INOVIO BIOMEDICAL CORP
Form 10-K
March 31, 2009

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UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 10-K

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

FOR THE FISCAL YEAR ENDED DECEMBER 31, 2008

OR

o **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 BIOMEDICAL CORPORATION

(EXACT NAME OF REGISTRANT AS SPECIFIED IN ITS CHARTER)

DELAWARE	**33-0969592**
(State or other jurisdiction of incorporation or organization)	(I.R.S. Employer Identification No.)
11494 SORRENTO VALLEY ROAD SAN DIEGO, CALIFORNIA	**92121-1318**
(Address of principal executive offices)	(Zip Code)

REGISTRANT'S TELEPHONE NUMBER, INCLUDING AREA CODE: **(858) 597-6006**

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 o No ý

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 o No ý

Indicate by check mark whether the Company (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 ý No o

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. ý

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 o	Accelerated filer o	Non-accelerated filer o (Do not check if a smaller reporting company)	Smaller reporting company ý

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

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, 2008 was approximately $47,498,118 based on $1.08, 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 44,041,800 as of March 16, 2009.

DOCUMENTS INCORPORATED BY REFERENCE

None.

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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 report include Inovio Biomedical Corporation and subsidiaries.

FORWARD-LOOKING STATEMENTS

This annual report contains forward-looking statements within the meaning of the Private Securities Litigation Reform Act of 1995, including statements with regards to our revenue, spending, cash flow, products, actions, intentions, plans, strategies and objectives. These statements are not based on historical facts or of current conditions. All such forward-looking statements are inherently uncertain. We have based those forward-looking statements on, among other things, projections and estimates regarding the economy in general, the biomedical industry and other factors that impact our results of operations and financial condition. Forward-looking statements include, without limitation, any statement that may predict, forecast, indicate or simply state future results, performance or achievements, and may contain the words "believe," "anticipate," "expect," "estimate," "intend," "plan," "project," "will be," "will continue," "will result," "could," "may," "might," "should" or any variations of such words with similar meanings, including the negatives of such words. Any such statements are subject to risks and uncertainties that could cause our actual results to differ materially from those which are management's current expectations or forecasts. Such information is subject to the risk that such expectations or forecasts, or the assumptions underlying such expectations or forecasts, become inaccurate and there can be no assurance that the forward-looking information in this report will in fact transpire or prove to be accurate. All subsequent written and oral forward looking statements attributable to us or persons acting on our behalf are expressly qualified in their entirety by this introduction.

Our forward-looking statements involve known and unknown risks, uncertainties and other factors that may cause our actual results, levels of activity, performance or achievements to be materially different from any results, levels of activity, performance or achievements expressed or implied by any forward-looking statements. Certain of these risks, uncertainties and other factors are discussed in Item 1A "Risk Factors" and elsewhere in this report. We operate in a very competitive and rapidly changing environment. New risk factors emerge from time to time and we cannot predict all such risk factors, nor can we assess the impact of all such risk factors on our business or the extent to which any factor, or combination of factors, may cause actual results to differ materially from those contained in any forward looking statements. Given these risks and uncertainties, investors should not place undue reliance on forward-looking statements which reflect management's view only as of the date of this report, as a prediction of actual results. We undertake no obligation to amend this report or revise publicly these forward-looking statements (other than pursuant to requirements imposed on registrants pursuant to Item 1A under Part II of Form 10-Q) to reflect subsequent events or circumstances. Readers should also carefully review the risk factors described in other documents we file with the Securities and Exchange Commission, or SEC, particularly our quarterly reports on Form 10-Q, and the cautionary statements contained in our press releases from time-to-time which may contain forward-looking information.

Investors should also be aware that while we do, from time to time, communicate with securities analysts, we do not disclose any material non-public information or other confidential commercial information to them. Accordingly, individuals should not assume that we agree with any statement or report issued by any analyst, regardless of the content of the report. Thus, to the extent that reports issued by securities analysts contain any projections, forecasts or opinions, such reports are not our responsibility.

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PART I

ITEM 1. BUSINESS

Overview

Inovio Biomedical Corporation, or "Inovio," a Delaware corporation, organized in 2001, is a San Diego-based biomedical company focused on the development of next-generation vaccines to prevent or treat cancers and chronic infectious diseases. Such vaccines, which could potentially protect millions of people from debilitation or death from diseases without adequate treatments, may represent multi-billion dollar market opportunities. Historically, successful development of this new generation of vaccines DNA vaccines has been hindered by the lack of safe, efficient and cost effective DNA delivery methods capable of enabling their potency. However, Inovio's electroporation-based DNA delivery technology has shown potential in pre-clinical and clinical studies to play a pivotal role in facilitating delivery and enhancing the potency of preventive and therapeutic vaccines.

Inovio is a leader in developing DNA delivery solutions based on electroporation, which uses brief, controlled electrical pulses to create temporary pores in cell membranes and enable increased cellular uptake of a useful biopharmaceutical. Once the DNA vaccine enters a cell, it can then "express" the proteins it was encoded to produce. These proteins, or antigens, are designed to be uniquely associated with a targeted cancer or infectious disease, and may then stimulate a more powerful immune response if the immune system encounters the targeted disease at a subsequent time.

