INOVIO PHARMACEUTICALS, INC.
Form 10-K
March 12, 2019

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, 2018

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 incorporation or organization)	(I.R.S. Employer Identification No.)
660 W. GERMANTOWN PIKE, SUITE 110 PLYMOUTH MEETING, PENNSYLVANIA	19462
(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	Nasdaq Global Select Market
(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 every Interactive Data File required to be submitted 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 such files). Yes x 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, a smaller reporting company, or emerging growth company. See definitions of "large accelerated filer," "accelerated filer," "smaller reporting company," and "emerging growth company" in Rule 12b-2 of the Exchange Act. (Check one):
Large accelerated filer ¨ Accelerated filer x

Non-accelerated filer ¨ Smaller reporting company ¨

Emerging growth company ¨

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act.

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, 2018 was approximately $335,998,116 based on $3.92, the closing price on that date of the Registrant's Common Stock on the Nasdaq Global Select Market.

The number of shares outstanding of the Registrant's Common Stock, $0.001 par value, was 97,636,364 as of March 8, 2019.

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 2019 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, 2018.

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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 Pharmaceuticals, Inc. and subsidiaries.

PART I

ITEM 1. BUSINESS

This Annual Report on Form 10-K (including the following section regarding Management's Discussion and Analysis of Financial Condition and Results of Operations), or this Annual Report, 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 identify 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.

This Annual Report includes trademarks and registered trademarks of Inovio Pharmaceuticals, Inc. Products or service names of other companies mentioned in this Annual Report may be trademarks or registered trademarks of their respective owners. References herein to "we," "our," "us," "Inovio" or the "Company" refer to Inovio Pharmaceuticals and its subsidiary.

Overview

We are a late-stage biotechnology company focused on the discovery, development and commercialization of DNA-based immunotherapies and vaccines that transform the treatment and prevention of cancers and infectious diseases. Our DNA-based immunotherapies and vaccines, in combination with our proprietary, efficacy-enabling delivery devices, are intended to generate robust immune responses, in particular functional CD8+ killer T cells and antibodies, to fight targeted diseases and conditions.

Our novel SynCon® immunotherapy design has shown the ability to help break the immune system's tolerance of cancerous cells. Our SynCon® product design approach is also intended to facilitate cross-strain protection against known and new unmatched strains of pathogens, such as influenza. Our CELLECTRA® delivery system facilitates optimized cellular uptake of the SynCon® immunotherapies, overcoming a key limitation of other DNA-based immunotherapies. Human data in clinical trials to date have shown a favorable safety profile of our SynCon® immunotherapies delivered using CELLECTRA® in over 6,000 administrations across almost 2,000 patients.

We or our collaborators are currently conducting or planning clinical studies of our proprietary SynCon® immunotherapies for HPV-caused pre-cancers, including cervical, vulvar, and anal dysplasia; HPV-caused cancers, including head & neck, cervical, anal, penile, vulvar, and vaginal; bladder cancer; glioblastoma multiforme, or GBM; hepatitis B virus; hepatitis C virus; HIV; Ebola; Middle East Respiratory Syndrome, or MERS; Lassa fever; and Zika virus.

Our corporate strategy is to advance, protect and exploit our differentiated immunotherapy platform. With our unique capabilities in terms of both design and development, we are progressing and validating an array of cancer and infectious disease immunotherapy and vaccine product candidates. We aim to advance product candidates through to commercialization and continue to leverage third-party resources through collaborations and partnerships, including product license agreements. Our partners and collaborators include AstraZeneca, Regeneron Pharmaceuticals, Inc., F. Hoffmann-La Roche AG/Genentech, Inc., ApolloBio Corporation, The Bill and Melinda Gates Foundation, The Wistar Institute, the University of Pennsylvania, The Parker Institute for Cancer Immunotherapy, Coalition for

Epidemic Preparedness Innovations (CEPI), Defense Advanced Research Projects Agency (DARPA), GeneOne Life Science, Inc., Plumbline Life Sciences, Inc., National Institutes of Health (NIH), HIV Vaccines Trial Network (HVTN), National Cancer Institute (NCI), United States Military HIV Research Program, Drexel University and Laval University.

Our Differentiated Technology Platform

We believe that stimulating the immune system specifically to treat or prevent cancers and infections is a compelling concept and that today the opportunity for immune activating technologies is promising, especially in light of notable technology advancements such as checkpoint inhibitors leading the way in oncology. Despite drug approvals in limited indications and promising results in clinical trials, there remains a significant need and opportunity for further advancements.

Our technology platform comprising our DNA-based SynCon® immunotherapy and CELLECTRA® delivery devices has versatile capabilities with a number of possible disease targets and product opportunities. The basic goal of our platform is to enable in vivo (in the body) generation of functional immune responses to achieve desired therapeutic and preventive outcomes. We have historically been primarily focused on in vivo production of disease-specific antigens directly in the body in order to stimulate prophylactic or therapeutic immune responses. More recently, we have explored an additional new application for the platform: in vivo generation of monoclonal antibodies to achieve preventive and therapeutic outcomes complementary to our antigen-generating immunotherapies.

The essence of our platform is that we encode a DNA plasmid (circular string of DNA) for an engineered and optimized genetic sequence of an antigen or monoclonal antibody specific to a targeted disease. We can combine multiple such plasmids into a "product," inject the plasmids into tissue of the body, and use CELLECTRA® devices to apply transient electrical energy to facilitate significant cellular uptake of the plasmids, which then enhances the ability of the intracellular machinery to temporarily produce the target antigen or monoclonal antibody. An antigen produced in this manner will then induce the immune system to generate polyclonal antibodies or T cells with the ability to perform their preventive or therapeutic functions. Similarly, DNA-encoded monoclonal antibodies (dMAbs™) generated in this manner can also trigger desired immune system functions.

With our core platform technologies, we have developed a pipeline of clinical-stage product candidates that have generated best-in-class in vivo immune responses, in particular CD8+ T cells that are fundamental in eliminating cancerous or infected cells. Our lead immunotherapy product candidate, VGX-3100, met all of its primary and secondary endpoints in a controlled Phase 2b clinical trial of patients with HPV-related cervical pre-cancer, achieving statistically significant and clinically relevant efficacy in association with robust T cell activation. This data was published in 2015 in the scientific journal The Lancet in a paper entitled, "Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomised, double-blind, placebo-controlled phase 2b trial."

These results were achieved without serious adverse events. The most common adverse event was temporary injection site pain and redness.

Our immunotherapies are non-live and non-replicating, and therefore do not cause the underlying disease. Compared to other technologies, our immunotherapies are designed to work more naturally with the immune system and within its controls to reduce or minimize the risk of unwanted inflammatory responses.

The results of our Phase 2b clinical trial of VGX-3100 suggest that our platform can be used to design and develop a number of cancer and infectious disease product candidates.

SynCon® Immunotherapies

Our SynCon® immunotherapies are designed to treat an existing disease (therapeutic) or prevent a disease (prophylactic) by activating and magnifying an immune response to one or more disease-specific antigens (proteins associated with a cancer or infectious disease that the body will recognize as foreign or not normal). Our product candidates are able to direct the patient's immune system to fight specific organisms or cells in a highly targeted and robust fashion, without the potential cost and quality control and manufacturing challenges of medicines involving ex vivo processes, such as T cells with chimeric antigen receptors, or CAR-Ts. We do this by introducing the genetic code for a target antigen into the cells of the body that will serve as a temporary antigen production facility.

Our immunotherapies consist of one or more DNA plasmids encoding one or more selected antigens. Our proprietary delivery technology enables significant uptake of the DNA plasmids by cells in localized tissue, which are typically muscle in the arm for immunotherapies or in the skin for vaccines, as described below.

After the DNA code for the targeted antigen(s) is introduced to cells, the cells' natural machinery for producing proteins temporarily produce the selected antigen(s) encoded by the DNA sequences. The antigenic proteins manufactured through this process are then presented to the immune system and trigger one or both of two arms of the

immune system:

- the production of preventive antibodies, known as a humoral immune response; and/or
- the activation of therapeutic CD8+ T cells, known as a cellular or cell-mediated immune response.

These responses then neutralize or eliminate infectious agents, such as viruses, bacteria, and other microorganisms, or abnormal cells, such as malignant tumor or infected cells. T cells can be immediately "trafficked" to parts of the body where cells are displaying the target antigen. Memory cells are also created for durable effects.

Our SynCon® immunotherapies are designed to generate antigen-specific antibody and T cell responses. First, we identify one or more antigens that we believe are the best targets to direct the immune system toward a particular cancer or infectious disease. We then apply our SynCon® design process, which uses the genetic make-up of the selected antigens from multiple variants of a cancer or strains of a virus.

For each antigen we synthetically create a new genetic sequence that represents a consensus of the slightly different DNA from multiple variants or strains of the targeted antigen. We can synthetically create a differentiated SynCon® variant to help the immune system better recognize a cancer self-antigen (a cell and antigen grown in the body) and "break the tolerance" of cancer cells in the body. In human clinical trials, we have generated immune responses with SynCon® immunotherapies that were not matched to different strains of an infectious disease, such as influenza or HIV, indicating that such immunotherapies may have more universal protective capabilities against unmatched strains of a circulating virus. As a result, these SynCon® constructs may provide a solution to broadly cover the genetic "shift" and "drift" that is typical of many infectious diseases. This new synthetically engineered sequence is similar to the originating sequences but does not match any. It does not exist in nature and is patentable.

The SynCon® sequence is inserted into a circular DNA plasmid with its own promoter. The plasmid is optimized at the DNA level for codon usage, improved mRNA stability, and provided with enhanced leader sequences for ribosome loading; it is optimized at the genetic level to enable high expression 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 immunotherapy to induce the desired immune response.

The plasmids are manufactured in a bacterial fermentation process using scalable technology. These DNA-based immunotherapies can be stable under normal environmental conditions for extended periods of time.

Our product development platform also allows for rapid design, pre-clinical testing, manufacturing and clinical development of our vaccine and immunotherapy product candidates. Speed is an important feature, particularly as it relates to developing a response to globally emerging infectious diseases. In 2016, we were the first entity able to advance a Zika vaccine into human clinical trials, just 4.5 months after World Health Organization, or WHO, declared the emerging Zika infections to be a Pandemic Health Emergency of International Concern. Previously, we led the development of the first MERS vaccine in human clinical trials. We believe that our development platform is well positioned to support global health agencies in order to develop preparedness countermeasures against bioterrorism and/or emerging pandemic agents.

CELLECTRA® Delivery Technology

Despite how compelling the idea of delivering DNA encoding an antigen has been, delivering the DNA or nucleic acids directly into a cell through the cell's protective membrane has been a significant challenge in the broad field of DNA and RNA vaccines. Our immunotherapies are delivered into cells of the body in a small local area of tissue using our proprietary CELLECTRA® in vivo DNA delivery technology. CELLECTRA® uses controlled, locally applied millisecond electric pulses to create temporary and reversible permeability, or pores, in the cell membrane. Using this method increases the cellular uptake of the DNA plasmids by more than one thousand times when compared to the injection of a DNA plasmid alone without other delivery mechanisms. This improved cellular uptake has enabled the immune responses that we have observed in our clinical trials, along with the efficacy results generated by these immune responses.

Alternative delivery approaches based on the use of viruses, bacteria, nanoparticles and lipids are complex and expensive and have generated concerns regarding their safety. Because the vector itself possesses many additional antigens specific to the vector, it can attract unwanted immune responses against itself that are believed to compromise the vectors' ability to deliver their DNA "payload" and provide protection. In contrast, DNA plasmid vectors possess no antigens of their own; the plasmid results in production of only the target antigen.

We have published preclinical data in which immune responses generated by our SynCon® immunotherapies delivered using CELLECTRA® were improved as compared to a leading viral vector (Adenovirus type 5) based approach. We are not aware of any published data indicating the capability of alternative technologies focused on using genetic code to generate preventive or therapeutic antigens to exceed our immune response data obtained to

date, nor to match the efficacy and immune response data generated in our controlled Phase 2b study based on in vivo production of such immune responses.

The delivery of our synthetic DNA immunotherapies using our CELLECTRA® devices has to date shown a favorable safety profile in clinical trials, without serious adverse events and only mild local injection-related side effects

such as redness and swelling. Our delivery is designed to be tolerable without the need for an anesthetic, and because it does not induce unwanted immune responses, it can be repeatedly administered for booster vaccinations.

We believe CELLECTRA® provides a relatively straightforward, cost-effective method for delivering DNA and RNA into cells with high efficiency, minimal complications and the ability to enable what we believe to be clinically relevant levels of gene expression, immune responses and efficacy.

Choice of Tissue for DNA Delivery

Skeletal muscle has been a core focus for delivery of DNA-based immunotherapies via CELLECTRA® because it is mainly composed of large elongated cells that are non-dividing, meaning that longer-term expression can be obtained without integration of the gene of interest into the genome. We have generated pre-clinical and clinical evidence that muscle cells may 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. In our Phase 2 clinical trial of VGX-3100 for HPV-related cervical dysplasia, intramuscular delivery by CELLECTRA® of DNA-encoded antigens induced both humoral (antibody) and cellular (T cell) immune responses. We envision that delivery of DNA by CELLECTRA® to muscle cells will circumvent the costly and complicated production procedures of viral gene delivery vectors, bacterial gene delivery vectors, protein-based drugs, conventional vaccines and monoclonal antibodies. This approach may provide long-term stable expression of a therapeutic protein or monoclonal antibody at a sustained level.

In addition to generating pre-clinical and clinical evidence that intramuscular DNA delivery can be effective for a number of immunotherapies, we are also exploring delivery to the skin, with early preclinical evidence suggesting that this 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 rich in immune cells and molecules. Skin specifically contains certain cells that are known to help in generating a robust immune response. With intradermal delivery, we may be able to demonstrate a comparable immune response to muscle delivery. Drug delivery into skin, or dermal tissue, is attractive given that the skin is the largest, most accessible, and most easily monitored organ of the human body, and it is highly immuno-competent, meaning that it is able to recognize antigens and mount an immune response to them.

Our CELLECTRA® Delivery Systems

There are several configurations in the CELLECTRA® device family. The first configuration covers intramuscular (IM) delivery of DNA; the second covers intradermal/subcutaneous delivery (ID) of DNA. Devices with these configurations have been validated, manufactured under Current Good Manufacturing Practices (cGMP) and are being used in human clinical trials. We have filed a device master file (MAF) with the U.S. Food and Drug Administration (FDA) covering the use of the CELLECTRA® devices in human clinical trials. These devices are intended to be used in combination with a DNA plasmid-based immunotherapy.

Our CELLECTRA®-SP devices combine the functionality of our current generation of skin and intramuscular devices in clinical testing with enhanced form, design and portability. All components of the pulse generator and applicator are integrated into a cordless, rechargeable device. The rechargeable battery can enable immunization of several hundred subjects, making the device useful for mass vaccinations. The devices are designed to accommodate different electrode arrays to meet the requirements of the particular immunotherapy and targeted tissue for delivery.

In preparation for our Phase 3 clinical trial of VGX-3100 and potential commercial use, we designed and manufactured a new delivery device, CELLECTRA®-5PSP, a fully automated, smaller and user-friendly device. The new CELLECTRA®-5PSP device is being used in our ongoing VGX-3100 Phase 3 trial, which started in June 2017.

Next-Generation Device Development

While our current IM and ID CELLECTRA® delivery technologies have been well tolerated, we are also advancing a new generation of ID delivery devices called CELLECTRA®-3P. Currently used ID devices penetrate no more than 3 mm into the target tissue, compared to IM devices that go deeper. All of our current vaccine studies in the clinic are using these CELLECTRA®-3P devices to deliver the vaccines.

We have also been researching other avenues for needle-free, contactless technology for immunotherapy delivery. In February 2011, Human Vaccines published our paper entitled, “Piezoelectric permeabilization of mammalian dermal

tissue for in vivo DNA delivery leads to enhanced protein expression and increased immunogenicity." This innovative method is based on the generation of an electric field or electric potential by certain materials in response to applied mechanical stress.

With the advancement of these devices our aim is to make DNA delivery amenable to mass prophylactic vaccination by decreasing dose levels, increasing tolerability of the vaccination, increasing the breadth of viable immunotherapy targets, and enhancing portability. Based on our data from preclinical studies of influenza, HIV, malaria,

and smallpox antigens, we believe that DNA delivery with this newer generation of ID delivery, including surface electroportation (SEP) devices, has the potential to yield levels of immunogenicity in terms of both antibody and T cell responses and/or efficacy against a virus challenge that are comparable to intramuscular delivery devices currently in clinical development.

In March 2016, we acquired needle-free jet injection technology, devices and intellectual property from Bioject Medical Technologies Inc. We are developing an integrated non-invasive delivery device combining Bioject's jet injection technology with our needle-free, SEP technology. Bioject's needle-free devices, which use high pressure gas or springs to propel liquid medicine into skin, have been observed to have desirable utility, safety and tolerability attributes in preclinical studies and clinical trials. Under a prior research agreement, we had assessed the combination of Bioject technology with our new delivery system and generated compelling antigen expression and immune responses in animal studies.

