INOVIO PHARMACEUTICALS, INC.
Form 10-K
March 16, 2011
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UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

x **ANNUAL REPORT PURSUANT TO SECTION 13 OR 15(d) OF THE SECURITIES EXCHANGE ACT OF 1934**
FOR THE FISCAL YEAR ENDED DECEMBER 31, 2010

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 NO. 001-14888

INOVIO PHARMACEUTICALS, INC.

(EXACT NAME OF REGISTRANT AS SPECIFIED IN ITS CHARTER)

DELAWARE	**33-0969592**
(State or other jurisdiction of	**(I.R.S. Employer**

incorporation or organization) **Identification No.)**

1787 SENTRY PARKWAY WEST

BUILDING 18, SUITE 400

BLUE BELL, PENNSYLVANIA **19422**
(Address of principal executive offices) **(Zip Code)**

REGISTRANT S TELEPHONE NUMBER, INCLUDING AREA CODE: (267) 440-4200

SECURITIES REGISTERED PURSUANT TO SECTION 12(B) OF THE ACT:

COMMON STOCK, $0.001 PAR VALUE	**NYSE Amex**
(Title of Class)	**(Name of Each Exchange on Which Registered)**

SECURITIES REGISTERED PURSUANT TO SECTION 12(G) OF THE ACT: NONE

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

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 x

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 x No ¨

Indicate by check mark whether the registrant has submitted electronically and posted on its corporate Web site, if any, every Interactive Data File required to be submitted and posted pursuant to Rule 405 of Regulation S-T during the preceding 12 months (or for such shorter period that the registrant was required to submit and post such files). 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 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. x

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 definitions of large accelerated filer, accelerated filer, and smaller reporting company in Rule 12b-2 of the Exchange Act. (Check one):

Large accelerated filer ¨	Accelerated filer ¨
Non-accelerated filer ¨ (Do not check if a smaller reporting company)	Smaller reporting company x

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

The aggregate market value of the voting and non-voting common equity (which consists solely of shares of Common Stock) held by non-affiliates of the Registrant as of June 30, 2010 was approximately $104,947,729 based on $1.02, the closing price on that date of the Registrant s Common Stock on the NYSE Amex.

The number of shares outstanding of the Registrant s Common Stock, $0.001 par value, was 127,254,031 as of February 24, 2011.

DOCUMENTS INCORPORATED BY REFERENCE

Portions of the registrant s definitive proxy statement to be filed with the Commission pursuant to Regulation 14A in connection with the registrant s 2011 Annual Meeting of Stockholders (the Proxy Statement) are incorporated by reference into Part III of this Report. Such Proxy Statement will be filed with the Commission not later than 120 days after the conclusion of the registrant s fiscal year ended December 31, 2010.

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Unless stated to the contrary, or unless the context otherwise requires, references to Inovio, the company, our company, our, or we in this rep include Inovio Pharmaceuticals, Inc. and subsidiaries.

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PART I

ITEM 1. BUSINESS

This Annual Report (including the following section regarding Management s Discussion and Analysis of Financial Condition and Results of Operations) contains forward-looking statements regarding our business, financial condition, results of operations and prospects. Words such as expects, anticipates, intends, plans, believes, seeks, estimates and similar expressions or variations of such words are intended to ident forward-looking statements, but are not the exclusive means of identifying forward-looking statements in this Annual Report. Additionally, statements concerning future matters, including statements regarding our business, our financial position, the research and development of our products and other statements regarding matters that are not historical are forward-looking statements.

Although forward-looking statements in this Annual Report reflect the good faith judgment of our management, such statements can only be based on facts and factors currently known by us. Consequently, forward-looking statements are inherently subject to risks and uncertainties and actual results and outcomes may differ materially from the results and outcomes discussed in or anticipated by the forward-looking statements. Factors that could cause or contribute to such differences in results and outcomes include without limitation those discussed under the heading Risk Factors below, as well as those discussed elsewhere in this Annual Report. Readers are urged not to place undue reliance on these forward-looking statements, which speak only as of the date of this Annual Report. We undertake no obligation to revise or update any forward-looking statements in order to reflect any event or circumstance that may arise after the date of this Annual Report. Readers are urged to carefully review and consider the various disclosures made in this Annual Report, which attempt to advise interested parties of the risks and factors that may affect our business, financial condition, results of operations and prospects.

Overview

We are engaged in the development of a new generation of vaccines, called DNA vaccines, focused on cancers and infectious diseases. Our SynCon technology enables the design of universal DNA-based vaccines capable of providing cross-protection against new, unmatched strains of pathogens such as influenza. Our electroporation DNA delivery technology uses brief, controlled electrical pulses to increase cellular DNA vaccine uptake. Initial human data has shown this method can safely and significantly increase gene expression and immune responses. Our clinical programs include cervical dysplasia/cancer (therapeutic), avian influenza (preventative), hepatitis C virus (HCV) and human immunodeficiency virus (HIV) vaccines. We are advancing preclinical research for a universal seasonal/pandemic influenza vaccine as well as other products including dengue fever and prostate cancer vaccines. Our partners and collaborators include University of Pennsylvania, Drexel University, National Microbiology Laboratory of the Public Health Agency of Canada, Program for Appropriate Technology in Health/Malaria Vaccine Initiative (PATH/ MVI), National Institute of Allergy and Infectious Diseases (NIAID), Merck, ChronTech, University of Southampton, United States Military HIV Research Program (USMHRP), U.S. Army Medical Research Institute of Infectious Diseases (USAMRIID) and HIV Vaccines Trial Network (HVTN).