Inovio's business strategy to realize value for the company and its stockholders is as follows:

First, Inovio has leveraged its patented technologies through licensing and collaborations, such as its licensing arrangements with Merck & Co., Inc., or "Merck," Wyeth Pharmaceuticals, or "Wyeth" and Vical Inc., or "Vical," among other research-driven biopharmaceutical companies as well as government and non-government agencies. Inovio is licensing the use of its electroporation-based DNA delivery systems for partners to use in conjunction with their proprietary DNA vaccines or DNA-based immunotherapies. These arrangements provide Inovio with some combination of upfront payments, development fees, milestone payments, royalties and a supply agreement. These partners are pursuing development of proprietary agents or conducting research using Inovio's technology. However, there is no assurance that these licensing partners will continue these electroporation-based activities. Currently, Merck has completed electroporation-based treatments in their initial Phase I cancer trial. Merck licensed from Inovio a second target in December of 2007 for which it has filed an IND. There is no assurance that Merck will continue to develop either program into a Phase II study. In addition, Wyeth continues to evaluate internal strategic options prior to initiating further development of electroporation-based infectious disease programs.

Second, Inovio is pursuing proprietary vaccine development or co-development, resulting in whole or partial ownership in promising vaccines to prevent or treat cancers and chronic infectious diseases.

Inovio's technology is protected by an extensive patent portfolio covering in vivo electroporation. Inovio's patent portfolio encompasses a range of apparatuses, methodologies, conditions, and applications including oncology, gene delivery, vascular, transdermal as well as ex vivo electroporation.

Inovio's Core Technology

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. In the 1970s it was discovered that the brief application of high-intensity, pulsed electric fields can create temporary and reversible permeability, or pores, in the cell membrane. This pulse-induced permeabilization of the cellular membrane is generally referred to as electroporation. One observable effect of cell membrane electroporation is less restricted exchange of molecules

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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 Inovio's electroporation instruments, which are designed to harness this phenomenon by delivering controlled electrical pulses into tissue to facilitate the uptake of useful biopharmaceuticals. Inovio's technology generates electric fields in target tissues 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.

DNA vaccines have potential as therapeutic agents for treating various diseases. One of the key obstacles to the successful development and commercialization of DNA vaccines has been the limitations associated with current delivery systems. Alternative approaches based on the use of viruses and lipids are complex and expensive, and have in the past created concerns regarding safety. Electroporation provides a 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.

Inovio has multiple systems designed to create different electroporation conditions for different applications. The current systems consist of two basic components: a pulse generator and an applicator that is inserted into selected tissue.

MedPulser® DNA Electroporation System

Inovio's MedPulser® DNA Electroporation System was designed to create conditions to deliver DNA into tumor cells that promote optimal responses to gene-based immunotherapeutic cytokines. The cytokine-encoding plasmid is first injected with a syringe/needle into the selected tumor. Using a remote control, the pulse generator is switched on. High-voltage electrical pulses are generated and delivered through an attached electrical cord into the injected tissue through an electrode-needle array on the applicator. The electrode-needle array consists of a total of six needle-electrodes. The needle-electrode arrays are available in different sizes and configurations to facilitate access to tumors of different sizes and in different locations.

MedPulser® DNA Delivery System

The MedPulser® DNA Delivery System (DDS) was developed to optimize the delivery of DNA into muscle cells. The modified system is similar to the MedPulser® Electroporation System. The primary differences are in the parameters of the electric pulses delivered by the generator and the needle- electrode configuration of the applicator. The pulse is designed specifically for DNA delivery with a lower strength electrical field of longer duration than for tumor electroporation. The applicator has a four needle-electrode array consisting of one set of opposite pairs. They are available in a range of configurations to meet the requirements of a variety of applications.

Elgen System

The Elgen® DNA Delivery System, Inovio's newest generation of electroporation systems, is designed primarily for muscle delivery. It consists of a computer-controlled, motorized two needle delivery device that injects DNA and delivers electroporation pulses through one pair of needles. An earlier prototype version of this experimental system is currently under evaluation in Inovio's clinical trial for a prostate cancer vaccine at the University of Southampton in the U.K.

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Choice of Tissue for DNA Delivery

Muscle Delivery

Inovio's proprietary electroporation method consists of a DNA delivery system designed to introduce a plasmid vector into muscle, skin or tumor tissue. The plasmid(s) may be encoded for therapeutic protein(s) for gene therapy, or antigens for immunization.

Skeletal muscle has been a core focus because it is mainly composed of large elongated cells with multiple nuclei. Muscle cells are non-dividing, hence long-term expression can be obtained without integration of the gene of interest into the genome. Muscle cells have been shown to have a capacity for secretion of proteins into the blood stream. Secreted therapeutic proteins may therefore act systemically and produce therapeutic effects in distant tissues of the body. In this respect, the muscle functions as a factory for the production of the biopharmaceutical needed by the body. It is envisioned that delivery of DNA by electroporation to muscle cells will circumvent the costly and complicated production procedures of viral gene delivery vectors, protein-based drugs, conventional vaccines and monoclonal antibodies. This approach may therefore provide long-term stable expression of a therapeutic protein or monoclonal antibody at a sustained level.

For vaccination the DNA cause muscle cells to produce antigenic proteins that the immune system will identify as foreign and against which it will mount an immune response. As with conventional vaccines, the immune system will then develop memory of this antigen (and related disease) for future reference. Intra muscular delivery by electroporation of DNA encoded antigens has been shown to induce both humoral (antibody) and cellular (T-cell) immune responses. Inovio is currently collaborating in three clinical programs (Merck, Tripep and the University of Southampton) related to DNA delivery to muscle for immunization.