Our Immunotherapy Products and Product Development

Our primary focus is to advance and potentially commercialize the product candidates developed from our integrated technology platform. Using this platform, we are currently developing a number of DNA-based immunotherapies for the prevention or treatment of cancer and infectious diseases. The table below summarizes the status of our product development programs.

Active SynCon® Immunotherapy Development Programs

		Development Status				
Product Area	Product and Indication(s)	Pre-Clinical	Phase 1	Phase 2	Phase 3	Partner/Funding/Sponsor
Cancer	Cervical dysplasia (cervical HSIL) (VGX-3100)	X	X	X	IP	Inovio
	Vulvar dysplasia (vulvar HSIL) (VGX-3100)	X	X	IP		Inovio
	Anal dysplasia (anal HSIL) (VGX-3100)	X	X	IP		Inovio
	Head and neck cancer (MEDI0457)	X	X	IP		AstraZeneca
	HPV-related cancers (cervical, anal, penile, vulvar, vaginal) (MEDI0457)	X	X	IP		AstraZeneca/MD Anderson
	Bladder cancer (INO-5401 + atezolizumab)	X	X			Roche/Genentech
	Glioblastoma (INO-5401 + cemiplimab)	X	X			Regeneron
	Prostate cancer (INO-5150 + INO-9012)	X	X	SP		Inovio
	hTERT expressing cancers (breast, lung, pancreatic) (INO-1400 + INO-9012)	X	IP			Inovio
Infectious Disease	Hepatitis B Virus (INO-1800)	X	X	SP		Inovio

Hepatitis C Virus (GLS-6150)	X	IP		GeneOne Life Science
Zika (GLS-5700)	X	IP		GeneOne Life Science
Ebola (INO-4212)	X	IP		GeneOne Life Science/DARPA
MERS (GLS-5300)	X	IP		GeneOne Life Science/IVI
HIV (preventive & therapeutic) (PENNVAX®-GP)	X	IP	SP	NIH/NIAID

X = Completed
IP = In Progress
SP= Seeking Partner

Cancer Vaccines/Immunotherapies

Background

In recent years there have been multiple technology advancements and product approvals that have highlighted the potential of immunotherapies to usher in a new era of cancer therapeutics. Monoclonal antibodies (mAbs) such as Herceptin® and dendritic cell therapy Provenge® for prostate cancer have had varying degrees of success. While a significant step forward, suitable monoclonal antibodies with desired characteristics have been difficult to design or identify and expensive to produce, and the technology does not lend itself to designing mAbs for many diseases. Dendritic or other cell-based therapy is a highly personalized medicine involving removing cells from the patient, modifying them, multiplying them, then returning them to the body. In addition to the high cost and complex processes to manufacture products, a weakness of this approach is that it has not been shown to generate high levels of cancer-specific T cells.

Progress in the field of immune checkpoint inhibitors (CIs) has resulted in optimism regarding the potential for new immunotherapies against a spectrum of cancers. The immune system relies on a safeguard system of checkpoint mechanisms to prevent excessive or incorrectly directed immune responses. Many cancer cells have the ability to "hijack" these checkpoints and neutralize T cells sent by the immune system to eliminate them. Checkpoint inhibitors prevent cancer cells' ability to interfere with these checkpoints and enable T cells (especially CD8+ killer T cells) to complete their appropriate and intended killing function against cancer cells. Clinical trials of checkpoint inhibitors have shown notable therapeutic impact against melanoma and other cancers, but with response rates in the 15-20% range (and only in the case of melanoma going up to the 40% range or higher), there remains a significant opportunity. Observations suggest CIs may be less effective if there is not a high enough pre-existing level of antigen-specific CD8+ T cells in the tumor micro-environment, meaning that the tumor is "cold" rather than "hot" (with a significant level of CD8+ T cells). More recently, scientists have recognized that a strong CD8+ T cell generating "active" immunotherapy may be able to transform a "cold" tumor into a "hot" tumor and in combination with CIs may possess significant therapeutic potential to fight cancers.

More recently, a new category of immunotherapies called adoptive cell transfer, for example CAR-T technology, has provided further evidence of the merit of providing an enhanced T cell presence to fight cancer. CAR-T therapies have achieved dramatic results in B cell cancers. Unfortunately, they have also been associated with significant side effects. When this technology has been applied to solid tumors, it has generated significant cytokine storms that have resulted in severe side effects, including deaths. Moreover, adoptive cell transfer such as CAR-T, like dendritic cell therapy, involves removing T cells from a patient, modifying them to better target a cancer cell, multiplying the T cells, then returning them to the patient. These complex therapeutic products need to be manufactured and released for each patient, leading to expensive manufacturing and increased supply chain complexity.

Even though there have been promising technology advancements in recent years that better harness or activate capable killer T cells, we believe there is still significant untapped potential to develop "ideal" immunotherapies to fight cancers and infectious diseases.

What is an "ideal" active immunotherapy? We seek to advance product candidates that are effective, efficient and safe, specifically those that:

- target disease-specific antigens or proteins unique to a cancer or infectious disease;
- do not depend on complex manufacturing processes such as removal of dendritic cells or T cells from the patient that are then modified in the laboratory, amplified and then re-introduced in the patient as autologous or allogeneic cell based therapies;
- activate functional killer T cells with the necessary killing tools, such as granzyme and perforin;
- generate robust T cell responses or a significant number of T cells that are persistent and durable over time (memory response);
- do not induce unwanted immune responses;
- do not induce toxic inflammatory responses; and
- are capable of "breaking tolerance" of cancer cells grown in the body.

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Data from our Phase 2b data of VGX-3100, discussed below, show that our product candidates are capable of achieving these characteristics with our approach to activating significant antigen-targeted T cells. Based on this approach, we are advancing a growing pipeline of pre-clinical and clinical immunotherapy product candidates.

VGX-3100 for the Treatment of HPV-related Precancerous Lesions

Overview and Background

Human papillomavirus, or HPV, is sexually-transmitted, persistent infection with one or more high-risk (HR) genotypes of that virus can lead to, and thus are the causative agents responsible for, cervical pre-cancers (cervical dysplasia), cervical cancer, other anogenital cancers, and head & neck cancer, which is one of the most rapidly growing cancers in men. Scientific literature estimates that, at any given time, approximately 43% of the U.S. and world's adult population is infected with HPV, and about 25% of adult men and 20% of adult women in the U.S. have a genital infection with one or more HR-HPV genotypes. The lifetime risk for acquiring an HPV infection of any genotype is about 70% in sexually active U.S. adults and about 80% worldwide.

HPV is the most common viral infection of the reproductive tract and is the major cause of cervical cancers. Almost 300 million women globally are estimated to be infected with HPV, with another 30 million additional cases that have progressed to the pre-cancerous stage. Nearly 570,000 new cases of cervical cancer are diagnosed annually world-wide, and more than 311,000 women die from this cancer each year. Virtually all cases are linked with persistent infection with HPV. Challenges with acceptance, accessibility and compliance of vaccines to prevent HPV infection and the resulting pre-cancers and cancers have resulted in only 40% of young women being vaccinated in the United States, and even less in some of the other countries around the world which have access to those vaccines. While roughly 90% of HPV infections are ultimately cleared naturally by the body's own immune system, persistent cervical infection with one or more HR-HPV genotypes can lead to cervical high grade squamous intraepithelial lesions (HSILs) and, if untreated, eventually invasive cervical cancer. Researchers have estimated the global prevalence of clinically pre-cancerous HPV infections at between 28 and 40 million. HPV-16 and HPV-18 are the two most prevalent high-risk types of HPV worldwide, causing the significant majority of HPV-related cancers. In the U.S., HPV-16/18 are found in about 45% to 50% of all cervical HSILs and about 70% of invasive cervical cancers. The estimated annual incidence of cervical HSIL caused by HPV-16 and/or HPV-18 is approximately 195,000 persons in the United States and 233,000 persons in Europe. We believe these patients represent a significant market opportunity for our product candidates. Cervical HSIL can only be treated by an invasive surgical procedure.

To prevent HPV infection, there is currently one FDA approved preventive vaccine available in the U.S., called Gardasil® 9. That vaccine protects against infection by nine total HPV genotypes, consisting of seven genotypes that confer high risk for cancer and two that confer risk for genital warts. Preventive HPV vaccines cannot treat or protect those already infected with the same HPV genotypes, which is a large population. In addition, many girls and women eligible to be vaccinated have not been receiving these vaccines. In 2017, a U.S. national survey found that only 57% of girls aged 13-17 years were up to date with the HPV vaccine series. Currently there is no viable immunotherapy or drug to fight established HPV infection or treat cervical dysplasia and/or cancer caused by HPV.

Current management options for cervical HSIL are unappealing. The "watch-and-wait" process associated with low grade squamous intraepithelial lesions (LSIL, formerly called low-grade dysplasia or CIN 1) and in some young women with higher grade lesions (CIN 2) is a stressful approach. The only available treatment option for cervical HSIL is surgery, which involves ablating or cutting a women's cervix to remove the pre-cancerous lesions. While surgical procedures are generally initially effective in removing lesions, they can lead to short-term adverse effects including cervical scarring, excess bleeding and infection, and to longer-term reproductive risks such as pre-term birth, miscarriage, and perhaps infertility. Current excisional and ablative procedures increase the overall risk of pre-term births from 5.4% to 10.7%, according to Kyrgiou et al in a major meta-analysis published June 2016 in the British Medical Journal. Anticipation of these procedures produces significant anxiety for patients, despite their doctor's reassurances, and full recovery from surgery can take up to several weeks. Because surgery does not clear the underlying HPV infection, there is a 10-16% chance of high-grade pre-cancer lesion recurrence after surgery as a result of persistent HPV infection and/or incomplete removal of the lesion, with the persistent HPV infection being the better predictor of recurrence.

Our product candidate VGX-3100 is designed to significantly increase T cell immune responses against the E6 and E7 antigens of HPV types 16 and 18 that are present in both precancerous and cancerous cells transformed by these HPV

types. E6 and E7 are oncogenes that play an integral role in transforming HPV-infected cells into precancerous and cancerous cells. The goal of the immunotherapy is to stimulate the body's immune system to mount a killer T cell response strong enough to cause the killing of cells producing the E6/E7 protein. The potential of such an immunotherapy would be to treat precancerous dysplasias caused by these HPV types.

VGX-3100 for the Treatment of Cervical High Grade Squamous Intraepithelial Lesion (HSIL)

Phase 2b Study Results

In March 2011, we initiated a randomized, placebo-controlled, double-blind Phase 2b study of VGX-3100 delivered using our CELLECTRA® device in women with HPV type 16 or 18 and diagnosed with, but not yet treated for, cervical high grade squamous intraepithelial lesion (HSIL) (also called high grade cervical intraepithelial neoplasia (CIN 2/3)). The women in the study received either 6 mg of VGX-3100 or a placebo. VGX-3100 and placebo were administered using the CELLECTRA® device at months 0, 1 and 3. The study assessed efficacy by measuring regression of cervical lesions from CIN 2/3 to CIN 1 or normal in the treated versus control subjects. Immunological responses were also measured in this clinical study to assess the ability of this therapy to generate strong T cell responses in a larger, controlled study. Safety was also assessed.

The primary endpoint of the trial, histologic regression, was evaluated 36 weeks after the first treatment. In the per protocol analysis of this three-immunization regimen, CIN 2/3 resolved to CIN 1 or no disease in 53 of 107 (49.5%) women treated with VGX-3100, compared to 11 of 36 (30.6%) who received placebo. This difference was statistically significant (p=0.017). Intent to treat results were also similar and statistically significant.

There was also a high level of complete clearance of CIN 2/3. In a post-hoc analysis, CIN 2/3 resolved to no disease in 43 of 107 (40.2%) women treated with VGX-3100, compared to 6 of 36 (16.7%) who received placebo (p=0.006).

A secondary endpoint of the trial was virological clearance of HPV 16 or 18 from the cervix in conjunction with histopathological regression of cervical dysplasia to CIN 1 or no disease. This endpoint was achieved in 43 of 107 (40.2%) VGX-3100 recipients, compared to 5 of 35 (14.3%) placebo recipients (p=0.001). We believe this is an important outcome, as persistence of the HPV virus is associated with recurrence of cervical dysplasia.

All Phase 2b patients were monitored for an additional 52 weeks for a safety follow up. No significant safety issues were observed through week 88 following treatment.

In September 2015, this data was published in The Lancet in a paper entitled, “Safety, efficacy, and immunogenicity of VGX-3100, a therapeutic synthetic DNA vaccine targeting human papillomavirus 16 and 18 E6 and E7 proteins for cervical intraepithelial neoplasia 2/3: a randomized, double-blind, placebo-controlled Phase 2b trial.”

This paper reported further details regarding the characteristics of T cells generated and their association with efficacy outcomes. Analyses of patient immune responses showed that overall antigen-specific T cell levels in women treated with VGX-3100 were greater than those treated by placebo at all observation periods. At week 14, levels of CD8+ T cells specific to the E6 and E7 HPV antigens in women treated with VGX-3100 were ten times greater than those in the placebo group. This response increased with each of the three immunizations, then declined modestly to a sustained and durable level of T cells (memory T cells) measured through 36 weeks (24 weeks post-treatment).

Patients whose lesions regressed had higher frequencies of HPV-specific CD8+ T cells which co-expressed key molecules important in the T cell killing cascade and directly correlated with clinical efficacy. Specifically, higher levels of CD8+ killer T cells co-expressing checkpoint molecule CD137 on their surface, as well as the cytolytic protein perforin, were observed to be a predictive tool for efficacy. As a strong activation marker for CD8+ T cells, stimulation through CD137 has been shown in some systems to confer resistance of CD8+ T cells to the suppressive activity of regulatory T cells, indicating that its presence can identify tumor reactive T cells. Perforin is a pore-forming protein deployed by killer T cells to bore holes into the target cell's plasma membrane and destroy the cell. The difference in frequencies of CD8+ T cells expressing CD137 and perforin was greatest in patients who had both regressed their lesions and cleared HPV as compared to patients who did not.

To our knowledge, this was the first published study from which a direct correlation between antigen-specific CD8+ T cells generated in vivo and clinical efficacy was observed. We have identified several key biomarkers of killer T cells that we believe can be used to predict the clinical efficacy of VGX-3100, as well as other immunotherapies, which we will seek to confirm in our ongoing Phase 3 trial.

Our Phase 2b clinical trial of VGX-3100 highlights the ability of a DNA-based immunotherapy to be locally administered in tissue distant from the diseased tissue target, generate robust functional CD8+ killer T cells, traffic those T cells to the diseased tissue, infiltrate diseased cells displaying the target antigen, and facilitate the elimination of these cells both in “healthy” tissue and in diseased tissue (a lesion) with a statistically significant, clinically relevant outcome. We believe these results have significant implications in displaying the broad therapeutic and preventive potential of our existing and future cancer and infectious disease products.