Industry Background

Historical Importance of Vaccines

We believe vaccines have saved more lives and prevented more human suffering than any other human invention. As recently as a century ago, infectious diseases were the main cause of death worldwide, even in the most developed countries. For instance, the Spanish flu pandemic of 1918 killed more people than all the bullets and bombs did during the Great War (WWI). Today, there is a vast range of vaccines available to protect against more than two dozen infectious diseases, especially for children. Our society has found that the only way to control or even eliminate diseases is consistent, widespread use of vaccines. For most of the past 25 years the vaccine industry was dominated by a few large pharmaceutical companies. Only in recent years improved pricing and technology have helped turned the vaccine market into a growth business.

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Challenges Facing Vaccines

Despite the advances made to quality of life as a result of the development and use of vaccines over the past century, several significant challenges continue to exist. The technical limitations of conventional vaccine technology have constrained the development of effective vaccines for many diseases. Development of vaccines based on conventional methods requires significant infrastructure in research and manufacturing, and can be time consuming. Safety risks associated with conventional vaccine approaches may offset their potential benefits, as the conventional vaccines we have depended upon employ live or weakened viruses or different parts of a virus as vaccines. Further, conventional vaccines are still grown in eggs or cells and harvested over weeks of time with a very inefficient manufacturing process.

In addition, it is important to note a changing dynamic in the broader vaccine marketplace. Traditionally, vaccines have been predominantly focused on the pediatric market, intended to protect children from diseases that could cause them serious harm. Today, there is a growing interest in vaccines against diseases that may affect adolescents and adults, which include both sexually transmitted diseases and infections that strike opportunistically, such as during pregnancy, in immuno-compromised individuals, and in the geriatric population. Furthermore, there is encouraging data from and ongoing development of immunotherapies against cancers.

Inovio s Solution

We believe our DNA vaccine platform comprising our SynCon DNA vaccine constructs and proprietary electroporation delivery technology has the potential to develop and deliver a new generation of vaccines that are safer than traditional vaccines (our platform uses a non-live, non-replicating vaccine), have equivalent or stronger immune-stimulating power than traditional vaccines (live viruses being among the best approaches for developing strong immune responses), are showing the potential to be used against diseases for which conventional vaccine technology cannot be applied, and have added advantages with respect to development time and cost. Preclinical studies in animals have demonstrated the safety and potential efficacy of our approach.

The Next Generation of Vaccines: DNA Vaccines

DNA vaccines may be designed to prevent a disease (prophylactic vaccines) or treat an existing disease (therapeutic vaccines). A DNA vaccine consists of a DNA plasmid encoding a selected antigen(s) that is introduced into cells of humans or animals with the purpose of evoking an immune response to the encoded antigen. Information encoded in the DNA plasmid directs the cells to produce antigenic proteins that may then trigger the immune system to mount one or both of two responses: the production of antibodies, known as a humoral immune response, and/or the activation of T-cells, known as a cellular or cell-mediated immune response. These responses can neutralize or eliminate infectious agents (e.g. viruses, bacteria, and other microorganisms) or abnormal cells (e.g. malignant tumor cells). DNA vaccines have several advantages over traditional vaccines in that they are non-pathogenic (meaning they cannot cause the disease), may be effective against diseases which cannot be controlled by traditional vaccines, and are relatively fast, easy and inexpensive to design and produce. DNA vaccines are stable under normal environmental conditions for extended periods of time and do not require continuous refrigeration. Another potentially major advantage of DNA vaccines is their relatively short development cycle. For example, DNA vaccines against newly identified viral agents may be developed within weeks or months, as opposed to the years often required to develop a traditional vaccine candidate. DNA vaccines against cancer use a portion of the genetic code of a cancer antigen to cause a host to produce proteins of the antigen that may induce an immune response.

Inovio s SynCon DNA Vaccines

Our DNA vaccines are designed to generate specific antibody and/or T-cell responses. Our SynCon technology provides processes that employ bioinformatics, which combine, extensive genetic data and sophisticated algorithms. Our design process uses the genetic make-up of a common antigen(s) from multiple strains of a virus within a viral sub-type or taxonomic group (family) of HIV, HCV, human papillomavirus

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(HPV), influenza and other diseases to synthetically create a universal antigen that does not exist in nature. This unmatched antigen has been shown to nevertheless induce a powerful immune response in humans against that antigen, providing protection not only against individual strains of the same sub-type that were used to develop this synthetic antigen but to also provide protection against newly emergent strains not used in designing the vaccine. These SynCon DNA vaccine constructs may provide a solution to the genetic shift and drift that is typical of infectious diseases. SynCon immunogens are able to elicit broad, diverse immune responses, which in theory are important to protect against variable pathogens such as influenza, dengue, HCV and HIV.

More technically speaking, SynCon DNA vaccine antigens are designed by aligning numerous primary sequences and choosing DNA-based triplets for the most common or important amino acid at each site. These antigens are further optimized for codon usage, improved mRNA stability, and enhanced leader sequences for ribosome loading. The DNA inserts are therefore optimized at the genetic level to give them high expression capability in human cells.

We believe these design capabilities allow us to better target appropriate immune system mechanisms and produce a higher level of the coded antigen to enhance the overall ability of the DNA vaccine to induce the desired immune response.

Pre-clinical studies have shown that immunization of mice and non-human primates using SynCon DNA vaccine constructs elicited an immune response against multiple, unmatched strains within different sub-types of HIV, HCV, HPV, dengue, prostate cancer and influenza viruses. Vaccine candidates for all these diseases are being advanced through preclinical and clinical studies.

