment identified key markers of p53 pathway abnormalities that are used to predict and evaluate the effects of ADVEXIN therapy. These markers included detection of abnormal levels of p53 protein that identify aberrant p53 pathways and the induction of molecular markers of tumor growth control and tumor cell death that validate ADVEXIN therapy's mechanisms of action. We believe these biomarkers can be used to identify patients most likely to benefit from ADVEXIN therapy.

The EMEA Committee for Orphan Medicinal Products has granted ADVEXIN therapy an Orphan Medicinal Product Designation in Europe for the treatment of Li-Fraumeni Syndrome. This designation has been ratified by the European Commission. The Orphan Medicinal Product Designation in Europe confers a number of regulatory benefits to ADVEXIN therapy, including access to protocol assistance, reduced regulatory fees and a 10-year period of marketing exclusivity from the date of approval.



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We have submitted, and the EMEA has accepted for review, a Marketing Authorization Application for ADVEXIN therapy under the EMEA's Exceptional Circumstances Approval rules for breakthrough therapies. The application is for the use of ADVEXIN therapy for the treatment of Li-Fraumeni Syndrome (LFS). Under these rules, approval, if granted by the EMEA, will be based on clinical results from the use of ADVEXIN therapy in LFS and also from results of other trials with ADVEXIN therapy in a wide variety of non-inherited solid tumors that share the p53 biomarker abnormalities, which characterize LFS.

The EMEA's Exceptional Circumstances Approval provisions are designed by EMEA to facilitate access to needed treatments for certain Orphan Medicinal Products. A Marketing Authorization Application filed with the EMEA under these provisions can be reviewed on an expedited basis. This registration approach is more streamlined than EMEA's Conditional Approval procedures, which are similar to the FDA's Accelerated Approval regulations. As a result of the encouraging clinical findings in treating Li-Fraumeni Syndrome, we are making ADVEXIN therapy available on a compassionate use basis to qualified Li-Fraumeni Syndrome patients with tumors refractory to standard treatment.

Li-Fraumeni Syndrome is an inherited genetic disorder that greatly increases the risk of developing several types of cancer typically with initial occurrence at a young age. The majority of Li-Fraumeni Syndrome families have inherited mutations in the p53 tumor suppressor. The findings described above have been presented at the annual meetings of the American Society of Gene Therapy (ASGT) and the American Society of Clinical Oncology (ASCO).

*Other ADVEXIN Therapy Activities*

We performed a Phase 2 clinical trial of ADVEXIN therapy combined with neoadjuvant chemotherapy and surgery in women with locally advanced breast cancer. The results of this study were published in the journal *Cancer*. Objective clinical responses were seen following the combined therapy in 100% of the patients with a median of 80% reduction in tumor size. Following tumor shrinkage, complete tumor removal by subsequent surgery was achieved in 100% of the patients. At a median follow-up of 37 months (range, 30-41 months), four patients (30%) developed systemic recurrence and two patients died. The estimated breast cancer-specific survival rate at three years was 84%. There was no increase in systemic toxicity. Neoadjuvant treatments are administered prior to surgery and represent a novel and increasingly applied approach to making surgical tumor resections less invasive, improving outcomes and facilitating breast conservation.

We completed a Phase 2 clinical trial of ADVEXIN therapy administered as a complement to radiation therapy in non-small cell lung cancer. In the 19 patients who participated in the trial, combined ADVEXIN therapy and radiation treatment resulted in 63% biopsy-proven complete responses at three months, which is approximately four times the expected rate using radiotherapy alone. The results of this study were published in *Clinical Cancer Research*.

We performed a Phase 1/early Phase 2 clinical trial of ADVEXIN therapy for the treatment of advanced, unresectable, squamous cell esophageal cancer. Results of this trial in patients with esophageal cancer refractory to chemotherapy and radiation indicate three of the ten patients treated, or 30%, had negative biopsies after receiving ADVEXIN therapy. The median survival of the patients treated with ADVEXIN therapy was approximately twelve months, which compared favorably to historical controls in which a median survival of less than ten months was observed for patients who did not respond to standard treatments. This clinical trial was performed at Chiba University in Japan.