Preparation and Launch of VGX-3100 Phase 3 Study

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In preparation for pivotal Phase 3 development and commercialization, we completed a manufacturing technology-transfer to a commercial manufacturing facility and scaled up manufacturing of VGX-3100.
We also designed and manufactured a new delivery device, our CELLECTRA® 5PSP device, which is fully automated, smaller and more user-friendly compared to our device previously used in the Phase 2b clinical trial.
We have conducted additional market research with physicians and patients that have further characterized the unmet medical needs relating to the treatment of CIN 2/3 cervical dysplasia. These include a preference for a non-invasive, non-surgical procedure for removing cervical lesions; a treatment that can clear HPV, the cause of the pre-cancer, throughout the body and not just in the limited area of the lesion; and a treatment that does not result in pre-term births or infertility. We believe that CIN 2/3 represents a unique market opportunity for a novel therapy capable of providing a first-line alternative to surgery and in some cases even an alternative to watchful waiting. This market research will help guide our communication and interaction with the physician, patient and support communities.
Phase 3 Program for VGX-3100 (REVEAL)
Our Phase 3 program, named REVEAL, consists of a primary study (REVEAL 1) and confirmatory study (REVEAL 2), in accordance with the FDA's general guidance for Phase 3 programs, to be conducted in parallel. The studies will each enroll 198 patients. Mark Einstein, MD, MS, FACS, FACOG, Professor and Chair Department of Obstetrics, Gynecology and Women’s Health Assistant Dean, Clinical Research Unit, Rutgers New Jersey Medical School, is Principal Investigator for the studies.
The REVEAL studies are prospective, randomized (2:1), double-blind, placebo-controlled trials evaluating adult women with HPV 16/18 positive biopsy-proven cervical HSIL (CIN 2/3). The primary endpoint is regression of cervical HSIL and virologic clearance of HPV-16 and/or HPV-18 in the cervix, which was a secondary endpoint that was achieved in our Phase 2b trial described above. Overall, the Phase 3 studies will evaluate cervical tissue changes at approximately 9 months after beginning a three-dose regimen of VGX-3100 administered at months 0, 1 and 3. Secondary endpoints include safety; tolerability; regression of CIN 2/3 to CIN 1 or normal; virologic clearance of HPV; efficacy measured by non-progression to cancer; and clearance of HPV from non-cervical anatomic locations. If the results of the REVEAL trials are positive, we are targeting the submission of a biologics license application, or BLA, to the U.S. Food and Drug Administration, or FDA, by the end of 2021.
VGX-3100 for the Treatment of Vulvar High Grade Squamous Intraepithelial Lesion (HSIL)
In April 2017, we commenced a Phase 2 trial to evaluate the efficacy of VGX-3100 in patients with pre-cancerous lesions of the vulva, or vulvar intraepithelial neoplasia (VIN). VIN has less than a 5% rate of spontaneous, or natural, regression and there are no FDA approved non-surgical treatments. Surgery, the most common treatment, is associated with high rates of disease recurrence and can cause disfigurement, long-term pain, and psychological distress for the women who undergo the procedure. VIN recurs in approximately one of every two patients who undergo surgical treatment.
This randomized, open-label Phase 2 clinical trial will assess the efficacy of VGX-3100 in 36 women with high-grade HPV-related vulvar lesions. The immunotherapy will be administered with our CELLECTRA® intramuscular delivery device. The primary endpoint of the study is histologic clearance of high-grade lesions and virologic clearance of the HPV virus in vulvar tissue samples. The study will also evaluate safety and tolerability of VGX-3100.
Interim efficacy results from the Phase 2 vulvar trial are anticipated in the second half of 2019.
VGX-3100 for the Treatment of Anal High Grade Squamous Intraepithelial Lesion (HSIL)
We have expanded the clinical development program for VGX-3100 to include treatment of HPV-16/18-associated anal high grade squamous intraepithelial lesions (anal HSIL, formerly called anal intraepithelial neoplasia, or AIN). This included launch of a Phase 2 study in 2018 for such patients who were also HIV-negative and a partnership with the AIDS Malignancy Consortium (AMC) for a similar trial in HIV-positive patients. The randomized, open-label trial in HIV-negative patients will assess the efficacy of VGX-3100 in 24 patients, and the immunotherapy will be administered with our CELLECTRA® intramuscular (IM) delivery device. The primary endpoint of the study is histologic clearance of the high-grade lesions and virologic clearance of the HPV-16/18 virus in anal/peri-anal tissue samples. The study will also evaluate safety and tolerability of VGX-3100.
Left untreated, anal HSIL may progress to cancer. Spontaneous regression of anal HSIL may occur, but only in the range of 20% to 29% of patients after one year of follow-up. Persistent infection with a high-risk HPV genotype is responsible for a large portion of anal cancer. In the U.S., about 55% to 80% of anal HSIL cases are associated with

HPV-16/18, and worldwide about 80% of anal HSIL cases are associated with HPV-16/18. In the U.S., over 90% of anal cancer is attributable to HPV, and about 87% of those HPV anal cancers are attributable to HPV-16/18 specifically.

It is estimated that nearly 8,600 new cases of and more than 1,100 deaths from anal cancer occurred in the United States in 2018. Anal cancer incidence has increased in the United States by an annual average 2.2% over the last ten years. The incidence of this cancer is considerably higher among certain risk groups, such as HIV-positive men and women, men who have sex with men, and other immunocompromised individuals, such as solid organ transplant patients, as compared to the overall population.

There are no validated screening tests or a general screening recommendation consensus for anal HSIL. Currently, the treatments for anal HSIL consist of excising or ablating the lesion(s). Treatment usually consists of repeated ablation, most commonly radiofrequency ablation (RFA), resections or laser therapy. However, treatment of anal HSIL represents a significant unmet medical need due primarily to the high recurrence rates up to 49% one year after treatment.

VGX-3100 Immune Correlates and Biomarker Signatures

In November 2017, we announced that a post-hoc analysis of data generated from our Phase 2b trial of VGX-3100 identified immune correlates and biomarker signatures that were predictive of potential treatment success. Details of the new biomarker and immunologic data are highlighted in the peer-reviewed journal Clinical Cancer Research in the article, “Clinical and Immunologic Biomarkers for Histologic Regression of High-grade Cervical Dysplasia and Clearance of HPV-16 and HPV-18 after Immunotherapy,” by Inovio and its academic collaborators.

ApolloBio Collaboration Agreement

In December 2017, we entered an amended agreement providing ApolloBio Corporation with the exclusive right to develop and commercialize VGX-3100 within Greater China (defined as China, Hong Kong, Macao and Taiwan). Additional details on the ApolloBio Agreement are provided below under "Business-License, Collaboration and Supply Agreements." The transaction closed in March 2018.

Upon the closing of the transaction in March 2018, we received proceeds of $19.4 million which comprised the upfront payment of $23.0 million less $2.2 million in foreign income taxes and $1.4 million in certain foreign non-income taxes. We may also receive potential milestone payments of up to $20 million in the aggregate. In addition, we are entitled to receive double-digit tiered royalty payments on sales. This collaboration of VGX-3100 encompasses the treatment and/or prevention of precancerous HPV infections and HPV-driven dysplasias (including cervical, vulvar and anal precancers) and excludes HPV-driven cancers and all combinations of VGX-3100 with other immunostimulants. The agreement also provides for potential inclusion of the Republic of Korea during the first three years of the term of the agreement.

MEDI0457 (VGX-3100 + INO-9012) for the Treatment of HPV-Related Cancers

Overview and Background

HPV is also associated with some head and neck cancers, especially those in the oropharynx and perhaps to some extent the larynx and oral cavity. The incidence of HPV-caused oropharyngeal squamous cell cancer (OPSCC) has increased significantly within the last 30 years in the U.S., including a 225% increase from 1988 to 2004, an average annual increase of 14%. More recently in the U.S., from 1999 to 2015, HPV-associated OPSCC incidence increased among men at an annual average rate of 2.7% and among women at an annual average rate of 0.8%, and in approximately 2009 the incidence of these HPV-associated mouth and throat cancers in men exceeded that of cervical cancers in women. Oropharyngeal cancer is the fastest-rising cancer among young white men in the United States, and U.S. men in general are about four times more likely than women to be diagnosed with HPV-associated oropharynx cancer. Increasing trends of the cancer in the U.S. are projected to continue at least through the year 2030. The estimated U.S. prevalence of HPV-caused oral cavity and pharynx cancer was approximately 108,000 cases in 2015. In 2015, OPSCC was the most common HPV-associated cancer in the U.S., with nearly 19,000 new cases diagnosed that year (15,479 cases among men and 3,438 cases among women). An estimated 51,540 new cases of this cancer in general, whether or not HPV-associated, occurred in 2018 in the U.S., and 10,030 persons died of this cancer that year. Worldwide, an estimated nearly 93,000 new cases of oropharyngeal cancer overall occurred in 2018, and about 25,400 to 29,000 cases per year of this cancer are HPV-associated.

Scientists have estimated that by 2030 OPSCC will constitute the majority of all head & neck cancers. About 70% of cancers of the oropharynx are now caused by HPV, with HPV-16 being the most prevalent genotype and causing about 86% of those HPV-caused cancers.

Improvements in primary treatment modalities (surgery and radiation) have produced significant improvements in morbidity, but intensive radiation has a profound long-term impact on mortality and quality of life. Based on these factors, we believe there is a significant opportunity for an effective immunotherapy.

Considering the several known cancers caused by HPV, the relative and total burden of those in terms of the annual U.S. average annual incidence rates and portions attributable to the HPV-16/18 genotypes for the period of 2008 to 2010

are shown in the table below. In total for that period, an average of more than 30,000 cases of HPV cancers per year were diagnosed in the U.S., and 80% (nearly 25,000) of those per year were specifically due to HPV-16/18 genotypes.

Annual Incidence of HPV-Attributable Invasive Cancers by Site in the United States, 2008-2010

Invasive Cancer tissue site	Avg. n in Sites where HPV is often found (i.e. HPV-associated cancers)	Cancers Attributable to Any HPV n (% of HPV-pos.)	Cancers Attributable to HPV-16/18 n (% of any HPV-attributable)
Oropharynx	14,972	10,567 (100%)	9,118 (86.3%)
Cervix	12,114	10,976 (100%)	8,018 (73.1%)
Anus	5,715	5,203 (100%)	4,537 (87.2%)
Vulva	4,131	2,840 (100%)	2,009 (70.8%)
Vagina	1,106	830 (100%)	609 (73.4%)
Penis	1,183	749 (100%)	567 (75.7%)
Total	39,221	31,164 (100%)	24,858 (80.0%)

Worldwide data estimates for the year 2012 are shown in the table below. For that year, an estimated 630,000 cases of new HPV cancer cases occurred, and more than 70% (430,000) of those cases were specifically due to HPV-16/18 genotypes.

Annual Incidence of HPV-Attributable Cancers by Site Worldwide

MEDI0457 for the Treatment of Head & Neck Cancer

In June 2014, we initiated a Phase 1 clinical trial assessing the immunogenicity and safety of our product candidate INO-3112 (consisting of a combination of VGX-3100 and our product candidate INO-9012) in head & neck cancer patients. INO-3112 is now called MEDI0457, following our collaboration with AstraZeneca, described below. We added INO-9012, a DNA-based IL-12 immune activator, to VGX-3100 for this cancer study because our prior HIV vaccine clinical study had indicated that the addition of IL-12 to our DNA immunotherapy could enhance the activation of CD8+ T cells.

We enrolled 22 adults with HPV16 and/or HPV18-positive head & neck squamous cell carcinoma (HNSCC) in this open-label Phase 1 trial. Patients were treated with 4 doses of MEDI0457 and then followed for safety, immune and clinical responses. In one part of the study, six patients were treated once with MEDI0457 before and after resection of their tumor. These patients received 3 additional doses subsequent to surgery and chemoradiation therapies. In the second part of the study, 16 patients were recruited into the study after their surgery and completion of chemotherapy

and radiation therapy. These patients were treated with 4 doses of MEDI0457 and followed. Each MEDI0457 treatment was administered using our CELLECTRA® delivery system.

In November 2016, at the Annual Meeting of the Society for Immunotherapy of Cancer (SITC), we reported interim immunology results showing that in the group of six patients treated before resection (one dose averaging 14 days and ranging 7 to 28 days prior to definitive surgery) and post-surgery (three additional doses), MEDI0457 generated robust HPV16/18 specific CD8+ T cell responses in peripheral blood in four of five subjects who also showed increased T cell activation in resected tumor tissue samples. One subject withdrew consent after surgery, leaving five evaluable subjects in this group.

In October 2018, we announced a paper published in Clinical Cancer Research, a major cancer journal, detailing results of a patient with head and neck cancer treated with MEDI0457 who achieved a sustained complete response (full remission) on treatment with a subsequent PD-1 checkpoint inhibitor. In the Inovio-sponsored study of 22 patients with head and neck squamous cell carcinoma we reported 91% (20/22) of patients showed T cell activity in the blood or tissue.

In January 2019, we announced that a second patient with HPV-related head and neck cancer treated with MEDI0457 in a Phase 1 trial achieved a sustained complete response (full remission) after subsequent treatment with a PD-1 checkpoint inhibitor.

Both patients who achieved full cancer remission were treated with four doses of synthetic DNA vaccine as part of the Phase 1 trial. This shows that synthetic DNA vaccine generated robust HPV16/18 specific CD8+ T cell responses in peripheral blood and increased CD8+ T cell infiltration in resected tumor tissue samples.

Of the four patients who developed progressive disease and were subsequently administered a PD-1 checkpoint inhibitor, two patients rapidly exhibited a complete response. The most recent patient for which data was presented in January 2019 received pembrolizumab (KEYTRUDA®), while the previously reported complete responder was treated with nivolumab (OPDIVO®). The patients moved from metastatic head and neck cancer to no evidence of disease and they remain alive two years after treatment.

Increasing evidence suggests that response rates from checkpoint inhibitors can be enhanced when used in combination with cancer vaccines like MEDI0457 that generate tumor-specific T cells. Interim data from a MEDI0457 monotherapy study of head and neck cancer patients demonstrated that MEDI0457 generated robust HPV16/18 specific CD8+ T cell responses in peripheral blood and increased CD8+ T cell infiltration in resected tumor tissue samples.

Collaboration with AstraZeneca

In August 2015, we formed a strategic collaboration with MedImmune, the global biologics research and development arm of AstraZeneca (AstraZeneca), focused on cancer immunotherapies. Under this agreement AstraZeneca licensed INO-3112 (renamed MEDI0457), to be studied in combination with selected immunotherapy molecules within its pipeline in HPV-driven cancers. See “Business- License, Collaboration and Supply Agreements” for additional information about the collaboration agreement.

In May 2017, we announced that AstraZeneca will conduct a Phase 1/2 clinical trial investigating the combination of MEDI0457 and durvalumab, a PD-L1 checkpoint inhibitor. The combination trial will enroll patients with metastatic HPV-related HNSCC with persistent or recurrent disease after chemotherapy treatment.

The open-label clinical trial is designed to evaluate the safety and efficacy of the combination therapy in approximately 50 subjects with metastatic head and neck cancer at multiple U.S. sites. Subjects will receive multiple doses of MEDI0457 and durvalumab. The primary endpoints of the trial are safety and objective response rate. The trial will also evaluate immunological impact, progression-free survival and overall survival. The Phase 2 portion of this study was initiated in December 2017 and this event triggered a $7 million milestone payment from AstraZeneca.

In December 2018, we announced the dosing of the first patient in an open-label, Phase 2 combination trial to evaluate MEDI0457, in combination with durvalumab, in patients with HPV-associated cervical, anal, penile and vulvar cancers. This trial, which is being funded by AstraZeneca, has an estimated total enrollment of 77 patients.

The first dosing of a cervical cancer patient in this trial resulted in an undisclosed milestone payment from AstraZeneca to us in 2018. A first dosing of a patient with a third distinct HPV-associated cancers other than H&N or cervical will trigger another Phase 2 milestone payment in 2019.

Under our collaboration agreement, AstraZeneca will fund all of the costs of developing MEDI0457.

INO-5150 for the Treatment of Prostate Cancer

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. In the United States in 2018, there were an estimated 164,690 new cases of prostate cancer and more than 29,000 deaths occurred due to this cancer. Worldwide in 2018, an estimated 1.28 million new cases of and nearly 360,000 deaths occurred due to this cancer.

In July 2015, we initiated a Phase 1 trial to evaluate our DNA immunotherapy for prostate cancer, INO-5150, in men with biochemically relapsed prostate cancer. This study is evaluating the safety, tolerability and immunogenicity of INO-5150 alone or in combination with INO-9012. The multi-centered study is also evaluating changes in prostate specific antigen, or PSA, levels, an important biomarker in prostate cancer. We have fully enrolled 62 patients in the trial across 4 dose cohorts.

An interim data analysis presented in September 2017 at the European Society of Medical Oncology (ESMO) meeting in Madrid, Spain showed that INO-5150 had generated antigen-specific CD8+ killer T cell responses measured in peripheral blood from subjects with biochemically recurrent prostate cancer. Treatment with INO-5150 as a monotherapy generated PSA and prostate specific membrane antigen, or PSMA, specific T cell responses in peripheral blood in 60% (35/58) of the subjects. Patients with specific CD8+ T cell responses experienced dampening in the rise of PSA and significant increases in PSA Doubling Times (PSADT).

In June 2018, additional prostate cancer data from the trial was presented at the American Society of Clinical Oncology (ASCO) annual meeting. The additional data showed clinically meaningful PSA stabilization after administration of INO-5150 in patients, with no documented disease progression during the study. Of note, this effect was also observed in the patients with the fastest PSA doubling at the time of study entry.

In October 2018, we announced new data from the trial in which a slowing of Prostate-Specific Antigen Doubling Time (PSADT) was observed in men with prostate cancer. Eighty-six percent (86%) of patients remained progression-free at Week 72 of the study, and immunogenicity was observed in 77% (47/61) of patients by multiple immunologic assessments. These data were presented in a poster entitled “Synthetic DNA immunotherapy in Biochemically Relapsed Prostate Cancer” at the 2018 European Society for Medical Oncology (ESMO) congress.

We have announced that we are seeking strategic collaborators in order to continue the development of INO-5150.

INO-1400 for the Treatment of Multiple Solid Tumor Types (hTERT antigen)

Human telomerase reverse transcriptase (hTERT) is a significant cancer immunotherapy target. High levels of hTERT have been detected in more than 85% of all human cancers, including breast, lung, and pancreatic cancers, while normal cells showed undetectable levels of telomerase expression. Immunological analysis indicated that hTERT is a widely applicable target recognized by T-cells and can be potentially used as a universal cancer immunotherapy. In 2018, over 555,000 new cases of breast, lung, or pancreatic cancers are estimated to have occurred in the United States and nearly 240,000 people died from these cancers collectively. Worldwide in 2018, more than 4.6 million new cases of these cancers occurred and more than 2.8 million people died from these cancers collectively. Despite available treatments, mortality rates remain unacceptably high in these tumor types. In addition, many existing treatment modalities are associated with significant adverse events.