Electroporation DNA Delivery Technology

Our DNA vaccine candidates are being delivered into cells of the body using our highly efficient, proprietary electroporation (EP) DNA delivery technology, which uses the brief application of high-intensity, pulsed electric fields to create temporary and reversible permeability, or pores, in the cell membrane. Efficient delivery of DNA vaccines in humans has been thought to be the shortcoming of earlier generations of DNA vaccines. Most drugs and biologics must enter into a cell through a cell membrane in order to perform their intended function. However, gaining entry into a cell through the outer cell membrane can be a significant challenge. Electronic pulse-induced permeabilization of the cellular membrane, generally referred to as electroporation, has the observable effect that there is a less restricted exchange of molecules between the cell exterior and interior the benefit being that it allows and enhances the uptake of, for example, a biopharmaceutical agent previously injected into local tissue. The extent of membrane permeabilization depends upon various electrical, physical, chemical, and biological parameters.

The transient, reversible nature of this electrical permeabilization of membranes is the underlying basis of our electroporation systems, which are designed to harness this phenomenon by delivering controlled electrical pulses into tissue to facilitate the uptake of useful biopharmaceuticals. Our technology generates localized electric fields in targeted tissue to induce electroporation, which increases cellular uptake even for large molecules such as DNA. Most cell types and tissue can be successfully electroporated as long as applicators with the appropriate configuration of needle electrodes can be used to expose cells and tissues to the electric field.

Alternative delivery approaches based on the use of viruses and lipids are complex and expensive, and have in the past created concerns regarding safety and cause unwanted immune responses against themselves. We believe electroporation provides a relatively straightforward, cost effective method for delivering DNA into cells with high efficiency and minimal complications (as compared to viral vectors) and, importantly, inducing clinically relevant levels of gene expression.

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Products and Product Development

Independently and together with our licensees and collaborators, we are currently developing a number of DNA-based vaccines and therapeutics for the prevention or treatment of cancer and chronic infectious diseases. The table below summarizes progress in our independent, collaborative and out-licensed product development programs as of December 31, 2010.

		Pre-Clinical Studies		Development Status				
Product Area	**Product Target and Indication(s)**	**In Vitro**	**In Vivo**	**Phase I**	**Phase II**	**Phase III**	**Phase IV**	**Development Lead**
Cancer DNA Vaccines	hTERT-expressing cancers	X	X	IP				Merck
	Chronic and acute myeloid leukemia (CML/AML)	X	X	X	IP			Univ. of Southampton
	Cervical cancer (VGX-3100)	X	X	IP	*			Inovio
	Prostate cancer (INO-5150)	X	X					Inovio
Infectious Disease DNA Vaccines								
	Avian influenza (VGX-3400x)	X	X	IP				Inovio
	Universal influenza (INO-3510)	X	X					Inovio
	HCV	X	X	X				ChronTech
	HCV	X	X					Inovio/UPENN/Drexel
	HIV (preventative) (PENNVAX-B)(1)	X	X	X				HVTN
	HIV (preventative) (PENNVAX-B)	X	X	IP				HVTN
	HIV (therapeutic) (PENNVAX-B)	X	X	IP				UPENN
	HIV (preventative) (PENNVAX-G)	X	X	IP				US MHRP
	HIV (preventative) (PENNVAX-GP)	X	IP					NIH/NIAID
	Biodefense targets	X	X					USAMRIID
	Unspecified targets	X	IP					Inovio

X = Completed
IP = In Progress
* = We initiated Phase II clinical trial in March 2011.
(1) = Without electroporation

Cancer DNA Vaccines

Cancer vaccines are medicines that belong to a class of substances known as biological response modifiers. Biological response modifiers work by stimulating or restoring the immune system s ability to fight infections and disease. There are two broad types of cancer vaccines:

Preventative (or *prophylactic*) vaccines, which are intended to prevent cancer from developing in healthy people; and

Treatment (or *therapeutic*) vaccines, which are intended to treat an existing cancer by strengthening the body s natural defenses against the cancer.

Two types of cancer preventative vaccines are available in the United States, and one cancer treatment vaccine has recently become available.

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The United States Food and Drug Administration (the FDA) has approved two vaccines, Gardasil® and Cervarix® that protect against infection by the two types of HPV types 16 and 18 that cause approximately 70 percent of all cases of cervical cancer worldwide. At least 17 other types of HPV are responsible for the remaining 30 percent of cervical cancer cases. HPV types 16 and/or 18 also cause some vaginal, vulvar, anal, penile, and oropharyngeal cancers.

In addition, Gardasil® protects against infection by two additional HPV types, 6 and 11, which are responsible for about 90 percent of all cases of genital warts in males and females but do not cause cervical cancer.

Cervarix®, manufactured by GlaxoSmithKline, is a bivalent vaccine. It is composed of virus-like particles (VLPs) made with proteins from HPV types 16 and 18. In addition, there is some initial evidence that Cervarix® provides partial protection against a few additional HPV types that can cause cancer. However, more studies will be needed to understand the magnitude and impact of this effect. Cervarix® is approved for use in females ages 10 to 25 for the prevention of cervical cancer caused by HPV types 16 and 18.

Gardasil®, manufactured by Merck, is approved for use in females for the prevention of cervical cancer, and some vulvar and vaginal cancers, caused by HPV types 16 and 18 and for use in males and females for the prevention of genital warts caused by HPV types 6 and 11. The vaccine is approved for these uses in females and males ages 9 to 26.

The FDA has also approved a cancer preventative vaccine that protects against hepatitis B virus (HBV) infection. Chronic HBV infection can lead to liver cancer. The original HBV vaccine was approved in 1981, making it the first cancer preventative vaccine to be successfully developed and marketed. Today, most children in the United States are vaccinated against HBV shortly after birth.

In April 2010, the FDA approved the first cancer treatment vaccine. This vaccine, sipuleucel-T (Provenge®, manufactured by United States based Dendreon), is approved for use in some men with metastatic prostate cancer. It is designed to stimulate an immune response to prostatic acid phosphatase (PAP), an antigen present on most prostate cancers. In a clinical trial, sipuleucel-T increased the survival of men with a certain type of metastatic prostate cancer by about 4 months Thanks to the success of Provenge®, the development of immune cell-based cancer treatments is expected to gain momentum.