Tumor Delivery

Inovio has an extensive intellectual property position relating to *in vivo* delivery of genes directly into tumor cells. Tumor cells can be readily transfected with genes encoding selected cytokines or potentially lethal proteins for the treatment of a variety of cancers. The goal of effective tumor delivery is the ultimate elimination of the transfected tumor, and Inovio has experienced very few concerns regarding the safety of the procedure in its trials to date. A Phase I/II clinical immunotherapy trial conducted by Vical was designed to deliver IL-2 directly to accessible melanoma lesions. In December 2008, Inovio announced final results of a similar clinical study conducted by Moffitt to deliver IL-12 directly to accessible melanoma lesions.

Skin Delivery

While Inovio has generated preclinical and preliminary clinical evidence that intramuscular electroporation-based DNA delivery will be effective for a number of vaccines, electroporation of the skin may also be a relevant route of administration. Skin or intradermal administration is important and is becoming an attractive site for immunization given its high density of antigen presenting cells (APCs). Unlike muscle, skin is the first line of defense against most pathogens and is therefore very rich in immune cells and molecules. Skin specifically contains certain cells that are known to help in generating a robust immune response. With intradermal administration of electroporation, Inovio may be able to demonstrate a comparable immune response to muscle delivery. Inovio will continue to invest research and patenting resources into developing a viable skin electroporation system for clinical evaluation.

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Applications of DNA Vaccine Technology

Inovio and its partners are developing DNA delivery technology for two broad applications:

Cancer

Cancer is a disease of uncontrolled cell growth. Although cancer has been a major focus of pharmaceutical companies for decades, cancer remains one of the leading causes of death in the United States. Traditionally, three approaches have been available for treatment of cancer: surgery, radiation therapy, and chemotherapy. When detected early and still confined to a single location, cancer may be cured by surgery or radiation therapy. However, neither surgery nor radiation therapy can cure cancer that has spread throughout the body. Although chemotherapy can sometimes effectively treat cancer that has spread throughout the body, a number of non-cancerous cells, such as bone marrow cells, are also highly susceptible to chemotherapy. As a result, these types of treatments cause significant side effects and morbidity. Finally, it is common to see cancer return after apparently successful treatment by each of these means. The limitations of current cancer treatments are clearly demonstrated by the mortality rate of this disease.

For many decades, it has been suggested that the immune system should also be able to recognize cancer cells as abnormal and destroy these cells. However, cancer cells have developed mechanisms that allow them to escape the surveillance of the immune system. Immunotherapy, a process which uses the patient's own immune system to treat cancer, may have advantages over surgery, radiation therapy, and chemotherapy. Many cancers appear to have developed the ability to "hide" from the immune system. A treatment that can augment the immune response against tumor cells by making the cancer more "visible" to the immune system would likely represent a significant improvement in cancer therapy. Immune- enhancing proteins such as IL-2 and IL-12, used by partners in Phase I/II trials, have shown encouraging results. There is also a need to stimulate a stronger cellular immune response (i.e. generating T-cells) to specifically attack cancerous cells. This requires the use of technology such as DNA vaccines.

Electroporation offers effective delivery of DNA and may help Inovio develop novel cancer therapies. Inovio's current clinical-stage approaches consist of directly injecting tumors with certain plasmids followed by intratumoral electroporation as well as directly delivering certain plasmids into muscle followed by intramuscular electroporation. Upon uptake into cells, the plasmid directs the production of the encoded immunostimulatory proteins. The convenience and ability to repeat administration may offer advantages over current modalities of therapy. In addition, cancer therapies using non-viral DNA delivery may offer an added margin of safety compared with viral-based delivery, as no viral DNA/RNA or viral particles are contained in the formulation. Studies in animals have demonstrated the safety and potential efficacy of electroporation-based delivery. Subsequently, in human studies, a very low incidence of treatment- related serious adverse events has been observed.

In addition to immunotherapy approaches, numerous cancer antigens have been identified over the past few decades and better identification tools are under development by others. Inovio will continue to evaluate opportunities to acquire or partner cancer antigens that may be useful for large market cancers such as breast, lung and prostate.

Infectious Diseases

DNA vaccines for infectious diseases use portions of the genetic code of a pathogen to cause the host to produce proteins of the pathogen that may induce an immune response. Compared with conventional vaccines that use live, weakened, or dead pathogens to produce an immune response, this method potentially offers superior safety and ease of manufacturing, as well as convenient storage and handling characteristics. DNA vaccines have the potential to induce potent T-cell responses against target pathogens as well as trigger production of antibodies. Over the past decade, many scientific

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publications have documented the effectiveness of DNA vaccines in contributing to immune responses in dozens of species, including non-human primates and humans. Since electroporation can increase uptake of DNA into cells, it may consequently increase the potency of DNA vaccines. Increased T-cell responses and antibody production when DNA vaccines are delivered using electroporation has been demonstrated in a large number of species including non human primates.