We have completed other clinical trials of ADVEXIN therapy, including Phase 1 studies in prostate cancer and bronchoalveolar carcinoma. To date, clinical investigators at sites in North America, Europe and Japan have treated over 600 patients with ADVEXIN therapy, establishing a large safety database. Findings from several of our clinical trials have been published in *Clinical Cancer Research* and *Proceedings of the American Society for Clinical Oncology* as well as presented at numerous conferences, including the San Antonio Breast Cancer Conference and various meetings of the ASCO, ASGT and the American Association for Cancer Research.

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A growing body of data suggests ADVEXIN therapy demonstrates clinical activity in a variety of cancer indications. Safety data from our clinical trials suggest this activity may be achieved without the treatment-limiting side effects frequently associated with many other cancer therapies.

Our clinical trials indicate ADVEXIN therapy is well tolerated as a monotherapy. The addition of ADVEXIN therapy to standard chemotherapy, surgery or radiation does not appear to increase the frequency or severity of side effects normally associated with these treatment regimens.

Pre-clinical studies have provided insight into the molecular pathways by which the p53 tumor suppressor, the active component of ADVEXIN therapy, kills tumor cells. These studies were undertaken to provide additional molecular data supporting the activity observed during the clinical development of ADVEXIN therapy and to provide additional information regarding the specific pathways, including anti-angiogenesis or the reduction of blood vessels supplying the tumor, that mediate the observed clinical effects of ADVEXIN therapy. The studies were conducted by our collaborators at Okayama University in Japan, The University of Texas M. D. Anderson Cancer Center and other academic institutions and were published in *Molecular Cancer Therapeutics* and other scientific journals..

Other data suggest the enhanced therapeutic effects of a combination of ADVEXIN therapy and Erbitux® therapy in an animal model of human non-small cell lung cancer. Other pre-clinical studies conducted by our collaborators at Wayne State University, the Karmanos Cancer Institute located in Detroit, Michigan and the University of California-Irvine, as published in *The Laryngoscope*, show that the combination of ADVEXIN therapy and docetaxel resulted in increased levels of programmed cell death in head and neck tumor cells.

We hold a worldwide, exclusive license to a family of patent applications directed to combination therapy using ADVEXIN therapy with inhibitors of epidermal growth factor receptors (EGFr inhibitors) such as Erbitux®, Vectibix®, Tarceva® and Iressa®. We licensed this family of patents from M. D. Anderson Cancer Center. This important technology is based on the discovery by scientists at M. D. Anderson Cancer Center that p53 therapies (which is the basis for our ADVEXIN therapy) and mda7 therapies (which is the basis for our INGN 241 product candidate discussed below) can work synergistically with inhibitors of epidermal growth factor receptors to arrest tumor growth. Preclinical studies have shown that this therapeutic approach results in a greater level of cancer cell death than when either therapy is used alone.

We hold the worldwide rights for pre-clinical and clinical development, manufacturing, marketing and commercialization of ADVEXIN therapy.

***INGN 241 (mda-7)***

INGN 241 uses the mda-7 tumor suppressor, that we believe, like the p53 tumor suppressor, has broad potential to induce apoptosis or cell death in many types of cancer. We have combined the mda-7 tumor suppressor with our adenoviral delivery system to form INGN 241. Our pre-clinical trials have shown the protein produced by INGN 241 suppresses the growth of many cancer cells, including those of the breast, lung, ovaries, colon, prostate and the central nervous system, while not affecting the growth of normal cells. Because INGN 241 kills cancer cells even if other tumor suppressors, including p53, are not functioning properly, it appears mda-7 functions via a novel mechanism of tumor suppression.