In December 2014, we initiated a Phase 1 clinical trial of INO-1400 alone or in combination with INO-9012 in adults with breast, lung or pancreatic cancer at high risk of relapse after surgery and other cancer treatments. This open label, dose escalation study is evaluating the safety, tolerability, and immunogenicity of INO-1400, as well as another hTERT construct called INO-1401. To date, we have treated 90 patients with nine different types of solid tumors. All patients received treatment using our CELLECTRA® delivery device.

In November 2017, in poster presentations at the SITC Annual Meeting, we reported additional results from the ongoing Phase 1 trial in which that INO-1400 generated hTERT-specific IFN-gamma secreting T cells, suggesting an ability to break immune tolerance.

INO-5401: Immunotherapy targeting WT1, hTERT, and PSMA cancer antigens

INO-1400 is also part of our product candidate INO-5401, an immunotherapy comprising hTERT and two other tumor-associated antigens, Wilms' tumor gene, or WT1, and PSMA, for which we intend to initiate a clinical study in combination with a checkpoint inhibitor.

In February 2017, we reported data indicating that our SynCon® WT1 cancer antigen was capable of breaking immune tolerance, a major challenge to researchers striving to develop potent cancer therapies, and induced neo-antigen-like T cell responses to cause tumor regression in pre-clinical studies. The results were published in the scientific journal Molecular Therapy in an article entitled, “A novel DNA vaccine platform enhances neo-antigen-like T cell responses

against WT1 to break tolerance and induce anti-tumor immunity."

While mice in the preclinical study did not mount an immune response to native mouse WT1 antigens, mice immunized with our SynCon® WT1 antigen broke tolerance and generated robust neo-antigen-like T cells. The immunized mice also

exhibited smaller tumors and prolonged survival in a tumor challenge study. SynCon® WT1 DNA vaccination also broke tolerance and generated neo-antigen-like T cell immune responses in Rhesus monkeys, a species whose immune system closely resembles that of humans. The ability to overcome the immune system's usual tolerance of WT1 antigen suggests the potential of our SynCon® WT1 antigen to tackle any WT1-expressing cancer in humans, including pancreatic, brain, lung, thyroid, breast, testicular, ovarian, and melanoma.

We previously reported similar results for our SynCon® hTERT and PSMA cancer antigens.

The National Cancer Institute previously highlighted WT1, hTERT and PSMA among a list of attractive cancer antigens, designating them as high priorities for cancer immunotherapy development. WT1 was at the top of the list. The hTERT antigen relates to 85% of cancers and WT1 and PSMA antigens are also widely prevalent in many cancers.

These attributes of breaking tolerance and having broader prevalence across different cancers create the potential for INO-5401 to be an effective universal cancer immunotherapy in combination with different checkpoint inhibitors.

INO-5401 for the Treatment of Metastatic Bladder Cancer

In the U.S., an estimated 81,190 new cases of bladder cancer and 17,240 deaths due to bladder cancer occurred in 2018. Worldwide, nearly 550,000 new cases of urinary bladder cancer are estimated to have occurred in 2018 worldwide, with this cancer accounting for nearly 200,000 deaths. Advanced unresectable or metastatic urothelial carcinoma, or UC, the most common type of bladder cancer, remains a high unmet medical need, as survival remains poor for most patients who experience disease progression or intolerance to treatment during or after platinum-containing chemotherapy. The approval of several checkpoint inhibitors for advanced unresectable or metastatic UC has improved response and survival rates for some patients; however, the majority of patients do not experience meaningful clinical responses to checkpoint inhibitor monotherapy.

In August 2018, we dosed the first patient in an open-label, Phase 1/2a study designed to evaluate the safety, immunogenicity and clinical efficacy of INO-5401, in combination with INO-9012 and Roche/Genentech's product, atezolizumab, PD-L1 inhibitor, for the treatment of advanced or metastatic bladder cancer. The trial, which we are managing, is expected to enroll approximately 85 patients at sites located in the United States and Spain.

Patients will be divided into two cohorts. Cohort A includes patients with confirmed disease progression during or following prior checkpoint inhibitor therapy, while Cohort B patients are treatment naïve and unfit for cisplatin-based therapy. Primary endpoints are incidence of adverse events (AEs), antigen-specific immunologic activation and objective response rate (ORR) in Cohort A. Secondary endpoints are Cohort B's ORR, duration of response, progression free survival and overall survival. Exploratory endpoints are correlation of biomarkers to anti-tumor activity. A safety run-in will be performed for the first six patients enrolled in Cohort A to monitor emergence of any dose limiting toxicities. INO-5401 and INO-9012 (10 mg DNA combined in 1ml) will be administered by intramuscular injection followed by electroporation every 3 weeks for first 4 doses, every 6 weeks for 6 doses and every 12 weeks until disease progression. Atezolizumab (1200 mg IV) will be administered every 3 weeks until disease progression. Tumor imaging, disease assessment (per RECIST and iRECIST) and biopsies, blood and urine samples will be collected at set time points including prior to study treatment, on treatment and at disease progression.

INO-5401 for the Treatment of Glioblastoma Multiforme (GBM)

GBM is a devastating disease for both patients and caregivers. It is the most aggressive brain cancer and its prognosis is extremely poor, despite a limited number of new therapies approved over the last 10 years. The latest available U.S. data for GBM is for the period of 2011 to 2015, when an average annual number of reported new cases was 11,229. The median overall survival for patients receiving standard of care therapy is approximately 15 months and the average five-year survival rate is only 5.8% for urban residents and only 3.9% for rural residents.

In June 2018, we dosed the first patient as part of a Phase 1/2 immuno-oncology trial in patients with newly diagnosed GBM. The trial is designed to evaluate INO-5401 and INO-9012, in combination with cemiplimab (REGN2810), a PD-1 inhibitor developed by Regeneron Pharmaceuticals.

The open-label trial of 50 newly diagnosed GBM patients will be conducted at approximately 25 U.S. sites, and the primary endpoint is safety and tolerability. The study will also evaluate immunological impact, progression-free survival and overall survival.

Infectious Disease Vaccines/Immunotherapies

INO-1800 for the Treatment of Hepatitis B Virus

Although an effective preventive vaccine against hepatitis B virus, or HBV, infection has existed for over three decades, HBV remains a major epidemic, especially among people of Asian and African descent. The World Health Organization estimates that 2 billion people globally are or have been infected with HBV, with over 257 million people chronically infected with the virus and at risk of developing the major complications of cirrhosis or liver cancer. It is

estimated that over two million people in the United States are chronically infected with the virus, including those who were foreign-born. Currently, the only therapies available for chronically infected individuals are interferon-alpha and nucleoside analog treatments, which function by controlling viral replication, but they do not clear infection. Interferon can prevent viral replication in only 30% of patients and does so with undesirable side effects.

Liver cancer is the fourth most common cause of death from cancer worldwide, and it kills the vast majority of patients within five years of diagnosis in the U.S. An estimated more than 841,000 new cases arose in 2018 worldwide, including 42,220 cases in the U.S. One of the major causes and risk factors for liver cancer is infection by hepatitis B. Chronically infected individuals may develop a permanent scarring of the liver, a condition called cirrhosis. Liver cirrhosis can evolve into hepatocellular carcinoma, which claimed an estimated 780,000 lives worldwide in 2018.

INO-1800 is encoded for the HBcAg antigen and represents a consensus of the unique HBcAg DNA sequences of all major HBV genotypes (A through E). When delivered by CELLECTRA®, in a preclinical study, INO-1800 elicited strong HBcAg-specific T cell and antibody responses in the periphery (outside of the liver) as measured by ELISpot, ICS and cell proliferation assays. Researchers observed that the immunization could also induce antigen-specific CD8+ and CD4+ T cells that produced both IFN-y and TNF-a in the liver, indicating that a strong immunotherapy-induced T cell response was also present in the liver.

In the preclinical study, the antigen-specific T cells exhibited a killing function and were able to migrate to and stay in the liver and cause clearance of target cells without any evidence of liver injury. This was the first study to provide evidence that intramuscular immunization could induce killer T cells that can migrate to the liver and eliminate target cells.

In April 2015, we initiated a Phase 1 trial to evaluate INO-1800 in patients chronically infected with HBV. This randomized, open-label, active-controlled, dose escalation study was designed to evaluate the safety, tolerability and immunogenicity of INO-1800 alone or in combination with INO-9012. This international study enrolled patients in the United States and Asia Pacific region with a primary endpoint of safety and tolerability of the therapy. Secondary endpoints are evaluating the cellular and humoral immune response to INO-1800 and its effect on several viral and antiviral parameters. All trial subjects are also medicated with standard-of-care antiviral therapies.

In March 2018, we announced interim results from the trial, in which INO-1800 was well-tolerated and generated virus-specific T cells, including CD8+ killer T cells, meeting the objectives of the clinical study. Preliminary immunology data from the trial revealed that treatment of patients with INO-1800 resulted in the generation of T cells that recognized key components of the hepatitis B virus and reacted by making antiviral cytokines such as Interferon gamma, a protein believed to be linked to clearance of HBV from the liver. In the trial, INO-1800 was also able to activate and expand CD8+ killer T cells that displayed markers believed to be important for retention in the liver as well as multiple potential mechanisms for killing virally infected cells.

We are currently seeking a collaboration partner in order to further advance the clinical development of INO-1800.

GLS-6150 for the Treatment of Hepatitis C Virus

In September 2018, we announced the dosing of the first patient in a Phase 1 study designed to evaluate a preventive vaccine candidate, GLS-6150, against hepatitis C infection. Recruitment has begun in South Korea, where our collaborator GeneOne Life Science, or GeneOne, is responsible for conducting and funding this Phase 1 trial to assess the ability of GLS-6150 to boost immunity in people who have been treated and cleared of the virus. We believe that the vaccine could potentially be employed to prevent infection and re-infection.

This jointly developed, open-label, Phase 1 study of GLS-6150 will evaluate a total of 24 patients who have a sustained virologic response (SVR) following treatment for Hepatitis C (n=8 per group) and an additional 8 healthy controls to compare immune responses. Subjects will receive one of two doses of vaccine, 1 or 2 mg, administered intra-dermally and followed by electroporation with our CELLECTRA®-3P device. Vaccinations will occur as a three-dose priming series (at 0, 4, 12 weeks) or as a two-dose priming series (at 0 and 8 weeks) and followed by a booster dose at 6 months. Final study visit is 4 weeks following the 6-month booster vaccination.

Zika Virus

Overview

First identified in the late 1940s in Uganda, Zika virus subsequently spread to equatorial Asia in 1969 and then rapidly spread through the Pacific, and still later, in the 2014-2016 period, to and through South America, Central America

and the Caribbean. In the end of that period, Zika virus emerged in two portions of the continental United States (extreme Southeastern Florida and extreme South Texas). Zika virus is a flavivirus, a family of viruses including yellow fever, dengue, and West Nile virus, which are introduced to people through mosquito bites. Because the Aedes species of mosquitoes that spread Zika virus are found in much of the world, there is concern that the virus will spread to new countries and cause additional outbreaks. There is also concern that Zika spreads sexually in humans, at least by males to

females, as has been reported for some returning travelers and documented in multiple studies. In February 2016, the WHO stated that 39 countries had reported locally acquired circulation of the Zika virus since January 2007. Geographical distribution of the virus had expanded since then, and although the incidence of infections has declined significantly since the 2014-2016 emergence in the Americas, currently the U.S. CDC still lists at least 94 countries and territories as having risk of Zika virus infection and notes that the virus is still a threat. No vaccine or therapy currently exists for the Zika virus.

The most common symptoms of Zika virus are fever, rash, joint pain, and conjunctivitis. More seriously, health authorities have observed neurological and autoimmune complications potentially associated with Zika virus, including microcephaly in newborn children and Guillain-Barre syndrome. Microcephaly is a rare condition marked by an abnormally small head and incomplete brain development. There may also be a link with Guillain-Barré syndrome, a disease in which the body's immune system mistakenly attacks peripheral nerves. Symptoms start with muscle weakness. In severe cases the person is almost totally paralyzed and the disorder can be life threatening.

In January 2016, we and GeneOne announced a joint research collaboration with academic collaborators of a SynCon® Zika virus vaccine known as GLS-5700.

Preclinical Studies - Zika Virus

In February 2016, we announced that our Zika vaccine administered using our CELLECTRA® delivery device resulted in seroconversion, or the development of detectable specific antibodies in the blood, in all vaccinated mice. The vaccinations also generated robust and broad T cell responses as analyzed by the standardized T cell ELISPOT assay. In data reported in May 2016, two doses of the Zika DNA vaccine delivered either intramuscularly or intradermally resulted in seroconversion, in all vaccinated non-human primates and broad T cell responses as analyzed by the standardized T cell ELISPOT assay.

These results were later published in Nature Partner Journals (npj) Vaccines in November 2016. Additional data indicated that in the study GLS-5700 protected animals from infection, brain damage and death. All GLS-5700 vaccinated animals were protected from Zika infection after exposure to the virus. In addition, vaccinated mice were protected from degeneration in the cerebral cortex and hippocampal areas of the brain while unvaccinated mice showed significant degeneration of the brain after Zika infection.

In another preclinical study, the results of which were published in June 2017, GLS-5700 was observed to have protected against Zika virus-induced damage to testes and sperm, and prevented persistence of the virus in the reproductive tract of all vaccinated male mice challenged with a high dose of the Zika virus. This preclinical study data was published in Nature Communications in an article entitled, “DNA Vaccination Protects Mice Against Zika Virus-Induced Damage to the Testes.”

Phase 1: 40 Patient Zika Study in U.S. & Canada

In June 2016, we were the first to commence a human Zika trial in healthy adult volunteers, with sites in the U.S. and Canada, with the first subject dosed in July. This Phase 1, open-label, dose-ranging study of 40 healthy adult volunteers was designed to evaluate the safety, tolerability and immunogenicity of GLS-5700 administered with CELLECTRA®-3P, our intradermal DNA delivery device.

In this Phase 1 trial, a total of 40 participants (20 in each of two groups) received GLS-5700 in a 1 mg or 2 mg dose. The vaccine was administered in 0.1 ml intradermal injections. In October 2017, we announced positive safety and immune response results from the Phase 1 trial. The GLS-5700 Zika vaccine induced binding antibodies in 100% of the participants after a three-dose vaccination regimen and in 95% after two doses of vaccine. In addition, neutralizing antibodies were observed in more than 95% of the serum samples that were assayed on neuronal-cell targets. Serum samples from vaccinated subjects when subsequently transferred to mice were found to be protective from death and illness in more than 90% of animals after they were challenged with a lethal dose of the Zika virus. These results appeared in the New England Journal of Medicine in the article, “Safety and Immunogenicity of an Anti-Zika Virus DNA Vaccine.”

Phase 1: 160 Patient Zika Study in Puerto Rico

In August 2017, we and GeneOne initiated a second clinical trial of GLS-5700. In this second trial, we have enrolled 160 subjects in Puerto Rico, where the Zika virus outbreak was declared a public health emergency. In this placebo-controlled, double-blind trial involving healthy adult volunteers, 80 subjects received GLS-5700 and 80 subjects received placebo. The study is evaluating the safety, tolerability and immunogenicity of GLS-5700

administered with our CELLECTRA®-3P device. We are also assessing differences in Zika infection rates in participants given either placebo or vaccine as part of an exploratory endpoint. We expect to report data from this trial in the first half of 2019.

Zika dMAb®

In December 2016, we received a sub-grant through The Wistar Institute to develop a DNA-based monoclonal antibody designed to provide a fast-acting treatment against Zika infection and its debilitating effects. The goal of this program, which was funded by the Bill & Melinda Gates Foundation, is for the researchers to develop a Zika dMAb® through human clinical trials. In the first quarter of 2019, we dosed our first subject with a Zika dMAb. See the section below entitled "Synthetic DNA-based Monoclonal Antibodies" for further information on our DNA-based monoclonal antibody program.

Ebola Virus

Overview

The Ebola virus has been described as one of the most virulent viral diseases, with lethality rates approaching 90%. Ebola can spread through human-to-human transmission by direct contact with the blood, secretions, organs or bodily fluids of an infected individual and with surfaces or materials that contain the contaminated fluids of an infected person, such as bedding and clothing. It is capable of causing death within two to twenty-one days of exposure. There are no approved preventive vaccines or effective therapeutic treatments for Ebola. In addition, various experimental approaches have already been associated with undesirable side effects and limited ability to scale manufacturing. According to the U.S. CDC, the 2014 West Africa Ebola epidemic was the largest in history, resulting in 28,610 suspected and confirmed cases and 11,308 deaths as of June 2016, when it was declared over.

In 2018, two Ebola outbreaks occurred, both in the Democratic Republic of Congo (DRC). The first of these outbreaks was declared in May and was relatively well-contained and short-lived, with a total of 54 cases and 33 deaths through the declared end of the outbreak in July. However, the second outbreak, which was declared in August, has persisted and continued into 2019. This latter, current outbreak is now the second largest Ebola outbreak in history, with a total of 838 cases, 534 deaths, and 6,772 contacts being followed as of February 2019. As of January 2019, 63 health workers had become infected with Ebola virus and 21 of them have died.