Vaccines are generally recognized as the most cost-effective approach for infectious disease healthcare. However, the technical limitations of conventional vaccine approaches have constrained the development of effective vaccines for many diseases. Development of vaccines based on conventional methods requires significant infrastructure in research and manufacturing. In addition, the safety risks associated with certain conventional vaccine approaches may offset their potential benefits. Inovio believes its potential vaccine products may be simpler to manufacture than vaccines made using live viruses or protein subunit approaches, including those involving mammalian, avian or insect cells, or egg-based culture procedures. In addition, Inovio's DNA delivery technologies may accelerate certain aspects of vaccine product development such as non-clinical evaluation and manufacturing.

Similar to the requirements for fighting cancer, it is apparent that an effective approach for addressing chronic infections, which are also deadly and debilitating, requires the ability to generate a strong cellular immune response. This new generation of vaccines DNA vaccines is showing this capability. In addition to the targets already partnered, Inovio has been evaluating other potential disease targets in its internal development program.

Business Strategy

Inovio's objective is to be a biomedical company focused on developing and commercializing products that address significant unmet medical needs and, as a result, improve patients' quality of life. To achieve this objective, Inovio's business strategy currently includes the following key elements.

Therapeutic Drug and DNA Delivery

Inovio develops equipment designed to enable the use of electroporation to achieve efficient and cost-effective delivery into patients of DNA vaccines targeting a variety of illnesses. Although there are many diseases for which improved drug or DNA delivery is important, Inovio believes that its greatest opportunities lie in applying electroporation to DNA-based therapies (including immunotherapy) in the areas of cancer and chronic infectious diseases.

Advancing Inovio's Product Pipeline

The strategy to advance Inovio's product pipeline has two key components: Inovio has leveraged its patented technologies through licensing arrangements with companies such as Merck, Wyeth and Vical, among other research-driven biopharmaceutical companies, as well as collaborations with government and non-government agencies. These partners are pursuing development of proprietary agents or conducting research using Inovio's electroporation-based DNA delivery systems. Resources used to support Inovio's partners in these efforts are funded by its partners. In addition, these arrangements provide Inovio with some combination of upfront payments, development fees, milestone payments, royalties and a supply agreement.

In addition to expanding and providing electroporation delivery expertise, Inovio is directing resources to proprietary vaccine development or co-development, resulting in whole or partial ownership in DNA vaccine candidates. Inovio is focusing on the development of DNA-based therapies in the areas of cancer and chronic infectious diseases. The selection of targets for Inovio's independent or co-development programs is driven by four key criteria: complexity of the product development program, competition, cost of development and commercial opportunities. Inovio intends to retain significant participation in product development and commercialization of any DNA vaccines and

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therapeutics in pre-clinical and human trials that receive regulatory approval, although it may choose to secure additional partnerships to accelerate product development and commercialization. Inovio currently has a collaborative commercialization agreement with Tripep AB to co-develop a novel DNA hepatitis C virus (HCV) therapeutic vaccine.

Expand Market Opportunity

Inovio is continually evaluating and implementing opportunities to enhance its core technologies and assessing other DNA delivery technologies. Inovio is developing future product candidates based on these technologies through pre-clinical and clinical testing to determine their safety and efficacy. Inovio also seeks to develop additional applications for its technologies by testing new approaches to disease control or prevention. These efforts could lead to further independent product development or licensing opportunities. In addition, Inovio continually evaluates compatible technologies or products that may be of potential interest for in-licensing or acquisition.

Expand the Application of Inovio's Technologies and Enable Product Development Through Strategic Collaborations

In pre-clinical trials and early clinical trials, Inovio's technology has enabled high levels of DNA uptake and gene expression without significant acute side effects. Based on the results obtained, Inovio believes that its technology is well positioned and is as capable as competing technologies to meet the delivery requirements for DNA vaccines and immunotherapy. Inovio's strategy is to develop DNA vaccine and immunotherapy applications with major pharmaceutical, biotechnology and government agency partners wherever reasonable and/or possible to license its DNA delivery technology for specific genes or specific medical indications. In most partnering situations, Inovio provides proprietary instruments and expertise to optimize the delivery of DNA for particular applications and the partner company provides its proprietary gene, allowing Inovio access to complementary technologies or greater resources. Inovio believes that entering into selective collaborations as part of its product development programs can enhance the success of Inovio's product development and commercialization, diversify Inovio's product portfolio and enable Inovio to better manage its operating costs. Inovio's collaboration with partners allows pre-clinical research, clinical trials and mutually beneficial opportunities to expand Inovio's product pipeline, which may lead to the introduction of a new treatment and/or products in the marketplace at a rate and range which Inovio may not be able to support on its own. Additionally, such collaborations enable Inovio to leverage investment by its collaborators and reduce its net cash burn while retaining significant economic rights. Inovio's goal is to enter into additional agreements to license its electroporation technology for use in the delivery of DNA for specific targets.

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Products and Product Development

Together with Inovio's licensees and collaborators, Inovio is currently developing a number of DNA-based vaccines and therapeutics for the prevention or treatment of cancer and chronic infectious diseases. Inovio's current independent development focus is on these areas as well. The table below summarizes progress in Inovio's independent, collaborative and out-licensed product development programs as of December 5, 2008.