We have completed a Phase 1/early Phase 2 clinical trial using INGN 241 to evaluate safety, mechanism of action and efficacy in approximately 22 patients with solid tumors. This trial indicated that in patients with solid tumors, INGN 241 was well tolerated, was biologically active and displayed minimal toxicity associated with its use. Although INGN 241 was administered directly to tumors, evidence of distant biologic activity was observed, suggesting this therapy may have utility in treating primary tumors as well as metastatic disease. We are conducting a Phase 2 clinical trial using INGN 241 in patients with metastatic melanoma. We are also conducting a Phase 3 clinical trial using INGN 241 in combination with radiation therapy for solid tumors.

Data from our Phase 1/early Phase 2 clinical trial of INGN 241 in patients with solid tumors demonstrate that direct injection of INGN 241 induced programmed cell death in 100% of the tumors treated, even in patients who had failed prior therapy with other anti-cancer drugs. Clinical responses were observed in 44% of the treated lesions,



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including complete and partial responses in two patients with melanoma. Patients treated with INGN 241 had increases in a subset of T-cells that help to destroy cancer cells, which is consistent with the role of the mda-7 protein as a member of the interleukin family of immune stimulating proteins.

We have conducted pre-clinical work indicating that in addition to its known activity as a tumor suppressor, the protein produced by mda-7 may also stimulate the body's immune system to kill metastatic tumor cells and to protect the body against cancer, thereby offering the potential of providing an added advantage in treating various cancers because it may attack cancer using two different mechanisms. Because the mda-7 tumor suppressor may act as a cytokine, or immune system modulator, it is also known as interleukin 24, or IL-24. The mda-7 molecule may also work as a radiation sensitizer to make several types of human cancer cells more susceptible to radiation therapy. We have seen evidence of this effect in pre-clinical and clinical settings.

We have identified the molecular pathways by which mda-7, the active component of INGN 241, induces growth arrest and programmed cell death or apoptosis in cancer cells. Pre-clinical studies using lung cancer cells have demonstrated the mda-7 protein binds to a critical cellular enzyme known as PKR. The binding of mda-7 to PKR is essential for the anti-cancer activity of INGN 241. The identification of this binding partner demonstrates a significant advancement in understanding how this therapeutic can be effective against cancer. Additional studies have identified bystander killing of pancreatic cancer cells by the mda-7 protein. Bystander killing involves the killing of neighboring tumor cells by the mda-7 protein released from adjacent INGN 241-treated tumor cells.

Pre-clinical data indicate the combination of INGN 241 and Velcade® (Bortezomib), marketed by Millennium Pharmaceuticals, Inc., can result in increased tumor cell killing in human ovarian cancer cells. These data showed that co-administration of INGN 241 and Velcade®, a known protein degradation inhibitor, further elevated mda-7 protein levels and caused a significant increase in killing of ovarian cancer cells. These findings are published in *Cancer Gene Therapy*.

Pre-clinical data indicate INGN 241 works synergistically with celecoxib, marketed by Pfizer as Celebrex®, to inhibit the growth and increase killing of breast cancer cells. The combination of celecoxib and INGN 241 showed greater than additive increases in cell death compared with either therapy alone and also resulted in the suppression of tumor cell growth.

Pre-clinical data indicate INGN 241 and bevacizumab, marketed by Roche Holding AG and Genentech, Inc. (Genentech) as Avastin®, each inhibit tumor angiogenesis through distinct mechanisms in models of lung cancer. Study results demonstrate the combination of INGN 241 and Avastin® significantly increases anti-tumor activity compared with either agent used separately. We have observed synergistic activity resulting in a positive therapeutic effect in the treatment of lung cancer in laboratory animals following the combination of the two agents. In contrast, treatment with Avastin® alone demonstrated only minor tumor regression in those animals. These findings have been published in *Molecular Therapy*, the journal of the American Society of Gene Therapy.

Pre-clinical data indicate the combination of INGN 241 and Tarceva®, marketed by Genentech, more significantly inhibits tumor cell growth than Tarceva® administered alone. The preclinical data suggest the two agents work in concert to inhibit activity of the epidermal growth factor receptor, a potent driver for cell growth in many types of cancer.