Therapeutic Cervical Cancer Vaccine VGX-3100

HPV is the causative agent responsible for most cases of cervical cancer. At any given time, approximately 10% of women worldwide are infected with HPV. While roughly 70% of HPV infections are cleared by the body on its own, persistent HPV can lead to dysplasia, or premalignant changes in cells, of the cervix. Researchers have estimated the global prevalence of clinically pre-cancerous HPV infections at between 28 and 40 million. These HPV infections may lead to pre-malignant cervical dysplasia; persistent dysplasias may then progress to cancer. Every year, 470,000 cases of cervical cancer are diagnosed worldwide, and about half of the afflicted women, primarily in developing countries, die.

Preventative vaccines such as Gardasil® and Cervarix® are playing an important role in limiting new HPV infections. However, preventative vaccines cannot provide protection for those already infected with HPV, which is a large population. In addition, not all girls and women eligible to be vaccinated are receiving these vaccines. There is no viable therapeutic vaccine or drug to fight HPV, nor dysplasias and cancers caused by HPV. Current ablative or surgical procedures to remove cervical dysplasias and cancers are unappealing due to the potential for disfigurement and the psychological stress with perceived negative impacts on childbirth.

HPV types 16 and 18 are responsible for about 70% of cervical cancer incidence. Inovio's VGX-3100 is designed to raise immune responses against the E6 and E7 genes common to HPV types 16 and 18 that are present in both pre-cancerous and cancerous cells transformed by these HPV types. E6 and E7 are oncogenes that

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play an integral role in transforming HPV-infected cells into cancerous cells. The goal is to stimulate the body s immune system to mount a T-cell response strong enough to cause the rejection of these infected or transformed cells from the body. The potential of such a vaccine would be to treat cervical cancers, pre-cancerous dysplasias (CINs), as well as persistent HPV infections and other cancers caused by these HPV types.

We recently completed enrollment of our Phase I study of our therapeutic cervical cancer vaccine (VGX-3100). VGX-3100 is a DNA vaccine targeting the E6 and E7 proteins of HPV types 16 and 18 and is delivered via in vivo electroporation. In September 2010, we presented top-line data showing achievement of best-in-class immune responses in our Phase I dose escalation study of VGX-3100. All dose groups developed significant antibody and T-cell immune responses. More notably, in the third and final dose group, five of six (83%) patients developed unprecedented T-cell responses not achieved by any other non-replicating vaccine platform in humans. Preliminary data from the trial indicated:

- Antigen-specific, dose-related T-cell responses across the three dose groups, averaging 1362 SFU per million cells in the high dose group responders;
- Strong antigen-specific antibody responses in all three dose groups;
- VGX-3100 delivered using Inovio s proprietary CELLECTRA® intramuscular electroporation delivery device was generally safe and well tolerated at all dose levels; and
- There were no vaccine-related serious adverse events. Reported adverse events and injection site reactions were mild to moderate and required no treatment.

This dose escalation study tested the safety and immunogenicity of VGX-3100 in women previously treated for moderate or severe cervical intraepithelial neoplasia (CIN 2/3), a high grade premalignant lesion that may lead to cervical cancer. The trial enrolled patients in three cohorts of six subjects each with DNA vaccine doses of 0.6 mg (0.3 mg each of two DNA plasmids), 2.0 mg, and 6.0 mg. Each subject received the respective dose at day 0, month 1 and month 3. All subjects in the first and second dose groups have completed the nine-month follow-up period. We expect that patients in the third dose group will complete their follow-up in the first quarter of 2011.

Immunological analyses of blood samples collected before and after vaccination indicate that antigen-specific immune responses were induced against the target proteins produced by Inovio s vaccine. Using a validated, standard ELISPOT assay, antigen-specific cytotoxic T-lymphocyte (CTL, or killer T-cell) responses were observed against all four antigens (E6 and E7 proteins for HPV types 16 and 18). In this third cohort, five of six vaccinated subjects (83%) developed significant CTL responses, with average responses of 1362 SFU per million cells after three immunizations. This was a 118% increase compared to the intermediate dose cohort average of 626 SFU per million cells (four responders out of six) and a 174% increase compared to the low dose cohort average of 497 SFU per million cells (four responders out of six).

Antibody responses to E6 and E7 antigens were also measured. Specific antibody responses to tumor antigens can function as an important surrogate potency marker for determining the immunogenicity of a vaccine, i.e. the ability of a vaccine to induce an immune response. Antibodies were generated against all four antigens, as tested by the enzyme-linked immunosorbent assay (ELISA). In the third cohort, antibody responses were observed in five of six subjects (83%).

Overall, in all three doses combined, 13 out of 18 vaccinated subjects (72%) developed significant CTL responses, with positive responses ranging from under 100 to over 5000 SFU per million cells. Fifteen out of 18 vaccinated subjects (83%) developed antibody responses to at least one antigen with most subjects developing responses to two or more antigens.

While the study targeted only safety and immunogenicity as endpoints and did not address clinical efficacy, several literature reports support the hypothesis that induction of tumor antigen specific T-cell responses is

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important in controlling cancer. Furthermore, there are examples of cancer vaccine candidates targeting the E6 and/or E7 proteins achieving significant clinical efficacy in patients with cervical or vulvar intraepithelial neoplasia, yet the CTL responses achieved in such studies were lower than those observed in the current VGX-3100 study.