		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
DNA Delivery Immunotherapy	Malignant Melanoma	X	X	X				Moffitt/RMR
	Metastatic Melanoma	X	X	X *				Vical
DNA Delivery Tumor-associated antigen therapeutic vaccines	HER-2 and CEA-expressing cancers	X	X	IP				Merck
	Prostate Cancer	X	X	IP				Univ. of Southampton
	hTERT-expressing cancers	X	X	IP				Merck
	Unspecified Cancer	X	X					Inovio
DNA Delivery Infectious disease vaccine	HCV Vaccine	X	X	IP				Tripep/Inovio
	CMV Vaccine	X	X					Vical
	Unspecified Targets	X	X					Wyeth
	Biodefense Targets	X	IP					US Army
	HIV Vaccine	X	IP					National Cancer Institute
		X	IP					International AIDS Vaccine Initiative
	HIV Vaccine							
	Unspecified Targets	X	IP					Inovio

X = Completed

IP = In Progress

* = Final data pending

DNA Vaccines and Immunotherapies

The technical limitations of conventional vaccine approaches have constrained the development of effective vaccines for many diseases. In addition, the safety risks associated with certain conventional vaccine approaches may offset their potential benefits. In the broader vaccine marketplace, it is important to note a changing dynamic. 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 or in immuno-compromised individuals, including the geriatric population. Inovio believes its technologies, because of their potential safety and development time advantages, could be ideally suited for the development of this new generation of vaccines. Preclinical studies in animals have demonstrated the safety and potential efficacy of this approach.

DNA vaccines are intended to prevent a disease (prophylactic vaccines) or to treat an existing disease (therapeutic vaccines). A DNA vaccine consists of DNA plasmid molecules encoding a selected antigen or fragment of an antigen that are introduced into cells of humans or animals with the purpose of evoking an immune response to the encoded antigen. Information encoded in the vaccine DNA plasmid molecules

directs the cells to produce proteins that may then trigger the immune system to mount one or both of two responses: the production of antibodies, also known as humoral immune

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response, and/or the activation of T-cells and "killer cells," collectively termed cell-mediated immune response. These responses can neutralize or eliminate infectious agents (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 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 has acquired considerable expertise in the delivery and efficacy evaluation of DNA vaccines, both against infectious agents and complex diseases, such as cancer. In most cases Inovio has chosen skeletal muscle as the target tissue for vaccine delivery as this muscle is known to facilitate robust and long-lasting immune responses. However, skin is also an attractive target for DNA vaccination and Inovio has developed and patented technology for DNA delivery into skin cells as well.

Inovio is building a DNA franchise around the use of Inovio's proprietary electroporation technology together with gene-based treatments. Inovio's development efforts involve license agreements with Wyeth, Merck and Vical, in which these companies are supporting the development and registration of therapies using Inovio's devices. To date, most of Inovio's DNA vaccine development programs have been primarily initiated by corporate partners who sustain the majority of the development expenses and have the ability to conduct the commercialization activities.

Cancer: DNA-Based Immunotherapies

In December 2004, Inovio initiated a Phase I clinical trial sponsored by the H. Lee Moffitt Cancer Center using its MedPulser® DNA Electroporation System to deliver plasmid DNA coding for IL-12 to tumors with the aim of treating malignant melanoma. The study was designed to assess the use of electrical pulses generated by Inovio's proprietary electroporation technology to deliver into tumor cells a plasmid DNA encoding a cytokine, interleukin-12, which stimulates adaptive and innate immunity. In December, 2008, Inovio reported that final results of this trial was presented in the peer-reviewed *Journal of Clinical Oncology* in a paper prepared by Drs. Adil Daud, Richard Heller et al, titled, "Phase I Trial of Interleukin-12 Plasmid Electroporation in Patients With Metastatic Melanoma."

The paper concluded: "This first human trial, to our knowledge, of gene transfer utilizing in vivo DNA electroporation in metastatic melanoma showed that it is safe, effective, reproducible, and titratable." The findings showed not only regression of treated melanoma skin lesions, but also regression of distant untreated lesions, suggesting a systemic immune response to the localized treatment.

Highlights of the study results, as reported in the paper, include:

Twenty-four patients were enrolled in seven cohorts with escalating dose levels of plasmid IL-12 between December 2004 and February 2007. Locally injected plasmid IL-12 was followed by electroporation.

The experimental regimen was found to be safe and well tolerated, with minimal systemic toxicity. Because there was no dose-limiting toxicity in cohorts one through five, the experimental plan was amended to add two additional cohorts. Transient pain with the administration of the electrical pulses was the most frequent adverse event experienced by patients.

The study demonstrated significant and dose-dependent increases in intratumoral IL-12 protein expression and concomitant increases in intratumoral levels of IFN-γ.

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Sixty lesions (76%) were observed to have greater than 20% necrosis (death of tumor cells), with 19 (24%) having 50% - 99% necrosis, and 25 (32%) having 100% necrosis.

Ten subjects (53%) showed evidence of a systemic response (either stable disease or a complete response) during the study.

Injected lesions and distant non-injected lesions showed regression after treatment. Of 19 patients with additional sites of disease outside of the treated lesions, two (10%) with untreated distant lesions and no other systemic therapy showing complete regression of all metastases. These responses occurred over 6 - 18 months, with gradual volume loss occurring at sites distinct from the electroporated sites, arguing for immune system involvement. Neither of these patients has developed any new evidence of distant disease to date. Six of 19 (32%) showed disease stabilization lasting from 4 - 20 months.

Electroporated tumors demonstrated CD4+ and CD8+ lymphocytic infiltrate in the treated lesions.