Our pre-clinical work indicates INGN 241 effectively kills cancer cells that are resistant to cisplatin, one of the most commonly used chemotherapeutic agents. These pre-clinical studies identified a novel defect in a protein degradation pathway in the cisplatin-resistant cells. This defect enhances the activity of INGN 241, suggesting that INGN 241 may have particular utility in treating cancers that do not respond to cisplatin. We have also observed that INGN 241 can restore cisplatin sensitivity to certain cancer cells that have become cisplatin-resistant.

In pre-clinical studies, we have observed the expression of mda-7 in ovarian cancer cells activates a cell death or apoptotic pathway regulated by the Fas signaling system, a key signaling system in immune regulation, apoptosis and drug resistance. This activation resulted in significant increases in apoptosis and inhibition of cancer cell proliferation that were specific to cancer cells. These effects were not observed in normal ovarian tissue, supporting previous data showing a cancer-selective effect of INGN 241.

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We have published preclinical data describing how an important tumor survival pathway impacts the anticancer activity of INGN 241. Inhibition of this pathway, known as NF- $\kappa$ B, enhanced the tumor killing effects of INGN 241 in cell culture and in preclinical models of human tumors. Researchers at Introgen and The University of Texas M. D. Anderson Cancer Center conducted these studies. The data appear in the publication *Molecular Cancer Therapeutics*.

We have published preclinical data demonstrating that vitamin E succinate (VES) enhances the cytotoxic effects of INGN 241 in ovarian cancer cells. VES is a derivative of Vitamin E that has demonstrated potent antitumor activity in cell and animal models of cancer. Researchers at Introgen and The University of Texas M. D. Anderson Cancer Center collaborated on the studies. The results appear in the publication *Cancer Letters*.

We have published the results of a pre-clinical study indicating INGN 241 may suppress the growth *in vivo* of non-small cell lung cancer through apoptosis in combination with anti-angiogenesis. The data demonstrate INGN 241 can inhibit production of the VEGF protein, a potent inducer of angiogenesis, within lung cancer cells, which in turn inhibits tumor angiogenesis, a key requirement for tumor growth.

Pre-clinical work has demonstrated administration of INGN 241 results in the development of systemic immune responses against tumor cells and suggests INGN 241 could be used as a novel cancer molecular immunotherapy. In pre-clinical studies, implantation of INGN 241-treated tumor cells into mice resulted in significant inhibition of tumor growth. Significantly, mice immunized with INGN 241-treated cells showed inhibition of tumor growth after a subsequent challenge with additional tumor cells.

We have conducted pre-clinical studies with INGN 241 in breast cancer cell lines as a single agent, as well as in combination with radiation therapy, with chemotherapy (Taxotere® or Adriamycin®), with the hormone inhibitor Tamoxifen® and with Herceptin®, a biologic cancer therapy. In all settings, INGN 241 reduced cell growth and increased programmed tumor cell death (apoptosis). This effect was enhanced when combined with drugs currently used to treat breast cancer. In animal models of breast cancer, treatment with INGN 241 alone or in combination with radiation therapy resulted in significant decreases in tumor growth. In particular, our pre-clinical studies have shown treatment with a combination of INGN 241 plus Herceptin® induces cell death in Her-2/neu positive breast cancer cells at a rate greater than that seen with either agent alone. In these studies, it was also noted while Herceptin® exhibited no activity on Her-2/neu negative cells, INGN 241 did induce cell death in these cells.

Pre-clinical studies indicate the mda-7 protein released from cells treated with INGN 241 can kill nearby, untreated breast cancer cells resulting in additional therapeutic effect. This bystander effect occurs when the therapeutic protein binds to certain receptors on nearby cancer cells. We believe this bystander effect is significant because it could indicate the number of cancer cells INGN 241 can kill is greater than the number of cells that take up this novel investigational cancer therapy.