Inovio is now planning a randomized, blinded Phase II study of VGX-3100 delivered using its CELLECTRA® intramuscular electroporation device in women with HPV Type 16 or 18 and diagnosed with, but not yet treated for, cervical intraepithelial neoplasia (CIN) 2/3. CIN 2/3s are precancerous lesions that may progress to cervical cancer. Patients in the control group will not receive the therapy. Inovio intends to initiate this clinical study in the first quarter of 2011.

Therapeutic Prostate Cancer Vaccine INO-5150

The development of a new treatment for prostate cancer would be a significant medical advance given that present treatment options (surgery, radiation and hormone deprivation), while somewhat effective, all carry deleterious side effects and often do not confer long-term cure. Across the United States, there were 218,000 new cases of prostate cancer and more than 32,000 deaths in 2010.

Inovio previously collaborated with the UK s University of Southampton and Institute of Cancer Research in a study evaluating a DNA vaccine for prostate cancer delivered using Inovio s electroporation delivery technology. The published data from this phase I/II study of a DNA vaccine encoding for human PSMA generated proof-of-concept levels of both antibody and T-cell immune responses in the 30 patients vaccinated in this study.

In January 2011, we announced the publication of a scientific paper in the journal *Human Vaccines* detailing potent immune responses in a preclinical study of Inovio s SynCon DNA vaccine for prostate cancer targeting two antigens, PSA and PSMA. While current prostate cancer therapies target single antigens, in this study Inovio tested the hypothesis in mice that a broader collection of antigens, administered with Inovio s electroporation-based delivery technology, would improve the breadth and effectiveness of a prostate cancer immunotherapy.

This study, conducted by Inovio scientists and their collaborators, is described in the published paper entitled, Co-delivery of PSA and PSMA DNA vaccines with electroporation induces potent immune responses. The SynCon DNA vaccine evaluated in this study was generated by the creation of PSA and PSMA synthetic consensus immunogens based on human and macaque sequences, which enabled the amino acid sequences of the antigens to differ slightly from the native protein. In humans, this difference may aid in the evasion of self-tolerance while still mounting an anti-tumor immune response. Mice received two immunizations of highly optimized DNA vaccine delivered by electroporation. Immunogenicity was evaluated one week after the second vaccination. The resultant data showed the induction of strong PSA and PSMA-specific cellular immune responses and also significant antigen specific seroconversion, illustrating that both humoral and cellular immune responses can be generated by this approach.

In this pre-clinical study of the first SynCon DNA vaccine against a cancer target, this dual-antigen immunotherapy generated strong antibody and T-cell immune responses. Taken together with the previous preclinical and clinical data, the current published results support the advancement of this product into a Phase I clinical study. Inovio is now advancing this program toward Phase I.

Southampton Collaboration: Leukemia

Leukemia is a malignant disease (cancer) of the bone marrow and blood characterized by the uncontrolled accumulation of blood cells. Leukemia accounts for at least 300,000 new cases and 222,000 deaths worldwide each year. This high ratio of deaths-to-cases (74%) reflects the poor prognosis of leukemia in many parts of the world, where the somewhat complex treatment regimes are not available. Approximately 45,000 new cases of leukemia were diagnosed in 2008 in the US, with 20,000 deaths. This represents 3% of all cancers in the United States, and 30.4% of all blood cancers. It is estimated that approximately $3 billion is spent in the United States each year to treat leukemia.

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There are five types of leukemia based on rate of development and types of blood cells affected. Two of these are being evaluated in the study discussed in this release: 1) Acute myeloid leukemia (AML), a cancer of the myeloid line of blood cells, is characterized by rapid growth of abnormal white blood cells that accumulate in the bone marrow and interfere with the production of normal blood cells. AML is the most common acute leukemia affecting adults and its incidence increases with age. Only about one-third of those between ages 18-60 who are diagnosed with AML can be cured. With conventional chemotherapy 70% of the patients in the group under study will relapse within 2 years and current therapy is devastating in older adults.

Chronic myeloid leukemia (CML) is a type of cancer that causes the body to produce large numbers of immature and mature white blood cells (myelocytes). Approximately 85% of patients with CML are in the chronic phase at the time of diagnosis. Ultimately, in the absence of curative treatment, the disease progresses to an accelerated phase where median survival is around 3-5 years. Chronic myeloid leukemia can occur at any age, but it more commonly affects middle-aged and older people.

In January 2011, we announced the regulatory approval of a Phase 2 clinical trial (WIN Trial) to treat leukemia utilizing Inovio s new ELGEN 1000 automated vaccine delivery device. This open-label, multi-center clinical trial being run by the University of Southampton is evaluating a DNA vaccine to treat chronic myeloid leukemia and acute myeloid leukemia. Financial support for the trial is being provided by the UK research charity Leukaemia and Lymphoma Research (LLR) and by the Efficacy and Mechanisms Evaluation (EME) programme (which is funded by the UK Medical Research Council and managed by the UK National Institute for Health Research). The DNA vaccine was developed at the University of Southampton with funding from LLR and the charity Cancer Research UK.

Wilms Tumor gene 1 (WT1) is highly associated with these types of cancer, which led the University of Southampton to design its leukemia DNA vaccine to target this antigen. Preclinical data from mice showed strong induction of antigen-specific CD8+ T cells and the ability to kill human tumor cells expressing WT1. There have been several prior clinical studies in humans using parts of the WT1 gene, notably as peptide vaccine candidates, demonstrating the production of modest levels of CD8+ T-cell responses and measurable clinical responses, although both effects were transient. This is the first study to combine DNA vaccination with electroporation delivery of WT1 antigens with the goal of stimulating high and durable levels of immune responses, which are considered critical for improving clinical outcomes.