In July 2005, Inovio announced, along with its partner, Vical, the initiation of a human Phase I clinical study of an investigational method of delivering plasmid DNA coding for interleukin-2 (IL-2), a potent immune system stimulant, for patients with recurrent metastatic melanoma. Intravenous delivery of IL-2 protein is already approved as a treatment for metastatic melanoma, but frequently causes severe systemic toxicities. The novel treatment approach being studied in this trial involves direct injection into a tumor lesion of plasmid DNA (pDNA) encoding IL-2, followed by electroporation in which local application of electrical pulses is intended to enhance the uptake of pDNA into tumor cells. The pDNA is designed to cause cells within the tumor to produce high levels of IL-2 protein locally and thereby stimulate the immune system to attack the tumor without the systemic toxicities associated with injected IL-2. Interim results on 19 patients from this trial were presented in June, 2007, and demonstrated that intratumoral delivery of pDNA encoding IL-2 into melanoma tumors, followed by electroporation, was administered safely following sedative premedication. No serious adverse events related to the study drug or to the administration procedure were reported and the treatment was well-tolerated. The majority of related adverse events were localized to the treatment site, with the most frequent being mild injection site pain. Individual tumor responses were seen in 12 of 39 (31%) evaluated tumors after injection of different escalating doses (0.5 to 5 mg per tumor). Treated tumors (7 of 18, or 38%) showed local responses more frequently than did untreated tumors (5 of 21, or 24%). No overall clinical responses by standard RECIST (Response Evaluation Criteria in Solid Tumors) criteria were observed among the 19 subjects evaluated following one or two cycles of treatment. Two subjects (11%) showed activity in distant, untreated tumors, including one subject showing shrinkage and disappearance of lung tumors. This trial has completed enrollment of 26 patients.

Cancer: DNA Vaccines

In April 2005, The University of Southampton initiated a U.K. Medicines and Healthcare products Regulatory Agency (MHRA) approved Phase I/II clinical trial undertaken in collaboration with Inovio. The study uses Inovio's electroporation technology to deliver a therapeutic plasmid-based DNA vaccine to skeletal muscle with the aim of treating recurrent prostate cancer. The trial, sponsored and led by the University of Southampton, is investigating whether the DNA vaccine, developed at the University of Southampton, can stimulate patients to develop immune responses against prostate cancer and whether use of Inovio's electroporation system enhances this response. In June, 2008, *Inovio* reported that Dr. Christian H. Ottensmeier, MD, PhD, Cancer Research UK Senior Clinical Research Fellow at the University of Southampton, presented updated interim data from this clinical study at the American Society of Gene Therapy 11th Annual meeting. The data reaffirmed that, post-treatment, this therapy has proven to be safe and well-tolerated. Additional data further validated higher levels of antibody

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and anti-DOM CD4 responses achieved in patients treated using electroporation. This academic study is a phase I/II study of 30 HLA A2+ patients with biochemical failure of prostate cancer. The study is testing a DNA fusion vaccine, developed in Southampton, encoding for an immunostimulant sequence from tetanus linked to a sequence from prostate specific membrane antigen (PSMA27). The study is also evaluating electroporation as a novel delivery strategy for DNA vaccines compared to DNA delivered without electroporation.

Patient enrollment for this study has been completed. Monitoring of antibody responses was completed for the 20 patients at the first and second dose levels. Monitoring of CD4 cellular immunity had been completed for the 10 patients at the lowest dose. These 10 patients had additionally been assessed for CD8 T-cell responses. Reported interim results included:

Vaccination with and without electroporation has been safe and well-tolerated.

14 of 20 patients developed increases in anti-DOM (the immunostimulant sequence from tetanus) antibody. Of these increased responses, 5 of 10 were in the arm not using electroporation; 9 of 10 were in the electroporation arm. Antibody responses were generally higher in patients treated using electroporation compared to those treated with the DNA vaccine alone (without electroporation).

In 9 of 10 patients in the low dose cohort, significant increases in CD4 responses were observed relative to pre-treatment. Of these increased responses, 4 of 5 were in the electroporation arm. Patients treated exclusively with electroporation produced a higher average CD4 response; patients initially treated without electroporation and later receiving a boost in conjunction with electroporation also displayed increased CD4 responses following the electroporation boost.

In the low dose cohort, the PSMA27 antigen induced CD8+ cytotoxic T-cells (measured by cultured IFNg ELISPOT) not detected before vaccination in 6 of 10 subjects.

In November 2005, Merck initiated a Phase I clinical trial of a DNA cancer vaccine based on Inovio's DNA gene delivery technology that uses pDNA encoding human epidermal growth factor receptor 2, or HER-2, and carcinoembryonic antigen, or CEA. As a result of Merck reaching this milestone, Inovio received a payment of $2.0 million. The Phase I trial is evaluating the safety, tolerability and immunogenicity of the vaccine.

In December 2007, Inovio received an additional $2.0 million milestone payment from Merck, resulting from the filing of a second Investigational New Drug (IND) application to the Food and Drug Administration ("FDA") by Merck for a DNA-based vaccine using Inovio's DNA delivery technology. The milestone relates to Inovio's collaboration and license with Merck initiated in May 2004 for the development of certain DNA vaccines. Further development of the product may lead to additional milestone payments and royalties to Inovio. Inovio received this milestone payment for its contribution to the collaboration, 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 these candidates to date.