Pre-clinical studies have demonstrated that INGN 241 can induce human lung cancer cells to undergo apoptosis, or programmed cell death, through the synergistic action of INGN 241 and a class of tumor-targeted drugs known as heat shock protein 90 (Hsp90) inhibitors. We have observed the combination of INGN 241 and two Hsp90 inhibitors can result in the enhancement of cell death in lung cancer cells. This combination treatment inhibited tumor cell movement, suggesting an anti-metastatic effect.

Findings and results arising from our development of INGN 241 have also been published in the *Journal of Leukocyte Biology*, *Cancer Gene Therapy*, *Cancer Research*, *Molecular Therapy*, *Oncogene*, *Surgery*, and *International Immunopharmacology*. Data from this work have also been presented at the annual San Antonio Breast Cancer Symposium.

We have exclusive licenses from Columbia University and The University of Texas M. D. Anderson Cancer Center to mda-7 tumor suppressor technology for our therapeutic applications. The technology licensed from M. D. Anderson Cancer Center was developed pursuant to sponsored and collaborative research programs over the past several years. Pre-clinical studies regarding the active component of INGN 241 have included research at The University of Texas M. D. Anderson Cancer Center and Columbia University. We have an exclusive license to a family of patent applications covering methods and compositions of the mda-7 tumor suppressor with several types of currently available therapies, including conventional chemotherapies, vascular endothelial growth factor

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inhibitors, such as Avastin® (bevacizumab), non-steroidal anti-inflammatory drugs, which include COX-2 inhibitors such as Celebrex®, (celecoxib) and proteasome inhibitors, which can increase therapeutic functionality, such as Velcade® (bortezomib).

**INGN 225 (p53 molecular immunotherapy)**

We are developing INGN 225 using the p53 tumor suppressor in a different manner to create a molecular immunotherapy for cancer that stimulates a particular type of immune system cell known as a dendritic cell. Research published in *Current Opinion in Drug Discovery & Development* concluded that the p53 tumor suppressor can be used with a patient's isolated dendritic cells as an antigen delivery and immune enhancing therapeutic strategy. Pre-clinical testing has shown that the immune system can recognize and kill tumors after treatment with dendritic cells stimulated by the p53 tumor suppressor, which suggests a molecular immunotherapy consisting of dendritic cells stimulated by p53 could have broad utility as a treatment for progression of tumors.

Moffitt Cancer Center is conducting a Phase 2 randomized, controlled study of INGN 225 involving as many as 80 patients with metastatic, small-cell lung cancer. Mutations in the p53 tumor suppressor occur in approximately 90 percent of the patients with this disease such that this patient population is well-suited for testing the clinical efficacy of INGN 225. The National Institutes of Health National Cancer Institute awarded to Moffitt Cancer Center a grant of approximately \$1.3 million to fund this trial. We have the right to, and expect we will, use the clinical data generated from this study as part of our INGN 225 commercial development efforts.

We have completed a Phase 1/2 clinical trial in collaboration with the Moffitt Cancer Center at the University of South Florida in patients with small cell lung cancer. We are also conducting a Phase 1/2 trial in patients with breast cancer in collaboration with the University of Nebraska. In this trial, INGN 225 was administered after the patients have been treated with standard chemotherapy.

The results from the Phase 1/2 trial in patients with extensive-stage small cell lung cancer who were previously treated with chemotherapy demonstrated a 45 percent response rate in patients with platinum-resistant small-cell lung cancer who received chemotherapy following INGN 225. The historical response rate is generally less than 15 percent in these patients. Among the 43 patients evaluable for survival following INGN 225 treatment, survival was also improved compared to historical controls.

**INGN 234 (p53 topical)**

We are developing INGN 234 for the prevention of oral cancers and the treatment of oral leukoplakia. We conducted a Phase 1 clinical trial in which p53 was administered in an oral mouthwash formulation to prevent precancerous oral lesions from developing into cancerous lesions.