The single dose level, Phase 2 study, called WT1 immunity via DNA fusion gene vaccination in haematological malignancies by intramuscular injection followed by intramuscular electroporation, led by Professor Ottensmeier and Dr. Katy Rezvani of Imperial College London and Hammersmith Hospital, London, is designed to recruit two patient groups. One group is planned to recruit up to 37 CML patients and the other up to 37 AML patients. All participants will initially receive six doses of two DNA vaccines (called p.DOM-WT1-37 and p.DOM-WT1-126) delivered at four week intervals. Vaccine responders may continue with booster vaccinations every three months out to 24 months. An additional 100-110 AML/CML patients will be enrolled across the two arms as non-vaccinated controls for comparison. The primary endpoints will be molecular response to a disease marker called BCR-ABL in CML patients and time to disease progression in AML patients. The study will also monitor WT1 transcript levels, immune responses to the WT1 antigen, time to progression and overall survival, and two-year survival in the AML group. The trial will take place at hospitals in Southampton, London and Exeter over the next two years. Regulatory approval to start this clinical study was provided by the UK Medicines and Healthcare Products Regulatory Authority (MHRA) and Gene Technology Advisory Committee (GTAC).

This is the first clinical trial using Inovio s new ELGEN-1000 automated device, which is based on its proprietary electroporation delivery platform. The device s needle electrodes automate vaccine delivery at the push of a button and co-locate subsequent controlled, millisecond electrical pulses that increase cell membrane permeability and dramatically improve cellular uptake of the vaccine. Inovio s electroporation systems have been shown to increase levels of gene expression (production of the antigen coded by the DNA vaccine) up to 1000-fold and increase immune responses to the antigen up to 100-fold.

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Merck Collaboration: Cancer Vaccines

In May 2004, we announced a collaboration and license with Merck for the development of certain DNA vaccines. Merck began patient enrollment for a second Phase I DNA vaccine cancer study in October 2008. This DNA vaccine encodes for hTERT, an antigen related to non-small cell lung, breast and prostate cancers. The vaccine is delivered using our electroporation DNA delivery technology. We have received milestone payments for our contribution to the collaboration with Merck, which has so far demonstrated the high level of gene delivery and expression that is thought to be necessary for the induction of a therapeutic immune response. Merck has funded all clinical development costs of the candidates under our collaboration and license agreement to date. Further development of products under the collaboration and license agreement may lead to additional milestone payments and royalties to us.

Infectious Disease DNA Vaccines

Therapeutic HCV Vaccine

Hepatitis is a disease characterized by inflammation of the liver. HCV is a major cause of acute hepatitis. HCV is spread primarily by direct contact with human blood, the major causes worldwide being the use of unscreened blood transfusions, and re-use of needles and syringes that have not been adequately sterilized. As many as 70% 90% of newly infected patients may progress to develop chronic infection. Of those with chronic liver disease, 5% 20% may develop cirrhosis. About 5% of infected persons may die from the consequences of long term infection (due to liver cancer or cirrhosis). Globally, an estimated 170 million people are chronically infected with HCV, which represents a reservoir sufficiently large for HCV to persist, and 3 to 4 million persons are newly infected each year. In the US, while new incidences of HCV have dropped dramatically, an estimated 4.1 million (1.6%) Americans have been infected with HCV, of whom 3.2 million are chronically infected. Persons with chronic HCV infection face an increased risk of developing hepatocellular cancer, a difficult-to-treat cancer with a poor prognosis.

In January 2006, we signed an agreement with Sweden-based ChronTech (formerly called Tripep) to co-develop a therapeutic vaccine for HCV using electroporation. The vaccine is based on ChronTech s proprietary HCV antigen construct and delivered to infected individuals using our MedPulser® DNA Delivery System.

In November 2009, we announced the completion of the Phase I clinical study with ChronTech of the ChronVac-C HCV DNA vaccine delivered using our electroporation technology. The study established the safety and tolerability of this therapy, with vaccine-induced immune responses and transient effects on the serum levels of HCV in these chronically infected patients providing proof-of-concept of DNA vaccines delivered using electroporation. We are preparing the next stage of the development plan for this program in collaboration with ChronTech.

In April 2010, we announced, along with our collaborators from Drexel University, Cheyney University, and the University of Pennsylvania, that we received a combined $2.8 million grant to further study and advance Inovio s proprietary DNA vaccine to treat HCV using Inovio s electroporation delivery system.

The grant is currently funding pre-clinical studies using an expanded set of SynCon immunogens to test the safety and effect on the immune system of our novel vaccines designed to treat persons who are chronically infected with HCV and have not responded to currently available therapies.

Preventative and Therapeutic HIV Vaccines

Since its discovery in 1981, AIDS has killed more than 25 million people. In 2005, the total number of HIV-infected people worldwide reached an estimated 38.6 million, with 4.1 million newly infected individuals. In 2005, the disease claimed approximately 3.1 million lives. UNAIDS estimates that 60,000 individuals were newly infected with HIV across the United States and Western Europe in 2005; bringing the number of HIV-infected people to approximately 1.75 million. Over half of these individuals live in the United States.

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In 2005, the HIV market accounted for 1.8% of global pharmaceutical sales and 17% of total anti-infective sales. Although this is relatively small compared to other therapeutic areas, the HIV market has experienced strong growth. It generated $7.4 billion of sales in 2005 and experienced a compound annual growth rate of 13.3% from 2001-2005, making it one of the fastest growing infectious disease markets.

Effective vaccines have been actively pursued for over 20 years, without success. HIV represents one of the most confounding targets in medicine. The virus high mutagenicity (ability to mutate) has made effective vaccine development very challenging. Its outer envelope, swathed in sugar molecules, is difficult to attack, and HIV strikes the very cells that the immune system launches to thwart such an infection. Although several drugs (antiretrovirals) are available to treat the patients once they are infected, vaccines are necessary to stop the spread of disease and perhaps reduce the need for antiretroviral treatment.