As of October, 2008, Merck had begun to enroll patients for this study, which is using a DNA vaccine encoding for hTERT to target non-small cell lung and prostate cancers. The vaccine is delivered using Inovio's electroporation DNA delivery technology.

Inovio reported in September, 2008, that in a preclinical study of a proprietary DNA-based therapeutic vaccine, in mice with metastatic melanoma treated with a DNA vaccine via intramuscular delivery, six of eight (75%) were tumor-free at the conclusion of the study.

Numerous cancer antigens have been identified over the past few decades and better identification tools are under development by others. Inovio will continue to evaluate opportunities to acquire or partner cancer antigens that may be useful in large market cancers such as breast, lung and prostate.

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Infectious Diseases: DNA Vaccines

In January 2006, Inovio signed an agreement with Sweden-based Tripep to co-develop a therapeutic vaccine for hepatitis C virus (HCV) using electroporation. The vaccine is based on Tripep's proprietary HCV antigen construct and delivered to infected individuals using Inovio's MedPulser® DNA Delivery System. The study is being conducted at the Karolinska Institute's University Hospital in Sweden. The terms of the development agreement call for each party to fund a portion of the Phase I and subsequent Phase II trials and thereafter share profit according to their contribution. Inovio has 33% ownership in the overall product with the option to increase this to 50% after the completion of the Phase I/II trial.

In November, 2008, Inovio announced that Tripep had reported interim results indicating that in the third and highest dose cohort of the study, two of three subjects demonstrated reductions in viral load of 93% and 99.7%. This compares to previously reported middle dose cohort results demonstrating an 87% and 98% reduction in HCV in two of three subjects; no anti-viral effect was observed in the low dose cohort. No safety issues have been noted to date in the trial. These data suggest a potential dose response of the vaccine and support the inclusion of three additional subjects in the high dose cohort.

In November 2006, Inovio entered into a collaboration and license agreement with Wyeth to develop DNA vaccines against multiple infectious disease targets. For further discussion about this agreement, see "*Partnerships and Collaborations"* below. The selection of targets for its proprietary infectious disease program is driven by three key criteria: the complexity of the product development program, competition, and commercial opportunities.

Inovio reported in July, 2008, that in a preclinical study of a proprietary DNA-based therapeutic vaccine, 100% of immunized mice given a lethal challenge of highly pathogenic H5N1 influenza virus (A/Vietnam/1203/04) survived and showed only minor weight loss. The DNA vaccine design was based on a different influenza strain (H1N1) than the influenza strain used in the challenge, providing evidence that a universal vaccine based on conserved genes common to multiple strains of seasonal influenza and even potential pandemic influenza may have the possibility to provide widespread protection against such viruses.

DNA Vaccines for Biodefense

With the adoption of the Project Bioshield Act in 2004 by the U.S. government, there is an opportunity to secure development funding for proof-of-principle DNA vaccine studies for biowarfare pathogens. Inovio has been successful in securing funding from the U.S. government. Inovio believes DNA vaccines delivered with electroporation for bio-defense have the following advantages:

- establishment of a platform technology that can be readily adapted for new threats;
- ability to rapidly manufacture and scale-up vaccine candidates for newly identified pathogens;
- rapid induction of protective immune responses following vaccination; and
- long shelf life of products for stockpiling.

As resources obtained from government funding can be leveraged to enhance the development of technology in the area of cancer and chronic infectious disease, Inovio will continue to pursue opportunities in the area of biodefense. As an example of potential applications in the area of biodefense, one of Inovio's partners (RMR, LLC) is currently employing its skin electroporation technology in the pre-clinical development of an anthrax vaccine under a Department of Defense Small Business Innovation Research Program (SBIR) grant. Inovio currently has commercial rights to this skin electroporation system. The technology may also be useful with respect to targets such as the

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Lassa fever virus currently being studied by the U.S. Army in collaboration with Inovio (as further outlined under Partnerships and Collaborations below).

Gene Therapy

Over the past decade, classic gene therapy or treatment of inherited disorders has proven difficult. Electroporation of genes encoding therapeutic proteins has, however, demonstrated the potential to resolve these difficulties. In vivo production of proteins such as Factor IX for hemophilia and EPO for anemia represent large market opportunities. Pre-clinical studies for Inovio's partners have demonstrated multiple desirable characteristics of Inovio's approach, including:

Long term expression of the desired gene for convenient dosing;

Lack of immune responses to the plasmid vector;

Ability to achieve therapeutic levels of desired protein at a steady state; and

More natural production of the therapeutic protein than current recombinant proteins.

The major technical hurdle for use of Inovio's technology for classic gene therapy is the induction of an unwanted immune response to the transgene product due to the highly efficient delivery and expression seen with electroporation. As this problem may take significant resources to overcome, Inovio has decided not to focus on this market in the near term.

Animal Health/Veterinary

While Inovio is primarily focused on the use of Inovio's technology in the development of novel human therapeutics, it retains certain rights to veterinary applications and may seek to exploit these rights in the future.

Additional Applications of Inovio's DNA Delivery Technology

In addition to using Inovio's electroporation technology for drug and vaccine delivery, it can be used for research to validate new drug targets and to deliver molecules. Such use of Inovio's technology may facilitate transition into clinical development. Inovio continues to pursue, on a limited basis, research and opportunities in the areas of stem cells, ex vivo applications and RNAi.