Preclinical and Clinical Development - Ebola

In 2014, we entered into a collaboration with GeneOne to advance a DNA immunotherapy for Ebola into clinical development. The decision to advance our Ebola immunotherapy was based on positive results observed in preclinical studies, in which 100% of immunized guinea pigs and mice were protected from death after being exposed to the Ebola virus. Unlike the non-immunized animals, immunized animals were also protected from weight loss, a measure of morbidity. Researchers found significant increases in neutralizing antibody titers and strong and broad levels of immunotherapy-induced T cells, including "killer" T cells, suggesting that DNA immunotherapy could provide both preventive and treatment benefits. This data was published in 2013 in the peer-reviewed journal Molecular Therapy in a paper titled, "Induction of Broad Cytotoxic T Cells by Protective DNA Vaccination Against Marburg and Ebola."

In April 2015, we received a contract from the Defense Advanced Research Projects Agency (DARPA) to lead a consortium to develop multiple treatment and prevention approaches against Ebola. Other collaborators are AstraZeneca; GeneOne and its manufacturing subsidiary, VGXI, Inc.; and David B. Weiner, Ph.D., a director of our company, who also serves as executive vice president at the Wistar Institute and retired professor of Pathology and Laboratory Medicine at The Perelman School of Medicine at the University of Pennsylvania, Emory University and Vanderbilt University. A previous collaboration agreement with GeneOne for Ebola was incorporated into this consortium funded by DARPA.

We are taking a multi-faceted approach to develop products to prevent and treat Ebola infection. These programs include development and early clinical testing of:

- a therapeutic DNA-based monoclonal antibody product against the Ebola virus infection, which we believe has properties that best fit a response to the outbreak in that they could be designed and manufactured expediently on a large scale using common fermentation technology, are thermal-stable, and may provide more rapid therapeutic benefit;
- a highly potent conventional protein-based therapeutic monoclonal antibody (mAb) product against Ebola virus infection; and
- a DNA-based vaccine against Ebola.

Our contract with DARPA covers the pre-clinical development costs for the dMAb products and protein mAb candidates, as well as GMP manufacturing costs and the Phase 1 clinical trial costs for the three product candidates described above.

In May 2015, we and our collaborators initiated a Phase 1 clinical trial of INO-4212, an Ebola DNA vaccine to evaluate its safety, tolerability and immune responses in 75 healthy subjects divided into five study arms. INO-4212 consists of two optimized SynCon® DNA plasmids coding for the Ebola glycoprotein antigen from circulating Ebola

strains from 1975-2014. The study was designed to evaluate INO-4212 and its components INO-4201 and INO-4202, alone or in combination with INO-9012, delivered into muscle or skin using our proprietary DNA delivery technology.

In March 2016, we reported initial results from the trial. Of 69 evaluated subjects, 64 (92.8%) seroconverted and mounted a strong antibody response to the Ebola glycoprotein antigen following the three dose immunization regimen; 48 subjects (69.6%) seroconverted after only two doses.

In the study arm using intradermal (skin) administration, 13 of 13 evaluable subjects (100%) generated antigen-specific antibody responses after only two doses, and all remained seropositive after three immunizations. Similarly, in the study arm receiving the vaccine with intramuscular administration in combination with plasmid IL-12, 13 of 13 evaluable subjects (100%) produced strong antibody responses after three immunizations, and 12 of 13 (92.3%) achieved strong antibody responses after only two immunizations.

The Ebola glycoprotein specific geometric mean antibody titers measured in the five cohorts ranged from over 2,000 to greater than 46,000. Significantly, a majority of vaccinated subjects in each of the five cohorts produced strong Ebola antigen specific T cell responses as measured by interferon gamma ELISpot analysis.

INO-4212 was well tolerated, with no systemic serious adverse effects observed. Side effects, such as fever, joint pain, and low white blood cell counts have previously been reported following treatment with some viral vector based Ebola vaccines currently in development. Moreover, unlike the viral vectored vaccines which must be kept frozen, the INO-4212 formulation used in the trial was kept in a solution which was refrigerated at 2-8 degrees Celsius.

In August 2016, we announced that enrollment of this study was being expanded to up to 200 subjects to further characterize and identify in humans the most optimal immunization regimen using intradermal (skin) delivery of the Ebola DNA vaccine.

In April 2017, we reported preliminary results from the expanded Phase 1 trial. Across both stages of the trial, including both intramuscular and intradermal delivery, 95% (170/179) of evaluable subjects generated an Ebola-specific antibody immune response, with the mean antibody titer comparable or superior to those reported from viral vector-based Ebola vaccines. Our Ebola vaccine was also well tolerated in the second stages of the trial, with a favorable safety profile compared to viral vector-based Ebola vaccines, some of which have been associated with serious adverse events including myalgia, arthralgia, fever, and rash.

In October 2018, we announced that INO-4212 provided 100% protection following a challenge with a lethal dose of the Ebola virus in a preclinical study. An article in the Journal of Infectious Diseases highlights that regimens of the INO-4212 vaccine delivered by intramuscular administration provided 100% protection against a lethal Ebola challenge in all preclinical subjects. In a separate study, two injections by intradermal administration generated strong immunogenicity and provided 100% protection against a lethal Ebola challenge. In the study, scientists observed that vaccination induced long-term immune responses in monkeys that were detectable for at least one year after the final vaccination.

Middle East Respiratory Syndrome (MERS)

Overview

MERS is a viral respiratory illness first reported in Saudi Arabia in 2012. MERS appears to have been transmitted from an animal reservoir to humans but human to human transmission has been confirmed. This communicable virus has not been shown to spread in a sustained way in communities, but rapid spread in the nosocomial setting, such as emergency rooms and/or hospitals without adherence to state-of-the-art infection control practices, can result in outbreaks with many cases, including superspreading events. Like the severe acute respiratory syndrome (SARS) outbreak in 2003, which made approximately 8,000 people ill and was fatal in nearly 10% of those cases, MERS is caused by a coronavirus and appears to cause a severe lung infection. However, the case-fatality rate (death rate) of MERS has typically been between 30% and 40%, which is significantly higher than that of SARS. While the SARS epidemic in 2003 killed 10% of those who became ill from the SARS virus, MERS has killed approximately 35% of people who people who became ill from the MERS virus from 2012 to December 2017. MERS differs in that it also causes rapid kidney failure. Its high death rate has caused serious concern among global health officials.

Despite the continuing threat of MERS outbreaks, there are no licensed vaccines or treatments for MERS. Since the virus was first identified in Saudi Arabia in 2012, the World Health Organization reports 2,298 laboratory-confirmed cases of MERS and 811 deaths from MERS worldwide as of January 2019. Twenty seven countries have reported

cases, including Korea where an outbreak in the summer of 2015 resulted in 186 cases and 38 deaths. The majority of MERS cases reported in the world by country have been reported from the Kingdom of Saudi Arabia, with a total of 1,915 cases, 735 associated deaths, and a case-fatality rate of 38% from 2012 through January 2019. In early 2019, a MERS outbreak occurred in the Saudi Arabian city of Wadi Aldwasir and continues. As of February 21, 2019, a total of 47 MERS cases had been reported in that outbreak.

Preclinical and Clinical Development - MERS

In November 2013, we announced that preclinical testing of our SynCon® MERS vaccine candidate, GLS-5300, had induced robust and durable immune responses in mice, demonstrating the potential for such a vaccine to prevent and treat this deadly virus. DNA vaccine constructs targeting multiple MERS antigens were designed using our SynCon® vaccine platform with the goal to universally protect against multiple strains of MERS, which has been shown to have diverse genetic variants. These SynCon® constructs were administered via our CELLECTRA® delivery technology. A consensus MERS "spike" protein vaccine construct was created based on multiple strains of the MERS virus. Our MERS DNA vaccine was immunogenic in mice and seroconversion was observed in all animals. The antibodies generated by the vaccine in 100% of mice (20 of 20) were able to neutralize or completely block actual infection of MERS virus in the cells, demonstrating the protective potential of this vaccine. In contrast, none of the 10 unvaccinated mice in the control group generated neutralizing antibodies.

The vaccinations were also highly T cell immunogenic, generating robust and broad T cell responses as extensively analyzed by the standardized T cell ELISPOT assay. The vaccine produced robust CD8+ and CD4+ T cell responses against multiple epitopes of the MERS spike protein. This increased diversity and magnitude of cellular responses may be critical for effectively mitigating MERS infection.

We believe these preclinical findings are vital given the importance of neutralizing antibodies in preventing infection and the role T cells play in clearing infection by killing cells that harbor the virus.

In August 2015, we announced that our MERS vaccine had induced 100% protection from a live virus challenge in a preclinical study in mice, camels and monkeys, or non-human primates. In all three species, the vaccine induced robust immune responses capable of preventing the virus from infecting cells. We believe the data from camels is an important finding because camels represent not only a host reservoir of the disease, but also act as a mode of transmission to humans. In monkeys, all vaccinated animals in the study were protected from symptoms of MERS disease when challenged with a live MERS virus.

The preclinical results appeared in the peer-reviewed journal Science Translational Medicine in an article entitled, "A synthetic consensus anti-spike protein DNA vaccine induces protective immunity against Middle East Respiratory Syndrome Coronavirus in non-human primates."

In February 2016, we and our collaborator GeneOne commenced a Phase 1, dose-escalation clinical trial of GLS-5300 in 75 healthy volunteers at the Walter Reed Army Institute of Research (WRAIR) in Maryland. The primary and secondary goals of this first-in-man Phase 1 trial are to obtain safety and immunogenicity data. This trial represents the first MERS vaccine to be tested in humans for this disease that has no approved vaccines or treatments.

In December 2016, we announced that the International Vaccine Institute (IVI) will provide new funding and support to further advance the clinical development of GLS-5300. IVI will add technical, laboratory and financial support for GLS-5300 clinical trials in Korea with the goal to advance clinical testing toward emergency use authorization by the Korean government as well as authorities of other countries. This collaborative funding is part of a grant from the Samsung Foundation to IVI to support the development of a MERS vaccine for emergency use in Korea and internationally.

In April 2018, we announced a collaboration with The Coalition for Epidemic Preparedness Innovations (CEPI) under which we will develop vaccine candidates against Lassa fever and Middle East Respiratory Syndrome (MERS). CEPI will fund up to $56 million of costs to support our pre-clinical and clinical advancement through Phase 2 of GLS-5300, as well as a Lassa fever vaccine. The goal of the collaboration is for the Lassa and MERS vaccines to be available as soon as possible for emergency use.

In June 2018, we announced positive results from the Phase 1 trial of GLS-5300. In the trial, treatment with GLS-5300 was well tolerated and resulted in overall high levels of antibody responses in roughly 95% of subjects, while also generating broad-based T cell responses in nearly 90% of study participants. Antibody responses were observed in 94% of subjects at week 14 (two weeks after the third dose). Additionally, there were no statistically significant dose-dependent differences in antibody response rates (91%, 95%, and 95% at doses of 0.67, 2, and 6 mg, respectively). Durable antibody responses were also maintained through 60 weeks following dosing.

In September 2018, we announced the dosing of the first subject in a Phase 1/2a study of GLS-5300 in South Korea funded by IVI. We expect to advance GLS-5300 into a Phase 2 field trial in the Middle East in 2019 with CEPI funding.

HIV (Human Immunodeficiency Virus)

Overview

Since its discovery in 1981, HIV, the virus which causes AIDS, has killed more than 35 million people. Worldwide in 2017, there were an estimated 1.8 million new HIV infections and 940,000 deaths due to HIV. That year worldwide,

an estimated approximately 37 million people were living with HIV worldwide. In 2017 in the United States, 38,739 people received an HIV diagnosis. At the end of 2015, 1.12 million people in the United States were living with HIV. Effective vaccines have been actively pursued for over 30 years, without significant success. HIV represents one of the most confounding targets in medicine. The virus's 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 (anti-retrovirals) are available to treat the patients once they are infected, vaccines and immunotherapies are necessary to stop the spread of disease and perhaps reduce the need for anti-retroviral treatment.

Noting that many long-term survivors have high counts of killer CD8+ T cells, the HIV vaccine and immunotherapy field has turned to stimulating the immune system to generate those cells. Recent HIV vaccine candidates used an adenovirus (a common human cold virus) genetically modified to contain code for HIV antigens to prevent viral replication. These vaccines have proven to not be effective. More recently, the RV-144 trial, which employed an ALVAC™ (canary pox) vaccine prime followed by a protein vaccine boost, demonstrated 30% efficacy in preventing acquisition of infection amongst the vaccinated population compared to the control group. Although the efficacy was relatively modest, the finding for the first time showed that an immunotherapy may be able to combat spread of HIV and has spurred the development of newer immunotherapy candidates. We believe, however, that a different approach is needed to develop an effective vaccine or immunotherapy for HIV.

PENNVAX®-GP - Preventive and Therapeutic Immunotherapies

PENNVAX®-GP is a developmental vaccine intended to prevent and treat HIV strains present in Africa, Asia, Europe, and North America. Using our SynCon® technology, it has been optimized to target two env antigens, as well as gag and pol antigens. This comprehensive targeting gives PENNVAX®-GP the potential to provide global coverage against HIV-1 subtypes. PENNVAX®-GP is delivered intramuscularly using the CELLECTRA® delivery device. The development of the PENNVAX®-GP program was funded by a seven-year, $25 million NIAID contract to us and our collaborators.

In September 2015, the first patient was dosed in a Phase 1 trial to evaluate the safety and tolerability of PENNVAX®-GP. This trial was conducted in collaboration with the HIV Vaccine Trials Network (HVTN). The trial measured immune responses following administration of the vaccine in four groups of healthy subjects receiving the vaccine with and without an immune activator (IL-12) and delivered into muscle or skin using our CELLECTRA® delivery technology.

In May 2017, we announced results from the trial, in which PENNVAX®-GP produced among the highest overall levels of immune response rates (cellular and humoral) ever observed in a human clinical trial by an HIV vaccine. Overall, 71 of 76 (93%) evaluable vaccinated participants showed a CD4+ or CD8+ T cells cellular immune response to at least one of the four vaccine antigens. Similarly, 62 of 66 (94%) evaluated participants had an env specific antibody response. None of the placebo recipients (0 of 9) had either a cellular or an antibody response in the study. Notably, amongst the participants receiving PENNVAX®-GP vaccine and IL-12 with intradermal immunization, 27 of 28 (96%) participants achieved a cellular response and 27 of 28 (96%) achieved an HIV env specific antibody response.

Amongst the evaluated participants receiving PENNVAX®-GP and IL-12 via intramuscular vaccination, 27 of 27 (100%) achieved a cellular response and 19 of 21 (90%) achieved an env specific antibody response. Similar immune responses and response rates were achieved via both intradermal and intramuscular administration of the vaccine, even though participants vaccinated via intradermal administration received 1/5th of the dose of vaccine compared to those vaccinated via intramuscular administration.

In addition to our NIAID contract that funded our Phase 1 clinical trial of PENNVAX®-GP, in 2015, we and our collaborators were awarded an additional $16 million Integrated Preclinical/Clinical AIDS Vaccine Development (IPCAVD) grant from the NIAID. We will use this additional grant to design and test new PENNVAX® envelope constructs with our DNA-based immune activator encoding novel cytokine genes in a prime-boost strategy with recombinant HIV envelope proteins. Our collaborators will assess different combinations in preclinical models with the goal of generating high levels of neutralizing antibodies mirroring the robust CD8+ T cell responses generated by our PENNVAX®-B DNA vaccine in previously published clinical studies. The overall goal of this project is to further build upon this important HIV vaccine approach as well as to gain fundamental insight into new technologies to

improve vaccination outcomes.

In March 2017, we and our collaborators received an additional multi-year $7.0 million grant from NIAID to develop a single or combination therapy using PENNVAX®-GP, with the goal of attaining long-term HIV remission in the absence of antiviral drugs. This is a two-step clinical study in HIV-positive subjects to assess PENNVAX®-GP with INO-9012 alone and with the addition of a PD-1 checkpoint inhibitor. All trials will be randomized, double-blind,

placebo-controlled assessments of PENNVAX®-GP and will be conducted at the University of California in San Francisco and Los Angeles.

In August 2018, we announced that the first participant had been dosed with PENNVAX®-GP in a Phase 1/2 clinical trial designed to evaluate its ability to drive remission of HIV infection. This Phase 1/2 HIV trial is a randomized, double-blinded, placebo-controlled study. The trial is divided into two cohorts and all vaccines are delivered via the CELLECTRA® device. In the main study (Cohort A), 45 HIV-infected adults who initiated antiretroviral therapy during chronic infection will receive either PENNVAX-GP, another vaccine formulation that contains only Gag/Pol antigens, or a placebo. Both vaccines are also co-administered with INO-9012. In the single arm and uncontrolled second study (Cohort B), individuals who initiated antiretroviral therapy during acute HIV infection will receive PENNVAX-GP together with INO-9012.