After many years of rapid development and introduction of new anti-retroviral drugs for treatment of HIV infection, the introduction of new drugs to the market for treatment of HIV infection appears to be waning. Available drugs, despite several limitations, have set a high standard that must be met in terms of efficacy. However, there is still a significant need for better HIV therapies and patents are beginning to expire on early HIV drugs. For example, zidovudine is already available as a generic drug and other early HIV drugs will soon face such generic competition. To maintain HIV-related revenues, as well as meet the needs of HIV-infected patients, pharmaceutical companies must develop new drugs with improved profiles, especially in terms of toxicity and increased barriers to development of viral resistance. As a result, the medical and commercial needs are fueling continued interest in the development of new nucleosides (NRTIs), non-NRTIs, and protease inhibitors (PI) for treatment of HIV infection.

Noting that many long-term survivors have high counts of killer CD8+ T cells, the HIV vaccine field has turned to stimulating the immune system to generate those cells. Recent HIV vaccine candidates adopted the use of an adenovirus or a common human cold virus that had been altered to prevent viral replication. These vaccines have proven to not be effective. We believe a different approach is needed to develop an effective vaccine for HIV.

Our HIV vaccines consist of candidates for HIV prevention as well as therapy or treatment. Furthermore, our vaccines are differentiated according to the targeted region of the world with the greatest prevalence of certain HIV subtypes. PENNVAX-B is designed to target HIV clade B (most commonly found in the United States, North America, Australia and the European Union (EU). PENNVAX-G is designed to target HIV clades A, C and D, which are more commonly found in Asia, Africa, Russia and South America.

Our PENNVAX -B vaccine (without electroporation delivery) Phase I trial (HVTN-070) was completed in 2009. This 120 patient study was sponsored by the National Institute of Allergy and Infectious Diseases (the NIAID) Division of AIDS (DAIDS) and was conducted by the HVTN to evaluate the vaccine s safety and immunogenicity in healthy volunteers. Following this study, in October 2009, along with the HVTN, we initiated a follow-on Phase I study (HVTN-080) of PENNVAX-B (with and without a cytokine) delivered with electroporation using the CELLECTRA® delivery device in healthy, uninfected individuals. Inovio previously reported data from non-human primates, demonstrating up to a 100-fold enhancement in immune responses resulting from the vaccine when delivered via in vivo electroporation compared to syringe injection without electroporation. This Phase I clinical study of PENNVAX-B (HVTN-080) vaccinated 48 healthy, HIV-negative volunteers to assess safety and levels of immune responses generated by Inovio s PENNVAX-B vaccine delivered with its CELLECTRA® electroporation device. PENNVAX-B is a SynCon DNA vaccine that targets HIV gag, pol, and env proteins. This randomized, double-blind, multi-center study is sponsored by the NIAID, an agency of the National Institutes of Health (the NIH), and conducted by the NIAID-funded HVTN, at several clinical sites.

Of the 48 total volunteers, eight subjects received a placebo, 10 subjects received a 1 mg dose of PENNVAX-B vaccine, and 30 subjects received a 1 mg dose of PENNVAX -B along with IL-12 DNA. All volunteers received vaccine or placebo administered with electroporation at months 0, 1, and 3. T-cell immune responses were detected using a validated flow cytometry-based intracellular cytokine staining (ICS) assay at the HVTN core immunology laboratory at the Fred Hutchinson Cancer Research Center in Seattle, WA.

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Preliminary data from the trial reported in November included safety data from all 48 trial participants and immunogenicity data from 38 out of 40 samples from vaccine recipients post-second-dose and from 31 out of 40 samples from vaccine recipients post-third-dose. The data indicate that antigen-specific T-cell responses were generated by the vaccine in a majority of subjects. Either CD4+ or CD8+ or both T-cell responses were observed against at least one of the vaccine antigens in 61% (23 out of 38) of evaluated subjects after two vaccinations. After three vaccinations, 84% (26 out of 31) of evaluated subjects had positive T-cell responses.

A second IND is now open, allowing testing of PENNVAX-B in a therapeutic setting. This Phase I trial (HIV-001) is being conducted in collaboration with the University of Pennsylvania and targets HIV-positive individuals. The electroporation-delivered PENNVAX-B arm of this trial started in 2011. If the Phase I studies are successful in demonstrating enhanced immunological responses to the HIV antigens, then we intend to partner with the HVTN or another governmental organization to further develop the HIV candidate vaccines through Phase II and Phase III clinical studies. It is anticipated that given the critical need for preventative and therapeutic vaccines for HIV, any commercialization will likely be through a big pharmaceutical company partner for the North American and EU markets and a world health agency for the developing world markets.

In September 2010, the United States Military HIV Research Program (MHRP) initiated a Phase I trial (RV262) using one of our prophylactic HIV vaccines in a prime-boost strategy. This program was developed to protect against diverse subtypes of HIV-1 prevalent in North America, Europe, Africa, and South America. The study is being conducted by the United States MHRP through its clinical research network in the US, East Africa and Thailand. This clinical trial was designed to test a unique prime-boost preventative HIV vaccination strategy aimed at global coverage. The prime is a plasmid DNA vaccine, PENNVAX-G, and the boost is a virus vector vaccine, Modified Vaccinia Ankara-Chiang Mai Double Recombinant (MVA-CMDR). Together, the vaccines are designed to deliver a diverse mixture of antigens for HIV-1 subtypes A, B, C, D and E. The study will test PENNVAX-G delivered with electroporation in conjunction with a modified vaccinia Ankara- Chiang Mai double recombinant boost. The NIAID is sponsoring the study, which we expect will enroll 92 total participants and is designed to assess safety and immune responses.