We are conducting pre-clinical work on other topical administrations of tumor suppressors to control or prevent oral or dermal cancers. We are investigating multiple delivery platforms, including both viral and non-viral approaches. We are also investigating combining delivery of our therapies with rinses, patches, ointments and enhancing polymers. We believe the opportunity exists to develop non-toxic treatments for pre-malignant and malignant cells that can be easily exposed to natural biological tumor suppressor and DNA repairing molecules.

We have entered into an alliance agreement with Colgate-Palmolive to develop and potentially market oral healthcare products. See Part I, Item 2. Management's Discussion and Analysis of Financial Condition and Results of Operation Business and Collaborative Arrangements Alliance with Colgate-Palmolive Company below for further discussion of this alliance agreement.

**INGN 401 (FUS-1)**

INGN 401 uses systemically administered nanoparticles to express the tumor suppressor FUS-1. We exclusively license the FUS-1 technology from M. D. Anderson Cancer Center.

A Phase 1/early Phase 2 clinical trial is in process at M. D. Anderson Cancer Center testing INGN 401 in patients with advanced non-small cell lung cancer who have been treated previously with chemotherapy. INGN 401

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was successfully delivered into the tumors of stage IV lung cancer patients and was found to be active in patients metastatic non-small cell lung cancer tumors. This finding is the first clinical demonstration that a gene can be injected intravenously and be taken up and expressed at high levels in cancer cells at distant sites.

The interim results of this clinical trial were presented by the M. D. Anderson Cancer Center investigators at the 2007 annual meeting of the American Association of Cancer Research. That presentation noted this clinical trial consists of thirteen patients first treated with front line cisplatin combination chemotherapy, which failed to halt their disease. They received INGN 401 as a second line therapy. At the time of this presentation, the median survival time for the patients in this study was 14.6 months which compares favorably to a seven-month median survival time for patients receiving conventional second line therapy. No significant drug-related toxicity has been observed with respect to INGN 401. The clinical trial continues and no maximum tolerated dose has been established.

Pre-clinical data suggests that INGN 401 may have utility as a monotherapy in lung cancer. We have observed significant inhibition of tumor growth in lung cancer animal models following INGN 401 monotherapy treatment when compared with untreated animals.

Pre-clinical data suggests that a combination of ADVEXIN therapy and INGN 401, administered intravenously in nanoparticle formulations, is capable of significantly shrinking metastatic tumors in models of human lung cancer. The data indicates that while ADVEXIN therapy and INGN 401 are each effective as a monotherapy, more powerful results were observed when the treatments were combined. The data also indicates that the nanoparticle treatments had no demonstrable adverse effects on normal cells.

INGN 401 has demonstrated synergistic activity with gefitinib (Iressa®), a novel class of anti-cancer agents that decrease tumor growth by inhibiting growth factor receptors that promote tumor proliferation. While gefitinib can produce dramatic responses in a small subset of lung cancer patients, most lung cancers are refractory to its effects. The data indicate nanoparticle delivery of INGN 401 can synergize with Gefitinib in killing lung tumor cells resistant to gefitinib alone. Furthermore, in gefitinib-sensitive tumors, INGN 401 delivery significantly enhanced anti-cancer activity.

Data and findings from our work to develop INGN 401 have been published in *Cancer Gene Therapy* and *Cancer Research*. We are working with investigators at MDACC to design a pivotal clinical trial for INGN 401.

**INGN 402 and INGN 403 (nanoparticle formulations of p53 and mda-7, respectively)**

We are developing two nanoparticle formulations for systemic delivery. INGN 402 contains the p53 tumor suppressor and INGN 403 contains the mda-7 tumor suppressor, also known as interleukin 24 (IL-24). Early studies with these new nanoparticle drug candidates have demonstrated a good safety profile and promising anti-cancer activity in murine lung tumor models. Data from the mda-7 nanoparticle studies was published in *DNA and Cell Biology* and presented at the annual meetings of the ASGT and ASCO.