In October 2018, we announced preliminary results from the Phase 1/2 trial, in which PENNVAX®-GP delivered via intradermal route resulted in durable and robust antibody and T cell immune responses measured throughout the duration of the study. In this study, PENNVAX-GP plasmids were delivered intradermally or intramuscularly with CELLECTRA® device in healthy volunteers. PENNVAX-GP delivered intradermally (ID) with CELLECTRA® generated equivalent or superior immune responses compared to the delivery via intramuscular (IM) route using the same delivery device, with ID delivery using only one-fifth of the dose compared to IM delivery.

HIV dMAb®

In July 2016, we announced that our DNA-based monoclonal antibody technology will be deployed to develop product candidates that could be used alone and in combination with other immunotherapies in the pursuit of new ways to treat and potentially cure infection from HIV. See the section below titled "Synthetic DNA-based Monoclonal Antibodies" for more details on this technology.

Universal Influenza Immunotherapy

Conventional vaccines are strain-specific and have limited ability to protect against genetic shifts in the influenza strains they target. They are therefore modified annually in anticipation of the next flu season’s new strain(s). If a significantly different, unanticipated new strain emerges, such as the 2009 swine-origin pandemic strain, then the current vaccines provide little or no protective capability. In contrast, we believe that our design approach to characterize a broad consensus of antigens across variant strains of each influenza sub-type creates the ability to protect against new strains that have common genetic roots, even though they are not perfectly matched. By formulating a single immunotherapy with some or all of the key sub-types, protection may be achieved against seasonal as well as pandemic strains such as swine flu or pandemic-potential strains, such as avian influenza. We are focused on developing DNA-based influenza immunotherapies able to provide broad protection against known as well as newly emerging, unknown seasonal and pandemic influenza strains.

Instead of targeting a specific strain or strains, we have developed a universal vaccine strategy to deal with ever-changing flu threats. Using our SynCon® process, our scientists have designed immunotherapies targeting an optimal consensus of HA, NA, and NP proteins derived from multiple strains of each of the Type A sub-types H1N1, H2N2, H3N2 (these three influenza sub-types having been responsible for the majority of seasonal and pandemic influenza outbreaks in humans during the last century), as well as H5N1. In theory, consensus HA vaccine constructs from each sub-type, delivered using our CELLECTRA® device, could potentially protect immunized subjects from 90-95% of all human seasonal and pandemic influenza concerns. Additionally, we have also developed an optimal consensus of HA sequences derived from influenza Type B strains. Type B is one of three components of current seasonal influenza vaccinations. Using our SynCon® constructs, we have now developed immunotherapy elements that can target both pandemic-risk (H5N1, H7N9, H1N1) as well as seasonal influenza strains (H3N2, H1N1, influenza B).

Moreover, using our approach the immunotherapies might not have to be administered annually after the first few priming sessions. Rather, the same combination could be used to boost the immune system every few years.

In January 2018, we announced results from a preclinical study in which our synthetic vaccine approach, using a collection of synthetic DNA antigens, generated broad protective antibody responses against all major deadly strains of H1 influenza viruses from the last 100 years, including the virus that caused “Spanish Flu” in 1918 in multiple animal models, including mice, guinea pigs and non-human primates. The vaccine also protected 100% of immunized ferrets from a lethal virus challenge. The preclinical results were detailed in a paper published in the journal Vaccine entitled,

“Broad cross-protective anti-hemagglutination responses elicited by influenza microconsensus DNA vaccine."
We are seeking additional grant and/or collaboration funding to further advance this program.
Immunotherapies for Biodefense and Biosecurity

A number of infectious agents that are relatively rare today are poised for an upsurge in incidence by either “natural” or terrorism-related means. For example, natural threats are posed by the influenza strains H5N1 and H7N9. At the same time, an engineered influenza virus for intentional release would pose a significant human threat.

Since 2001, the United States government has spent or allocated over a billion dollars in funding to address the threat of biological weapons. United States funding for bioweapons-related activities focuses primarily on research for and acquisition of medicines for defense. Biodefense funding also goes toward stockpiling protective equipment, increased surveillance and detection of biological agents, and improving state and hospital preparedness. The increase in this type of funding is mainly due to the Project BioShield Act adopted in 2004.

There are opportunities to secure development funding and for proof-of principle immunotherapy studies for bio-warfare pathogens. We have secured funding from the U.S. government for these projects.

We continue to actively pursue grant and contract funding from the NIH, Department of Defense and other government funding agencies as a source of non-dilutive funding to support development of specific technologies that are broadly applicable across multiple product development programs in the areas of cancer, infectious diseases and biodefense. Based on various initiatives and with the support of NIH funding we are an active collaborator with the Department of Defense (U.S. Army) and continue research and development of DNA-based immunotherapies delivered via our proprietary CELLECTRA® delivery system. Specifically, our projects are focused on identifying immunotherapy candidates with the potential to provide rapid, robust immunity to protect against bio-warfare and bioterror attacks as well as development of our CELLECTRA® devices.

In October 2014, we announced that DARPA had awarded $12.2 million to our scientists and those from the Perelman School of Medicine at the University of Pennsylvania and AstraZeneca to develop and assess dMAb products for influenza and antibiotic resistant bacteria in preclinical studies. This collaboration aims to demonstrate that DNA plasmids can activate sufficient quantities of disease-specific monoclonal antibodies in the body to be protective against a pathogen challenge. See the section below titled "Synthetic DNA-based Monoclonal Antibodies" for more details on our dMAb programs.

Synthetic DNA-based Monoclonal Antibodies Program

Monoclonal antibodies (mAbs) have become one of the most valuable therapeutic technologies of recent years. In 2012, global sales of mAbs exceeded $50 billion. Among the top 10 best-selling drugs in 2012, six were monoclonal antibodies, each with annual sales exceeding $5 billion.

mAbs are designed to enhance the immune system's ability to regulate cell functions. They are designed to bind to a very specific epitope (area) of an antigen or cell surface target and can bind to almost any selected target. They have the ability to alert the immune system to attack and kill specific cancer cells (as in the case of Yervoy®) or block certain biochemical pathways (such as those leading to rheumatoid arthritis, as in the case of Humira®). However, mAb technology has limitations. As a passive immunotherapy, meaning they are manufactured outside the body, mAbs require costly large-scale laboratory development and production. Additional limitations include high cost to develop and manufacture, their limited duration of in vivo potency, and a pharmacokinetic profile that can result in toxicity. We have created DNA based monoclonal antibodies that we believe overcome many of the limitations associated with conventional mAb technology.

Using our core platform technology, we encode the DNA sequence for a specific monoclonal antibody in a DNA plasmid. We deliver the plasmid directly into cells of the body using CELLECTRA®, enabling these cells to manufacture the mAbs in vivo, - unlike conventional mAb technology that requires manufacture outside of the body. We believe this approach provides potentially significant advantages in terms of lower production costs, as well as the ability to target a pharmacokinetic profile that provides control in terms of dosing regimen, peak responses, duration of responses and toxicity.

We expect to design dMAb product candidates not only for new disease targets not currently addressable with conventional mAbs, but also targets of existing, commercially available mAb products. We have already designed and produced dMAb product candidates targeting cancer mechanisms including checkpoint inhibition, anti-cancer pathways and anti-Tregs, as well as prophylactic and therapeutic dMAb product candidates for infectious diseases including Ebola, influenza, antibiotic resistant bacteria, dengue and Chikungunya. When the mAb binds to an infectious disease receptor, the immune system then generates natural killer cells and macrophages to clear the virus or bacteria-bound mAbs.

Proof of Concept

Our first published research on a DNA-based monoclonal antibody was presented in October 2013 in Human Vaccines & Immunotherapeutics in a paper entitled, “Optimized and enhanced DNA plasmid vector based in vivo construction of a neutralizing anti-HIV-1 envelope glycoprotein Fab.” In a preclinical study, a single administration in mice of a highly optimized dMAb® HIV immunotherapy generated antibody molecules in the bloodstream that possessed

desirable functional activity, including high antigen-binding and HIV-neutralization capabilities, against diverse strains of HIV viruses. In the study, this delivery strategy resulted in an increase in Fab levels in as little as 48 hours, when compared with protein-based immunization.

A second paper was published in July 2015 in Scientific Reports, a Nature Publishing Group journal, in the paper, "Protection against dengue disease by synthetic nucleic acid antibody prophylaxis/immunotherapy." In this study, a single intramuscular injection of a DNA plasmid encoding a monoclonal antibody targeting dengue protected mice subsequently exposed to the dengue virus. The protection conferred by the monoclonal antibodies expressed by these dMAb product candidates was very rapid, with 100% survival in mice challenged with lethal enhanced dengue disease less than a week after dMAb administration. While conventional vaccine and monoclonal antibody technologies have shown limited ability to provide an effective solution to dengue to date, the unique attributes and data generated by dMAb immunotherapies show their potential to provide a needed solution. Furthermore, this short time frame to achieve full protection is significantly more rapid than vaccine-driven protection, which can take weeks to months to reach peak efficacy levels.

A paper published in March 2016 in The Journal of Infectious Diseases entitled, “Rapid and long-term immunity elicited by DNA encoded antibody prophylaxis and DNA vaccination against Chikungunya virus,” discussed the results of our preclinical study in which animals transfected with our DNA-based mAb targeting Chikungunya virus (CHIKV) exhibited the specific ability to bind to the CHIKV envelope antigen, and this serum possessed CHIKV-neutralizing activity. CHIKV is a serious mosquito-borne alpha-virus responsible for several recent epidemics in tropical Africa and Asia. In mid-2015, the CDC reported that suspected or confirmed cases of Chikungunya had reached 1.74 million in 45 countries or territories in the Americas. There is currently no vaccine or therapeutic against this virus. In the study, the treatment of the animals with anti-CHIKV mAb plasmids protected 100% of the treated animals from a lethal injection of CHIKV virus while 100% of the control animals died. The treated animals were also spared virus-related morbidity, as measured by dramatic weight loss and lethargy.

Next Steps

In October 2014, we announced that the DARPA had awarded a $12.2 million grant to our scientists and those from the Perelman School of Medicine at the University of Pennsylvania and AstraZeneca in order to develop and assess dMAb product candidates in preclinical studies.

This collaboration aims to demonstrate that DNA plasmids can activate sufficient quantities of disease-specific monoclonal antibodies in the body to be protective against a pathogen challenge. Using the capabilities and advantages of DNA plasmids delivered using CELLECTRA®, the team is constructing and evaluating multiple dMAb product candidates focused on influenza virus and antibiotic resistant bacteria, such as Pseudomonas aeruginosa and Staphylococcus aureus.

In 2016, we expanded the collaboration to include The Wistar Institute after the collaborating investigator, Dr. David Weiner, a member of our board of directors, moved to the Institute.

Depending on the outcome of the preclinical studies, we and our collaborators may seek to advance a dMAb product candidate into clinical trials, if we are able to obtain additional governmental or non-governmental funding to do so.

As described above, in April 2015, we received a grant from DARPA to lead a consortium to develop multiple treatment and prevention approaches against Ebola. The aim of the research funded by this grant is to compare combinations of a DNA vaccine with conventional or DNA-based monoclonal antibodies.

In July 2016, we announced that our DNA-based monoclonal antibody technology will be deployed to develop product candidates which could be used alone and in combination with other immunotherapies in the pursuit of new ways to treat and potentially cure infection from HIV. Funding for this research is part of a $23 million grant from the National Institutes of Health to our collaborator, The Wistar Institute.

As described above, we have also received a sub-grant through The Wistar Institute to develop a DNA-based monoclonal antibody designed to provide a fast-acting treatment against Zika infection and its debilitating effects.

In February 2019, we announced that in collaboration with The Wistar Institute and the University of Pennsylvania, the first subject was dosed as part of the first-ever human study of our dMAb technology. Funded fully by the Bill & Melinda Gates Foundation, this trial's focus is on evaluating our dMAb's ability to prevent or treat Zika virus infection. This open-label trial is a single center, dose escalation trial that will enroll up to 24 healthy volunteers who will receive up to four doses of dMAbs.

License, Collaboration and Supply Agreements

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We have entered into various arrangements with corporate, academic, and government collaborators, licensors, licensees and others. These arrangements are summarized below.

AstraZeneca

In August 2015, we entered into a strategic cancer vaccine collaboration and license agreement with AstraZeneca. Under the agreement, AstraZeneca acquired exclusive rights to our immunotherapy candidate INO-3112 (renamed MEDI0457), which targets cancers caused by human papillomavirus (HPV) types 16 and 18.

Under the terms of the agreement, AstraZeneca made an upfront payment of $27.5 million to us in the third quarter of 2015. AstraZeneca will fund all development costs. The agreement also calls for potential future payments totaling up to $700 million upon reaching specified development and commercial milestones. We are entitled to receive up to double-digit tiered royalties on MEDI0457 product sales.

AstraZeneca is studying MEDI0457 in combination with its PD-L1 checkpoint inhibitor, durvalumab, in a Phase 1/2 clinical trial in patients with recurrent or metastatic head and neck squamous cancer associated with HPV. On December 28, 2017, we received a $7.0 million milestone payment from AstraZeneca, which was triggered by the initiation of the Phase 2 portion of this ongoing clinical trial. In January 2019, we received a $2.0 million milestone payment from AstraZeneca, which was triggered by the initiation of a Phase 2 combination trial to evaluate MEDI0457 in combination with durvalumab targeting a broad array of cancers associated with HPV.

Within the broader collaboration, we and AstraZeneca are co-developing an additional DNA-based cancer vaccine product candidate (not included in our current product pipeline), and AstraZeneca will have the exclusive rights to develop and commercialize. We will receive development, regulatory and commercialization milestone payments and will be eligible to receive royalties on worldwide net sales for this cancer vaccine product.

GeneOne

In September 2014, we and GeneOne announced a collaboration in which the companies will co-develop our DNA-based Ebola vaccine through a Phase 1 clinical trial. In April 2015, the collaborators received an award from DARPA to further advance the Ebola project. The previous collaboration agreement with GeneOne for Ebola vaccine was incorporated into this consortium funded by DARPA. In May 2015, a Phase 1 study of the DNA vaccine part of the project was initiated. Enrollment of this study has been completed. Details of this project are provided under "Ebola" above.

In May 2015, we announced that we will advance a DNA vaccine for MERS into a Phase 1 clinical trial in healthy volunteers in a collaboration with GeneOne. Under the terms of the agreement, GeneOne will be responsible for funding all preclinical and clinical studies through Phase 1. In return, GeneOne will receive up to a 35% milestone-based ownership interest in the MERS immunotherapy upon achievement of the last milestone event of completion of the Phase 1 safety and immunogenicity study. In January 2016, the collaborators announced the initiation of recruitment for the Phase 1 study in partnership with the Walter Reed Army Institute of Research (WRAIR) in Maryland, where the trial was conducted. We announced results from the trial in June 2018.

In January 2016, we and GeneOne expanded the collaboration agreement to test and advance our DNA-based vaccine for preventing and treating Zika virus.

ApolloBio

In December 2017, we entered into an Amended and Restated License and Collaboration Agreement with Beijing Apollo Saturn Biological Technology Limited, a corporation organized under the laws of China, or ApolloBio. Under the terms of this License and Collaboration Agreement, which became effective in March 2018, we granted to ApolloBio the exclusive right to develop and commercialize VGX-3100, our DNA immunotherapy product candidate designed to treat pre-cancers caused by HPV, within the territories of China, Hong Kong, Macao and Taiwan. The territory may be expanded to include Korea in the event that no patent covering VGX-3100 issues in China within the first three years of the term of the agreement.

As part of the License and Collaboration Agreement, we have granted to ApolloBio an option to negotiate an exclusive license to research, develop and commercialize MEDI0457 in the event of termination of our current collaboration with AstraZeneca for the development of MEDI0457 in the territory covered by the License and Collaboration Agreement. As part of the collaboration, ApolloBio will fund all clinical development costs within the licensed territory, and the parties will discuss in good faith the inclusion of clinical trial sites in China as part of our ongoing Phase 3 clinical development program for VGX-3100.

Under the License and Collaboration Agreement, we received proceeds of $19.4 million in March 2018, which comprised an upfront payment of $23.0 million less $2.2 million in foreign income taxes and $1.4 million in certain foreign non-income taxes. The foreign income taxes were recorded as a provision for income taxes and the foreign non-

income taxes were recorded as a general and administrative expense, on the condensed consolidated statement of operations during the year ended December 31, 2018.

In addition to the upfront payment, we are entitled to receive up to an aggregate of $20.0 million, less required income, withholding or other taxes, upon the achievement of specified milestones related to the regulatory approval of VGX-3100 in the United States, China and Korea. In the event that VGX-3100 is approved for marketing in these territories, we will be entitled to receive royalty payments based on a tiered percentage of annual net sales, with such percentage being in the low- to mid-teens, subject to reduction in the event of generic competition in a particular territory. ApolloBio's obligation to pay royalties will continue for 10 years after the first commercial sale in a particular territory or, if later, until the expiration of the last-to-expire patent covering the licensed products in the specified territory. The License and Collaboration Agreement, once effective, will continue in force until ApolloBio has no remaining royalty obligations.