Due to its prevalence and global health importance, there is a large amount of funding available through various governmental and non-governmental organizations. Most notably, the NIH awarded us a contract to develop a preventative HIV DNA vaccine candidate in conjunction with electroporation technology for intradermal delivery of DNA vaccines. The contract was awarded under the NIAID s HIV Vaccine Design and Development Teams program and brings together HIV vaccine experts from the University of Pennsylvania School of Medicine and our company. The contract provides up to $24.6 million of funding over seven years, including a five-year base period and follow-on option years. The program is focusing on the vaccine candidate, PENNVAX-GP, which was developed in the laboratory of DNA vaccines pioneer Professor David B. Weiner at the University of Pennsylvania School of Medicine and licensed to us. The DNA-based vaccine will be delivered using our novel intradermal electroporation technology. This program expands our portfolio of candidate HIV vaccines. The funding and development program covers preclinical optimization, immunogenicity and challenge studies in animal models, IND-enabling toxicology studies, cGMP (current good manufacturing practices) manufacturing of all components of the DNA vaccine and CELLECTRA® device, and the conduct of a Phase I human clinical trial. cGMP manufacture of the PENNVAX-GP constructs to support clinical trials will be conducted at the manufacturing facility of our affiliate, VGX International, Inc. (VGX Int l).

HIV remains a challenging and tremendously important area of medical research, and we value the NIH s support to further evaluate the immunogenicity and efficacy of our electroporation delivery system and novel preventative HIV vaccine candidate.

Avian Influenza (H5N1) Vaccine VGX-3400x

Influenza is one of the most communicable diseases and it typically affects children and the elderly most severely. Complications from influenza cause more than 200,000 hospitalizations and lead to approximately

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36,000 deaths each year in the United States alone, according to the Centers for Disease Control. The world is annually subjected to two influenza sessions (one per hemisphere), between three and five million cases of severe illness, and up to 500,000 deaths. A pandemic occurs every ten to twenty years, which infects a large proportion of the world s population and can kill tens of millions of people as the Spanish Flu did in just two years (50-100 million deaths during 1918-1919).

New influenza viruses are constantly produced by mutation or reassortment, and can develop resistance to standard antiviral drugs. H5N1 has been spreading from Asia despite the belief that it was under control immediately after outbreaks there in 2004. In 2005, there were reports of H5N1 in wild birds in Europe. In 2006, there were reports of a H5N1 strain in wild birds and poultry in Africa and the Near East. According to the World Health Organization, the H5N1 bird flu has infected 467 people in 15 countries since 2003, with 282 deaths (60% death rate). While H5N1 has never been passed person-to-person and has not spread widely, one concern is the potential for the lethal H5N1 to reassort with another of the influenza sub-types that have been prone to spread more rapidly in humans, possibly creating a more dangerous influenza strain. Through 2006, over 140 million birds have been killed and over $10 billion has been spent to try to contain H5N1 avian influenza.

In pre-clinical studies, vaccination with VGX-3400 generated broadly protective levels of hemaglutination inhibition titers in 100% of the immunized animals in five separate animal models mice, ferrets, rabbits, pigs, and rhesus monkeys. Vaccination with VGX-3400x also protected animals from an unmatched, lethal H5N1 virus challenge in mouse, ferret, and monkey models. VGX-3400x also induced significant levels of antigen-specific CD8+ killer T cell responses.

In June 2010, we initiated our United States Phase I clinical trial to evaluate our SynCon H5N1 (avian) influenza DNA vaccine, VGX-3400X. This H5N1 vaccine study represents the first step in demonstrating Inovio s novel universal influenza vaccine approach, which aims to bypass the current requirement for annual strain and subtype-specific influenza vaccines by developing a single vaccine to potentially protect against all strains within multiple targeted sub-types, such as H5N1 and H1N1, posing risk to humans.

This dose escalation study is designed to test the safety and immunogenicity of VGX-3400x. VGX-3400x consists of three distinct DNA plasmids containing a universal consensus hemaglutinin (HA) antigen derived from different H5N1 flu viruses; a universal consensus neuraminidase (NA) antigen encompassing different N1 subtypes such as H5N1 and H1N1; and a universal consensus nucleoprotein (NP) fused to a small portion of the m2 protein (m2E), both also encompassing N1-based viruses. We expect the clinical trial to be conducted at two sites in the United States. Thirty healthy subjects will be enrolled in three dose groups of 0.2 mg, 0.67 mg, and 2.0 mg of each plasmid delivered via Inovio s proprietary electroporation technology. The primary objectives are to assess safety and tolerability. The secondary objective is to measure antigen-specific antibody and cellular immune responses, in particular hemaglutination inhibition (HI) responses, i.e. a measure of protection, against multiple strains of H5N1 influenza.

In March 2010, we announced that VGX received approval in Korea to begin a Phase I clinical trial in healthy volunteers for our SynCon preventative DNA vaccine (VGX-3400) targeting H5N1 avian influenza. We are co-developing VGX-3400x with Korea-based VGX Int l. We anticipate that the 30-subject 3-dose Phase I study will be conducted in multiple clinical research sites in Korea and, using a similar study design, evaluate three dose levels of the vaccine for safety and immunogenicity.

The results from both of these intramuscular (IM) EP delivered vaccine studies will be utilized in support of the intradermal (ID) EP delivered INO-3510 universal flu vaccine program.

Although a number of companies have well-developed avian influenza programs and lead vaccine candidates have entered into national stockpiles (US and EU), we believe there exists a need for new antigen-sparing, rapidly adaptable and easily scalable technologies to prepare for the as yet unknown target presented by the next form of avian influenza. Our SynCon technology provides protection from known avian influenza viruses (in animal studies) and has also shown the ability to protect agains