**INGN 007 (oncolytic viral therapy)**

We are developing INGN 007, a replication-competent viral therapy, which is also called an oncolytic virus, in which viruses bind directly to cancer cells, replicate in those cells, and cause those cancer cells to die. Pre-clinical testing in animal models indicates INGN 007 over-expresses a molecule that allows the vector to saturate the entire tumor. This testing has demonstrated that INGN 007 has a favorable safety profile and significantly inhibits tumor growth. Findings from this work to develop INGN 007 have been published in *Cancer Research* and were presented at a meeting of the ASCO. We are developing this replication-competent viral therapy through our strategic collaboration with VirRx. We have submitted to the FDA our Investigational New Drug application for INGN 007 in solid tumors.

**Other Research and Development Programs**

We are conducting a number of pre-clinical and research programs involving a variety of targeted therapies for the treatment of cancer. These programs involve molecules that act through diverse mechanisms to inhibit the growth of or kill cancer cells.

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We license from M. D. Anderson Cancer Center a group of molecules known as the 3p21.3 family. Pre-clinical research performed on these molecules by collaborators at The University of Texas Southwestern Medical Center and M. D. Anderson Cancer Center suggests that the 3p21.3 family plays a critical role in the suppression of tumor growth in lung and other cancers. This family of molecules includes the FUS-1 tumor suppressor we are testing as INGN 401 and the NPRL2 gene. We are working with M. D. Anderson Cancer Center to further evaluate other 3p21.3 family molecules as clinically relevant therapeutics.

The NPRL2 gene is believed to be important in the genesis of multiple types of cancer, including lung cancer and renal cell cancer. Preclinical data with the NPRL2 tumor suppressor gene demonstrated that systemic treatment using NPRL2 nanoparticles in combination with cisplatin resulted in a 90% inhibition of tumor growth in human lung cancer cells compared to control treatments. The ability to use a biomarker assay for NPRL2 to identify patients who might not experience significant benefit from treatment with cisplatin alone could represent an important advance in cancer treatment. Development of NPRL2 systemic nanoparticles may help patients whose tumors are resistant to cisplatin by re-sensitizing tumors to this commonly used therapy. Study results involving the NPRL2 treatment have been published in *Cancer Research*, a biomedical journal, and *Cancer Wise*, an electronic publication of M. D. Anderson Cancer Center.

We are evaluating additional molecules, including BAK, which hold promise as therapeutic candidates. BAK is a pro-apoptotic molecule that kills cancer cells. We are working with our collaborators at M. D. Anderson Cancer Center to identify and develop both viral and non-viral vectors containing this therapeutic molecule. We have exclusive rights to use the BAK molecule under a license with Genentech, Inc.

We believe our research and development expertise gained from our molecular therapies for cancer is also applicable to other diseases that, like cancer, result from cellular dysfunction and uncontrolled cell growth. As a result, we are conducting research in collaboration with medical institutions to understand the safety and effectiveness of our molecular therapy product candidates in the treatment of other diseases.

### **Introgen Enabling Technologies**

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

#### ***Nanoscale Viral Delivery Systems***

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

#### ***Nanoparticle Systemic Delivery Platform***

We hold an exclusive, worldwide license to a portfolio of patents from M. D. Anderson Cancer Center focused on the delivery of biologically active proteins, polypeptides and peptides using novel nanoparticle delivery complexes. These systemically-delivered nanoparticles are applicable to a wide variety of bioactive protein-derived molecules. This technology is directed to specially designed nanoparticles that carry and deliver therapeutic bioactive proteins, polypeptides and peptides to targeted cells, such as cancer cells.

These nanoparticle formulations have certain therapeutic advantages. While peptides alone may be rapidly removed from circulation, requiring frequent administration and high doses, our nanoparticle-polypeptide formulations can increase therapeutic activity and protect against rapid degradation normally associated with peptide

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therapy. Our peptide nanoparticles can include special targeting molecules to further enhance cellular uptake and to improve therapeutic efficacy. These formulations can be expected to have a systemic effect.