Collaborations

In September 2008, Inovio announced it has received a contract for $933,000 from the Department of Defense (US Army) to continue research and development of DNA-based vaccines delivered via its proprietary electroporation system. The contract, titled "Design and Engineering of the Elgen Gene Delivery System for Screening and Validation of Vaccine Candidates of Military Relevance," will run through May 2010. This project is focused on identifying DNA vaccine candidates with the potential to provide rapid, robust immunity to protect against bio-warfare and bioterror attacks.

In November 2006, Inovio entered into a collaboration and license agreement with Wyeth for a worldwide non-exclusive license to Inovio's technology for certain infectious disease targets, for which Inovio received an upfront payment of $4.5 million. Inovio will also receive research support, annual maintenance fees, royalties on any net product sales and, contingent upon the achievement of clinical and regulatory milestones, payments of up to $60.0 million over the term of the agreement.

We may not receive any future payments from Wyeth and we believe Wyeth is evaluating internal strategic options prior to initiating further development of electroporation based infectious disease programs.

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In October 2006, Inovio announced that it acquired from Valentis, Inc. certain DNA delivery and expression assets, including Valentis' DNAvax® polymer delivery system and GeneSwitch® gene regulation technology.

In July 2006, Inovio announced it extended its license with RMR Technologies, LLC ("RMR") by exercising an existing option to license certain patented technology relating to the delivery of gene-based therapeutics into skin. This extends a long-standing relationship with the University of South Florida scientists and RMR founders Drs. Heller (now Executive Director, Frank Reidy Research Center for Bioelectrics, Old Dominion University), Jaroszeski, and Gilbert. This relationship dates back to the co-development of Inovio's MedPulser® Electroporation Instrument for treatment of solid tumors, including head and neck cancers. RMR is the collective effort of three scientists in collaboration with the University of South Florida and the H. Lee Moffitt Cancer Center and Research Institute. The license included other patents involving the delivery of genes or drugs via ex vivo, intratumoral, and intramuscular electroporation. Recent pre-clinical studies suggest that, for certain indications, needle-less skin electroporation of DNA plasmids encoding selected antigens may also be effective at inducing desired immune responses. The patented technology licensed from RMR covers various skin electroporation electrode designs and methods, including a needle-less design using a flexible material. RMR has agreed to collaborate in an effort to develop research prototypes into commercial grade electrodes for skin delivery as well as other novel forms of electroporation-assisted DNA delivery. Inovio has agreed to provide RMR with other development expertise pertinent to projects such as RMR's SBIR-funded pre-clinical study using RMR's proprietary dermal electrodes to deliver a DNA vaccine against anthrax. In connection with the acquisition of this exclusive license, Inovio issued 86,956 shares of Inovio common stock at a price of $2.30 per share, worth $200,000 on the date of issuance.

Inovio also licensed from RMR patents that claim the intratumoral delivery method used in the ongoing clinical trial at the Moffitt Cancer Center & Research Institute, which is delivering the gene encoding IL-12 directly to melanoma lesions. RMR, Inovio, the University of South Florida and Moffitt Cancer Center have been collaborating in the development of this novel therapy for melanoma for the past two years.

In May 2006, Inovio announced the acquisition, under a license with Sphergen SARL, of rights to several patent families relating to the use of electroporation technology. The rights Inovio licensed included two patents with broad claims regarding electroporation of nucleic acids in muscle and tumor tissue. This intellectual property acquisition enhanced the breadth of Inovio's patent portfolio directed to the use of electroporation technology to deliver therapeutic biopharmaceuticals. The license also includes grants of rights to know-how, future improvements, and provisions for exclusivity in applications to human medicine.

In January 2006, Inovio signed a collaborative agreement with Tripep to co-develop a therapeutic hepatitis C virus (HCV) DNA vaccine using electroporation. Under the terms of this agreement, Inovio pledged certain electroporation equipment toward an ongoing Phase I/II study of the proprietary Tripep vaccine in exchange for a minimum of 33% of the licensing revenues or commercial income that might be derived from the vaccine. Under the terms of the agreement, Tripep will only commercialize the electroporation-based vaccine with Inovio equipment. If Inovio decides not to continue to support the co-development, Inovio will retain a profit share of sub-licensing fees or commercial revenues going forward.

In May 2005, Inovio announced that Merck exercised an option for a non-exclusive license for an additional antigen to be used with Inovio's MedPulser® DNA Delivery System. This option exercise was provided for under the 2004 license and research collaboration agreement between Merck and Inovio, and brought the total number of antigens licensed by Merck to three. Inovio received an option fee for the additional target antigen. Under the terms of Inovio's licensing agreement with Merck,

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Inovio is eligible for milestone and royalty payments if certain development goals and commercialization of the device are achieved by Merck.

In April 2005, Inovio announced the initiation of a U.K. Medicines and Healthcare products Regulatory Agency (MHRA) approved Phase I/II clinical trial undertaken in collaboration with the University of Southampton. Inovio's electroporation technology is being used to deliver a therapeutic plasmid-based DNA vaccine to skeletal muscle with the aim of treating recurrent prostate cancer. The trial, sponsored and led by the University of Southampton, is investigating whether the DNA vaccine, developed at the University of Southampton, can stimulate patients to develop immune responses against prostate cancer and whether use of Inovio's electroporation system enhances this response.