Agreements Focused on Advancing Immuno-Oncology

In May 2017, we entered into a supply agreement with Genentech to obtain supply of TECENTRIQ® (atezolizumab) for use in our clinical trials evaluating INO-5401 and INO-9012, an immune activator encoding IL-12, in combination with TECENTRIQ®, in approximately 80 patients with advanced bladder cancer. We will manage and fund the costs of the multi-center, open-label trial.

In May 2017, we entered into a clinical study and supply agreement with Regeneron to provide its PD-1 inhibitor, REGN2810, for use in our clinical trials evaluating INO-5401 and INO-9012, in combination with REGN2810, in patients with newly diagnosed GBM. Under the terms of the agreement, we will conduct and fund the trial based upon a mutually agreed upon study design.

In January 2018, we entered into a Clinical Collaboration Agreement with the Parker Institute for Cancer Immunotherapy to undertake clinical evaluation of novel combination regimens within the field of immuno-oncology. We expect to benefit from the Parker Institute's innovative research model, which brings together leading academic cancer institutions and companies to share resources, data and technology, accelerate research through unifying and managing clinical trial design, and conduct multi-center clinical trials. The goal of our collaboration is to design studies that have the potential to address cancers with high unmet need. The initial trial under consideration would address muscle-invasive bladder cancer with INO-5401 in combination with other immunotherapies.

Under the agreement, the Parker Institute will have responsibility for clinical study execution, working in collaboration with its established network of clinical academic and industry cancer centers. We will provide financial contributions if the product candidate studied under the collaboration reaches the initiation of a Phase 3 clinical trial.

Geneos Therapeutics

In August 2016, we incorporated a subsidiary, Geneos Therapeutics, Inc., to develop and commercialize neoantigen based personalized cancer therapies. As of December 31, 2018, we owned 100% of the outstanding equity of Geneos. In February 2019, Geneos raised capital from the issuance of equity to us and other third parties, which reduced our ownership percentage. While we leverage our SynCon® immunotherapy and CELLECTRA® delivery technologies to break tolerance and create cancer products targeting shared tumor specific antigens, Geneos is focusing exclusively on leveraging our immunotherapy technology platform to advance the field of patient-specific neoantigen therapies for cancer. We believe that our clinically validated DNA-based platform is well suited for advancing individualized therapies due to its rapid product design and manufacturing benefits, ability to combine multiple neoantigens into formulations, and generation of potent killer T cell responses that are needed to drive clinical efficacy. We have exclusively licensed our SynCon® immunotherapy and CELLECTRA® technology platform to Geneos to be used in the field of personalized, neoantigen based therapy for cancer. The license agreement provides for potential royalty payments to us in the event that Geneos commercializes any products using the licensed technology.

Core DNA Immunotherapy Technology and Product License

In March 2016, we entered into a collaborative research agreement with the Wistar Institute for preventive and therapeutic DNA-based immunotherapy applications and products for cancers and infectious diseases developed by David B. Weiner, Ph.D., and his Wistar laboratory. We will have the exclusive right to in-license new intellectual property developed in this collaboration.

We also have license agreements for intellectual property relating to DNA-based immunotherapy technology and multiple products developed at the University of Pennsylvania, or UPenn. Under the terms of the license agreement

with UPenn, we have obtained exclusive worldwide rights to develop multiple DNA plasmids and constructs with the potential to treat and/or prevent cancer therapeutic vaccines targeting WT1, prostate cancer, other undisclosed cancer antigen targets, HPV, HBV, HCV, HIV, influenza, RSV (respiratory syncytial virus), cytomegalovirus, Chikungunya, dengue fever, malaria, herpes viruses, MERS, Ebola and the family of Filovirus such as Marburg, tuberculosis, foot-and-

mouth disease, intestinal infections including Clostridium difficile, and MRSA (methicillin-resistant staphylococcus aureus). In addition, the amended agreement provides us with global rights to DNA-based monoclonal antibodies and new chemokine and cytokine molecular adjuvant technologies.

This agreement, as amended to date, provides for royalty payments, based on future sales of licensed products, to UPenn.

The Wistar Institute Collaboration for Programs against Tuberculosis and Malaria

In early 2018, we announced that we will collaborate with The Wistar Institute to advance two novel SynCon® vaccine programs against tuberculosis (TB) and malaria, fully funded by more than $4.6 million in total grants from the Bill & Melinda Gates Foundation and the National Institutes of Health (NIH). Grants from the Gates Foundation (for malaria) and from the National Institute of Allergy & Infectious Diseases (for TB) will support our efforts to develop new DNA vaccines employing our technology platform.

Competition

As we develop and seek to ultimately commercialize our product candidates, we face and will continue to encounter competition with an array of existing or development-stage drug and immunotherapy approaches targeting diseases we are pursuing. We are aware of various established enterprises, including major pharmaceutical companies, broadly engaged in vaccine/immunotherapy research and development. These include Janssen Pharmaceuticals (part of J&J), Sanofi-Aventis, GlaxoSmithKline plc (following its acquisition of Novartis Vaccines), Merck, Pfizer, and our collaborator AstraZeneca. There are also various development-stage biotechnology companies involved in different vaccine and immunotherapy technologies including Aduro Biotech, Advaxis, BioNTech, CureVac, Dynavax, Immune Design, Moderna, Novavax, and Translate Bio. If these companies are successful in developing their technologies, it could materially and adversely affect our business and our future growth prospects.

Bavarian Nordic, Merck and GlaxoSmithKline have commercialized preventive vaccines against HPV to protect against cervical cancer. Some companies are seeking to treat early HPV infections or low grade cervical dysplasias. Loop Electrosurgical Excision Procedure, commonly known as LEEP, is the current standard of care for treating high grade cervical dysplasia. Advaxis and Gilead Sciences have therapeutic cervical cancer product candidates under development. Many companies are pursuing different approaches to prostate, breast, lung and other cancers we are targeting.

We also compete more specifically with companies seeking to utilize antigen-encoding DNA delivered with electroporation or other DNA delivery technologies such as viral vectors or lipid vectors to induce in vivo generated antigen production and immune responses to prevent or treat various diseases. These competitive technologies have shown promise, but they each also have their unique obstacles to overcome.

Viral DNA Delivery

This technology utilizes a virus as a carrier to deliver genetic material into target cells. The method is efficient for delivering immunotherapy antigens and has the advantage of mimicking real viral infection so that the recipient will mount a broad immune response against the immunotherapy. The greatest limitation of the technology stems from problems with unwanted immune responses against the viral vector, limiting its use to patients who have not been previously exposed to the viral vector and making repeated administration difficult. In addition, complexity and safety concerns increase their cost and complicate regulatory approval.

Lipid DNA Delivery

A number of lipid formulations have been developed that increase the effect of DNA/RNA immunotherapies. These work by either increasing uptake of the DNA/RNA into cells or by acting as an adjuvant, alerting the immune system. While there has been progress in this field, lipid delivery tends to be less efficient than viral vectors and is hampered by concerns regarding toxicity and increased complexity.

DNA Immunotherapy Delivery With Electroporation

There are other companies with electroporation intellectual property and devices. We believe we have significant competitive advantages over other companies focused on electroporation for multiple reasons:

- We have an extensive history and experience in developing the methods and devices that optimize the use of electroporation in conjunction with DNA-based agents. This experience has been validated with multiple sets of interim data from multiple clinical studies assessing DNA-based immunotherapies and vaccines against cancers and infectious disease.

- We have a broad product line of electroporation instruments designed to enable DNA delivery in tumors, muscle, and skin.

- We have been proactive in filing for patents, as well as acquiring and licensing additional patents, to expand our global patent estate.

If any of our competitors develop products with efficacy or safety profiles significantly better than our product candidates, we may not be able to commercialize our products, and sales of any of our commercialized products could be harmed. Some of our competitors and potential competitors have substantially greater product development capabilities and financial, scientific, marketing and human resources than we do. Competitors may develop products earlier, obtain FDA approvals for products more rapidly, or develop products that are more effective than those under development by us. We will seek to expand our technological capabilities to remain competitive; however, research and development by others may render our technologies or products obsolete or noncompetitive, or result in treatments or cures superior to ours.

Our competitive position will be affected by the disease indications addressed by our product candidates and those of our competitors, the timing of market introduction for these products and the stage of development of other technologies to address these disease indications. For us and our competitors, proprietary technologies, the ability to complete clinical trials on a timely basis and with the desired results, and the ability to obtain timely regulatory approvals to market these product candidates are likely to be significant competitive factors. Other important competitive factors will include the efficacy, safety, ease of use, reliability, availability and price of products and the ability to fund operations during the period between technological conception and commercial sales.

The FDA and other regulatory agencies may expand current requirements for public disclosure of DNA-based product development data, which may harm our competitive position with foreign and United States companies developing DNA-based products for similar indications.

Government Regulation

Government authorities in the United States at the federal, state and local level and in other countries extensively regulate, among other things, the research, development, testing, manufacture, quality control, approval, labeling, packaging, storage, record-keeping, promotion, advertising, distribution, post-approval monitoring and reporting, marketing and export and import of biological products, or biologics, and medical devices, such as our product candidates. Generally, before a new biologic or medical device can be marketed, considerable data demonstrating its quality, safety and efficacy must be obtained, organized into a format specific to each regulatory authority, submitted for review and approved by the regulatory authority.

Review and Approval of Combination Products in the United States

Certain products may be comprised of components that would normally be regulated under different types of regulatory authorities, and frequently by different centers at the FDA. These products are known as combination products. Specifically, under regulations issued by the FDA, a combination product may be:

- a product comprised of two or more regulated components that are physically, chemically, or otherwise combined or mixed and produced as a single entity;
- two or more separate products packaged together in a single package or as a unit and comprised of drug and device products;
- a drug, device, or biological product packaged separately that according to its investigational plan or proposed labeling is intended for use only with an approved individually specified drug, device or biological where both are required to achieve the intended use, indication, or effect and where upon approval of the proposed product the labeling of the approved product would need to be changed, e.g., to reflect a change in intended use, dosage form, strength, route of administration, or significant change in dose; or
- any investigational drug, device, or biological packaged separately that according to its proposed labeling is for use only with another individually specified investigational drug, device, or biological product where both are required to achieve the intended use, indication, or effect.

Our product candidates are combination products comprising an electroporation device for delivery of a biologic. Under the Federal Food, Drug, and Cosmetic Act, or FDCA, the FDA is charged with assigning a center with primary jurisdiction, or a lead center, for review of a combination product. That determination is based on the “primary mode of action” of the combination product, which means the mode of action expected to make the greatest contribution to the overall intended therapeutic effects. Thus, if the primary mode of action of a device-biologic combination product is attributable to the biologic product, that is, if it acts by means of a virus, therapeutic serum, toxin, antitoxin, vaccine,

blood, blood component or derivative, allergenic product, or analogous product, the FDA center responsible for premarket review of the biologic product would have primary jurisdiction for the combination product. We believe that

all of our product candidates will have a biologic primary mode of action, with the device component reviewed under a Device Master File.

U.S. Biological Product Development

In the United States, the FDA regulates biologics under FDCA, and the Public Health Service Act, or PHSA, and their implementing regulations. Biologics are also subject to other federal, state and local statutes and regulations. The process of obtaining regulatory approvals and the subsequent compliance with appropriate federal, state, local and foreign statutes and regulations require the expenditure of substantial time and financial resources. Failure to comply with the applicable U.S. requirements at any time during the product development process, approval process or after approval, may subject an applicant to administrative or judicial sanctions. These sanctions could include, among other actions, the FDA's refusal to approve pending applications, withdrawal of an approval, a clinical hold, untitled or warning letters, product recalls or withdrawals from the market, product seizures, total or partial suspension of production or distribution injunctions, fines, refusals of government contracts, restitution, disgorgement, or civil or criminal penalties. Any agency or judicial enforcement action could have a material adverse effect on us.

Our product candidates must be approved by the FDA through the Biologics License Application, or BLA, process before they may be legally marketed in the United States. The process required by the FDA before a biologic may be marketed in the United States generally involves the following:

- completion of extensive nonclinical, sometimes referred to as pre-clinical laboratory tests, pre-clinical animal studies and formulation studies in accordance with applicable regulations, including the FDA's Good Laboratory Practice, or GLP, regulations;
- submission to the FDA of an IND, which must become effective before human clinical trials may begin;
- performance of adequate and well-controlled human clinical trials in accordance with applicable IND and other clinical trial-related regulations, sometimes referred to as good clinical practices, or GCPs, to establish the safety and efficacy of the proposed product candidate for its proposed indication;
- submission to the FDA of a BLA;
- satisfactory completion of an FDA pre-approval inspection of the manufacturing facility or facilities where the product is produced to assess compliance with the FDA's current good manufacturing practice, or cGMP, requirements to assure that the facilities, methods and controls are adequate to preserve the product's identity, strength, quality, purity and potency;
- potential FDA audit of the pre-clinical and/or clinical trial sites that generated the data in support of the BLA; and
- FDA review and approval of the BLA prior to any commercial marketing or sale of the product in the United States.

The data required to support a BLA is generated in two distinct development stages: pre-clinical and clinical. The pre-clinical development stage generally involves laboratory evaluations of drug chemistry, formulation and stability, as well as studies to evaluate toxicity in animals, which support subsequent clinical testing. The conduct of the pre-clinical studies must comply with federal regulations, including GLPs. The sponsor must submit the results of the pre-clinical studies, together with manufacturing information, analytical data, any available clinical data or literature and a proposed clinical protocol, to the FDA as part of the IND. An IND is a request for authorization from the FDA to administer an investigational drug product to humans. The central focus of an IND submission is on the general investigational plan and the protocol(s) for human trials. The IND automatically becomes effective 30 days after receipt by the FDA, unless the FDA raises concerns or questions regarding the proposed clinical trials and places the IND on clinical hold within that 30-day time period. In such a case, the IND sponsor and the FDA must resolve any outstanding concerns before the clinical trial can begin. The FDA may also impose clinical holds on a product candidate at any time before or during clinical trials due to safety concerns or non-compliance. Accordingly, we cannot be sure that submission of an IND will result in the FDA allowing clinical trials to begin, or that, once begun, issues will not arise that could cause the trial to be suspended or terminated.

The clinical stage of development involves the administration of the product candidate to healthy volunteers or patients under the supervision of qualified investigators, generally physicians not employed by or under the trial sponsor's control, in accordance with GCPs, which include the requirement that all research subjects provide their informed consent for their participation in any clinical trial. Clinical trials are conducted under protocols detailing, among other things, the objectives of the clinical trial, dosing procedures, subject selection and exclusion criteria, and the parameters to be used to monitor subject safety and assess efficacy. Each protocol, and any subsequent

amendments to the protocol, must be submitted to the FDA as part of the IND. Further, each clinical trial must be reviewed and approved by an independent institutional review board, or IRB, at or servicing each institution at which the clinical trial

will be conducted. An IRB is charged with protecting the welfare and rights of trial participants and considers such items as whether the risks to individuals participating in the clinical trials are minimized and are reasonable in relation to anticipated benefits. The IRB also approves the informed consent form that must be provided to each clinical trial subject or his or her legal representative and must monitor the clinical trial until completed.

There are also requirements governing the reporting of ongoing clinical trials and completed clinical trial results to public registries. Sponsors of certain clinical trials of FDA-regulated products, including biologics, are required to register and disclose specified clinical trial information, which is publicly available at www.clinicaltrials.gov. Information related to the product, patient population, phase of investigation, study sites and investigators, and other aspects of the clinical trial is then made public as part of the registration. Sponsors are also obligated to disclose the results of their clinical trials after completion.

Clinical trials are generally conducted in three sequential phases that may overlap, known as Phase 1, Phase 2 and Phase 3 clinical trials. Phase 1 clinical trials generally involve a small number of healthy volunteers who are initially exposed to a product candidate. The primary purpose of these clinical trials is to assess the action, side effect tolerability and safety of the product candidate and, if possible, to gain early evidence on effectiveness. Phase 2 clinical trials typically involve studies in patients to determine the dose required to produce the desired benefits. At the same time, safety and preliminary evaluation of efficacy is assessed. Phase 3 clinical trials generally involve large numbers of patients at multiple sites, in multiple countries (from several hundred to several thousand subjects) and are designed to provide the data necessary to demonstrate the efficacy of the product for its intended use, its safety in use, and to establish the overall benefit/risk relationship of the product and provide an adequate basis for product approval. Phase 3 clinical trials may include comparisons with placebo and/or other comparator treatments. The duration of treatment is often extended to mimic the actual use of a product during marketing. Generally, two adequate and well-controlled Phase 3 clinical trials are required by the FDA for approval of a BLA.

Post-approval trials, sometimes referred to as Phase 4 clinical trials, may be conducted after initial marketing approval. These trials are used to gain additional experience from the treatment of patients in the intended therapeutic indication. In certain instances, FDA may condition approval of a BLA on the sponsor’s agreement to conduct additional clinical trials to further assess the biologic’s safety and effectiveness after BLA approval.