We have licensed and are developing a non-viral, nanoparticle delivery platform as a complementary delivery technology for certain types of cancers, or clinical indications, particularly those that require systemic administration. We are using this technology in INGN 401, INGN 402 and INGN 403.

Data published in *DNA and Cell Biology* highlight the potential utility of combining our nanoparticle delivery system with the mda-7 tumor suppressor for the treatment of lung cancer. This data demonstrate that combining this innovative delivery system with the mda-7 tumor suppressor results in potent anti-cancer effects and systemic tumor growth inhibition in an animal model of lung cancer. We believe combining potent anti-cancer tumor suppressors, such as mda-7 or p53, with our nanoparticle delivery system could allow development of clinical strategies to attack metastatic cancers.

**Replicating Viral Delivery Systems**

Through our strategic collaboration with VirRx, we are developing replication-competent viral therapies, also known as oncolytic viruses, in which viruses bind directly to cancer cells, replicate in those cells, and cause those cancer cells to die. This technology forms the basis for our INGN 007 product development. We anticipate pursuing clinical confirmation as to whether this self-amplifying delivery system can complement our existing adenoviral delivery system, which is replication disabled, in selected therapeutic scenarios, in applications beyond INGN 007.

**Additional Enabling Technologies**

Our research and licensing activities include a number of additional technologies that expand our capabilities. These activities include the following:

*Multi-Molecule Vector System.* This technology is designed to combine multiple therapeutic molecules with a vector. This approach has the potential for use with both viral and non-viral delivery systems to allow the activity of more than one molecular therapy at a time for disease treatment.

*Pro-Apoptotic Molecule Delivery System.* This technology is designed to allow the activity of pro-apoptotic, or apoptosis-inducing, molecules during treatment only, while temporarily suppressing the ability of the apoptotic molecule to kill producer cells during production. This system could facilitate more efficient production of pro-apoptotic agents.

*Tissue-Specific Targeting Systems.* This technology is designed to promote the activity of the therapeutic molecule in only those cells which have been affected by the disease being targeted. It is intended to be applied to both viral and non-viral vectors.

**Manufacturing and Process Development**

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

We own and operate state-of-the-art manufacturing facilities, including a commercial-scale, validated manufacturing facility designed to comply with the FDA's Current Good Manufacturing Practice requirements, commonly known as CGMP requirements. We have produced numerous batches of ADVEXIN therapy clinical material for use in our Phase 1, 2 and 3 clinical trials. The design and processes of the facility used for ADVEXIN therapy production have been reviewed with the FDA. We plan to use our facilities for the market launch of ADVEXIN therapy. We also use our facilities to produce INGN 241 and other investigative materials for use in clinical trials of those product candidates. From time to time, as requirements for our own products allow, we also manufacture pre-clinical and clinical materials for outside parties for a fee under contract services arrangements.

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As a result of an audit and inspection by a European Union Qualified Person (QP), we are certified with the Medicines and Healthcare Products Regulatory Agency (MHRA) that our facilities and production processes are compliant with European Good Manufacturing Practices for the manufacture and testing of ADVEXIN therapy. The MHRA is the competent authority in the UK and is a component of the EMEA.

**Business and Collaborative Arrangements**

***Alliance with Colgate-Palmolive Company***

In November 2005, we entered into an alliance agreement with Colgate-Palmolive to develop and potentially market oral healthcare products. In connection with the alliance agreement and pursuant to a common stock purchase agreement, Colgate-Palmolive purchased 3,610,760 shares of our common stock at a price of \$5.539 per share for a total of approximately \$20.0 million. Under the common stock purchase agreement, Colgate-Palmolive agreed to vote these shares and any other shares of our capital stock owned by it in favor of corporate actions approved by our Board of Directors. This voting agreement is subject to suspension or termination upon certain events specified in the common stock purchase agreement.

Pursuant to the alliance agreement, we are conducting research and development activities involving specialized formulations of our molecular therapies (such as p53, mda-7 and FUS-1) targeted at precancerous conditions of