Progress reports detailing the results of the clinical trials must be submitted at least annually to the FDA and written IND safety reports must be submitted to the FDA and the investigators for serious and unexpected suspected adverse, findings from other studies suggesting a significant risk to humans exposed to the drug, findings from animal or in vitro testing suggesting a significant risk to humans, and any clinically important rate increase of a serious suspected adverse reaction over that listed in the protocol or investigator brochure. Phase 1, Phase 2 and Phase 3 clinical trials may not be completed successfully within any specified period, if at all. The FDA, the IRB, or the sponsor may suspend or terminate a clinical trial at any time on various grounds, including a finding that the research subjects or patients are being exposed to an unacceptable health risk. Similarly, an IRB can suspend or terminate approval of a clinical trial at its institution if the clinical trial is not being conducted in accordance with the IRB’s requirements or if the drug has been associated with unexpected serious harm to patients. Additionally, some clinical trials are overseen by an independent group of qualified experts organized by the clinical trial sponsor, known as a data safety monitoring board or committee. This group provides authorization for whether or not a trial may move forward at designated intervals based on access to certain data from the trial. We may also suspend or terminate a clinical trial based on evolving business objectives and/or competitive climate. Concurrent with clinical trials, companies usually complete additional animal studies and must also develop additional information about the chemistry and physical characteristics of the product candidate as well as finalize a process for manufacturing the product in commercial quantities in accordance with cGMP requirements. The manufacturing process must be capable of consistently producing quality batches of the product candidate and, among other things, must develop methods for testing the identity, strength, quality and purity of the final product. Additionally, appropriate packaging must be selected and tested and stability studies must be conducted to demonstrate that the product candidate does not undergo unacceptable deterioration over its shelf life.

BLA and FDA Review Process

Following trial completion, trial data is analyzed to assess safety and efficacy. The results of pre-clinical studies and clinical trials are then submitted to the FDA as part of a BLA, along with proposed labeling for the product and

information about the manufacturing process and facilities that will be used to ensure product quality, results of analytical testing conducted on the chemistry of the product candidate, and other relevant information. The BLA is a request for approval to market the biologic for one or more specified indications and must contain proof of safety, purity, potency and efficacy, which is demonstrated by extensive pre-clinical and clinical testing. The application includes positive findings from pre-clinical and clinical trials as well as ambiguous or negative results. Data may come from company-sponsored clinical trials intended to test the safety and efficacy of a use of a product, or from a number of alternative sources, including studies initiated by investigators. To support marketing approval, the data submitted must

be sufficient in quality and quantity to establish the safety and efficacy of the investigational product to the satisfaction of the FDA.

Under the Prescription Drug User Fee Act, or PDUFA, as amended, each BLA must be accompanied by a significant user fee, which is adjusted on an annual basis. PDUFA also imposes an annual program fee for approved products. Fee waivers or reductions are available in certain circumstances, including a waiver of the application fee for the first application filed by a small business.

Once a BLA has been accepted for filing, which occurs, if at all, sixty days after the BLA's submission, the FDA's goal is to review BLAs within ten months of the filing date for standard review or six months of the filing date for priority review, if the application is for a product intended for a serious or life-threatening condition and the product, if approved, would provide a significant improvement in safety or effectiveness. The review process is often significantly extended by FDA requests for additional information or clarification. If not accepted for filing, the sponsor must resubmit the BLA and begin the FDA's review process again, including the initial sixty day review to determine if the application is sufficiently complete to permit substantive review.

After the BLA submission is accepted for filing, the FDA reviews the BLA to determine, among other things, whether the proposed product candidate is safe and effective for its intended use, and whether the product candidate is being manufactured in accordance with cGMP to assure and preserve the product candidate's identity, strength, quality, purity and potency. The FDA may refer applications for novel drug product candidates or drug product candidates which present difficult questions of safety or efficacy to an advisory committee, typically a panel that includes clinicians and other experts, for review, evaluation and a recommendation as to whether the application should be approved and under what conditions. The FDA is not bound by the recommendations of an advisory committee, but it considers such recommendations carefully when making decisions. The FDA will likely re-analyze the clinical trial data, which could result in extensive discussions between the FDA and us during the review process. The review and evaluation of a BLA by the FDA is extensive and time consuming and may take longer than originally planned to complete, and we may not receive a timely approval, if at all.

Before approving a BLA, the FDA will conduct a pre-approval inspection of the manufacturing facilities for the new product to determine whether they comply with cGMPs. The FDA will not approve the product unless it determines that the manufacturing processes and facilities are in compliance with cGMP requirements and adequate to assure consistent production of the product within required specifications. In addition, before approving a BLA, the FDA may also audit data from clinical trials to ensure compliance with GCP requirements. After the FDA evaluates the application, manufacturing process and manufacturing facilities, it may issue an approval letter or a Complete Response Letter. An approval letter authorizes commercial marketing of the product with specific prescribing information for specific indications. A Complete Response Letter indicates that the review cycle of the application is complete and the application will not be approved in its present form. A Complete Response Letter usually describes all of the specific deficiencies in the BLA identified by the FDA. The Complete Response Letter may require additional clinical data and/or an additional pivotal Phase 3 clinical trial(s), and/or other significant and time-consuming requirements related to clinical trials, pre-clinical studies or manufacturing. If a Complete Response Letter is issued, the applicant may either resubmit the BLA, addressing all of the deficiencies identified in the letter, or withdraw the application. Even if such data and information is submitted, the FDA may ultimately decide that the BLA does not satisfy the criteria for approval. Data obtained from clinical trials are not always conclusive and the FDA may interpret data differently than we interpret the same data.

There is no assurance that the FDA will ultimately approve a product for marketing in the United States and we may encounter significant difficulties or costs during the review process. If a product receives marketing approval, the approval may be significantly limited to specific populations, severities of allergies, and dosages or the indications for use may otherwise be limited, which could restrict the commercial value of the product. Further, the FDA may require that certain contraindications, warnings or precautions be included in the product labeling or may condition the approval of the BLA on other changes to the proposed labeling, development of adequate controls and specifications, or a commitment to conduct post-market testing or clinical trials and surveillance to monitor the effects of approved products. For example, the FDA may require Phase 4 testing which involves clinical trials designed to further assess the product's safety and effectiveness and may require testing and surveillance programs to monitor the safety of approved products that have been commercialized. The FDA may also place other conditions on approvals including

the requirement for a Risk Evaluation and Mitigation Strategy, or REMS, to assure the safe use of the product. If the FDA concludes a REMS is needed, the sponsor of the BLA must submit a proposed REMS. The FDA will not approve the BLA without an approved REMS, if required. A REMS could include medication guides, physician communication plans, or elements to assure safe use, such as restricted distribution methods, patient registries and other risk minimization tools. Any of these limitations on approval or marketing could restrict the commercial promotion, distribution, prescription or dispensing of products. Product approvals may be withdrawn for non-compliance with regulatory standards or if problems occur following initial marketing.

Post-Marketing Requirements

Following approval of a new product, a manufacturer and the approved product are subject to continuing regulation by the FDA, including, among other things, monitoring and recordkeeping activities, reporting to the applicable regulatory authorities of adverse experiences with the product, providing the regulatory authorities with updated safety and efficacy information, product sampling and distribution requirements, and complying with promotion and advertising requirements, which include, among others, standards for direct-to-consumer advertising, restrictions on promoting products for uses or in patient populations that are not described in the product's approved labeling, also known as off-label use, limitations on industry-sponsored scientific and educational activities, and requirements for promotional activities involving the internet. Although physicians may prescribe legally available drugs and biologics for off-label uses, manufacturers may not market or promote such off-label uses. Modifications or enhancements to the product or its labeling or changes of the site of manufacture are often subject to the approval of the FDA and other regulators, which may or may not be received or may result in a lengthy review process. Prescription drug promotional materials must be submitted to the FDA in conjunction with their first use. Any distribution of prescription drug products and pharmaceutical samples must comply with the U.S. Prescription Drug Marketing Act, or the PDMA, a part of the FDCA.

In the United States, once a product is approved, its manufacture is subject to comprehensive and continuing regulation by the FDA. The FDA regulations require that products be manufactured in specific approved facilities and in accordance with cGMP. Moreover, the constituent parts of a combination product retain their regulatory status, for example, as a biologic or device, and as such, we may be subject to additional requirements in the Quality System Regulation, or QSR, applicable to medical devices, such as design controls, purchasing controls, and corrective and preventive action. We rely, and expect to continue to rely, on third parties for the production of clinical and commercial quantities of our products in accordance with cGMP regulations. cGMP regulations require, among other things, quality control and quality assurance as well as the corresponding maintenance of records and documentation and the obligation to investigate and correct any deviations from cGMP. Manufacturers and other entities involved in the manufacture and distribution of approved products are required to register their establishments with the FDA and certain state agencies, and are subject to periodic unannounced inspections by the FDA and certain state agencies for compliance with cGMP and other laws. Accordingly, manufacturers must continue to expend time, money, and effort in the area of production and quality control to maintain cGMP compliance. These regulations also impose certain organizational, procedural and documentation requirements with respect to manufacturing and quality assurance activities. BLA holders using contract manufacturers, laboratories or packagers are responsible for the selection and monitoring of qualified firms, and, in certain circumstances, qualified suppliers to these firms. These firms and, where applicable, their suppliers are subject to inspections by the FDA at any time, and the discovery of violative conditions, including failure to conform to cGMP, could result in enforcement actions that interrupt the operation of any such facilities or the ability to distribute products manufactured, processed or tested by them. Discovery of problems with a product after approval may result in restrictions on a product, manufacturer, or holder of an approved BLA, including, among other things, recall or withdrawal of the product from the market.

The FDA also may require post-approval testing, sometimes referred to as Phase 4 testing, REMS and post-marketing surveillance to monitor the effects of an approved product or place conditions on an approval that could restrict the distribution or use of the product. Discovery of previously unknown problems with a product or the failure to comply with applicable FDA requirements can have negative consequences, including adverse publicity, judicial or administrative enforcement, warning letters from the FDA, mandated corrective advertising or communications with doctors, and civil or criminal penalties, among others. Newly discovered or developed safety or effectiveness data may require changes to a product's approved labeling, including the addition of new warnings and contraindications, and also may require the implementation of other risk management measures. Also, new government requirements, including those resulting from new legislation, may be established, or the FDA's policies may change, which could delay or prevent regulatory approval of our products under development.

Coverage and Reimbursement

Patients in the United States and elsewhere generally rely on third-party payors to reimburse part or all of the costs associated with their prescription drugs. Accordingly, a pharmaceutical company's ability to commercialize its products successfully depends in part on the extent to which private health insurers, other third-party payors, and

governmental authorities, including Medicare and Medicaid, establish appropriate coverage and reimbursement levels for its product candidates and related treatments. As a threshold for coverage and reimbursement, third-party payors generally require that products be approved for marketing by the FDA.

Coverage decisions may not favor new products when more established or lower cost therapeutic alternatives are available. The process for obtaining coverage for a product or service is separate from the process to obtain the associated reimbursement. Reimbursement levels can affect the adoption of products and services by physicians and

patients. Additionally, products used in connection with medical procedures may not be reimbursed separately, but their cost may instead be bundled as part of the payment received by the provider for the procedure only. Separate reimbursement for a product or the treatment or procedure in which the product is used may not be available. Coverage and reimbursement policies for drug products can differ significantly from payor to payor as there is no uniform policy of coverage and reimbursement for drug products among third-party payors in the United States. There may be significant delays in obtaining coverage and reimbursement as the process of determining coverage and reimbursement is often time consuming and costly which may require the provision of scientific and clinical support for the use of the product to each payor separately, with no assurance that coverage or adequate reimbursement will be obtained.

A significant trend in the U.S. healthcare industry and elsewhere is cost containment. Third-party payors have attempted to control costs by limiting coverage and the amount of reimbursement for particular products and services. Third-party payors are increasingly challenging the effectiveness of and prices charged for medical products and services. Moreover, the U.S. government, state legislatures and foreign governmental entities have shown significant interest in implementing cost containment programs to limit the growth of government paid healthcare costs, including price controls, restrictions on reimbursement and coverage and requirements for substitution of generic products for branded prescription drugs.

Healthcare Reform

In both the United States and certain foreign jurisdictions there have been, and continue to be, a number of legislative and regulatory changes to the healthcare system that impact the ability to sell pharmaceutical products profitably. In the United States, the federal government enacted the Patient Protection and Affordable Care Act, as amended by the Health Care and Education Reconciliation Act, or collectively, the ACA. Among the ACA's provisions of importance to the pharmaceutical industry are that it:

- created an annual, nondeductible fee on any entity that manufactures or imports certain specified branded prescription drugs and biologic agents apportioned among these entities according to their market share in some government healthcare programs;
- increased the statutory minimum rebates a manufacturer must pay under the Medicaid Drug Rebate Program, to 23.1% and 13% of the average manufacturer price for most branded and generic drugs, respectively and capped the total rebate amount for innovator drugs at 100% of the Average Manufacturer Price, or AMP;
- created new methodology by which rebates owed by manufacturers under the Medicaid Drug Rebate Program are calculated for certain drugs and biologics that are inhaled, infused, instilled, implanted or injected;
- expanded eligibility criteria for Medicaid programs by, among other things, allowing states to offer Medicaid coverage to additional individuals and by adding new mandatory eligibility categories for individuals with income at or below 133% of the federal poverty level, thereby potentially increasing manufacturers' Medicaid rebate liability;
- expanded the entities eligible for discounts under the Public Health program;
- created a new Patient-Centered Outcomes Research Institute to oversee, identify priorities in, and conduct comparative clinical effectiveness research, along with funding for such research;
- established a Center for Medicare & Medicaid Innovation at the Centers for Medicare & Medicaid Services, or CMS, to test innovative payment and service delivery models to lower Medicare and Medicaid spending, potentially including prescription drug spending that began on January 1, 2011; and
- created a licensure framework for follow on biologic products.

Some of the provisions of the ACA have yet to be implemented, and there have been judicial and Congressional challenges to certain aspects of the ACA, as well as recent efforts by the Trump administration to repeal or replace certain aspects of the ACA. Since January 2017, President Trump has signed two Executive Orders and other directives designed to delay the implementation of certain provisions of the ACA. Concurrently, Congress has considered legislation that would repeal or repeal and replace all or part of the ACA. While Congress has not passed comprehensive repeal legislation, it has enacted laws that modify certain provisions of the ACA such as removing penalties, starting January 1, 2019, for not complying with the ACA's individual mandate to carry health insurance and delaying the implementation of certain ACA-mandated fees. On December 14, 2018, a Texas U.S. District Court Judge ruled that the ACA is unconstitutional in its entirety because the "individual mandate" was repealed by Congress as part of the Tax Cuts and Jobs Act of 2017. While the Texas U.S. District Court Judge, as well as the Trump

administration and CMS, have stated that the ruling will have no immediate effect pending appeal of the decision, it is unclear how this decision, subsequent appeals, and other efforts to repeal and replace the ACA will impact the ACA.

Further there has been heightened governmental scrutiny in the United States of pharmaceutical pricing practices in light of the rising cost of prescription drugs and biologics. Such scrutiny has resulted in several recent congressional inquiries and proposed and enacted federal and state legislation designed to, among other things, bring more transparency to product pricing, review the relationship between pricing and manufacturer patient programs, and reform government program reimbursement methodologies for products. For example, the Trump administration released a "Blueprint" to lower drug prices and reduce out of pocket costs of drugs that contains additional proposals to increase drug manufacturer competition, increase the negotiating power of certain federal healthcare programs, incentivize manufacturers to lower the list price of their products, and reduce the out of pocket costs of drug products paid by consumers. On January 31, 2019, the U.S. Department of Health and Human Services, Office of Inspector General, proposed modifications to the federal healthcare program Anti-Kickback Statute discount safe harbor for the purpose of reducing the cost of drug products to consumers which, among other things, if finalized, will affect discounts paid by manufacturers to Medicare Part D plans, Medicaid managed care organizations and pharmacy benefit managers working with these organizations. While some of these and other proposed measures may require additional authorization to become effective, Congress and the Trump administration have each indicated that it will continue to seek new legislative and/or administrative measures to control drug costs.

Moreover, on May 30, 2018, the Trickett Wendler, Frank Mongiello, Jordan McLinn, and Matthew Bellina Right to Try Act of 2017, or the Right to Try Act, was signed into law. The law, among other things, provides a federal framework for certain patients to access certain investigational new drug products that have completed a Phase I clinical trial and that are undergoing investigation for FDA approval. Under certain circumstances, eligible patients can seek treatment without enrolling in clinical trials and without obtaining FDA permission under the FDA expanded access program. There is no obligation for a drug manufacturer to make its drug products available to eligible patients as a result of the Right to Try Act.

Healthcare Laws

Certain federal, state, local and foreign healthcare laws and regulations pertaining to fraud and abuse, transparency, patients' rights, and privacy are applicable to the business of a pharmaceutical company. The laws that may affect a pharmaceutical company's ability to operate include:

- the federal healthcare program Anti-Kickback Statute, which prohibits, among other things, people from soliciting, receiving or providing remuneration, directly or indirectly, to induce or reward either the referral of an individual, or the purchasing, ordering, or leasing of an item, good, facility or service, for which payment may be made by a federal healthcare program such as Medicare or Medicaid;
- federal civil and criminal false claims laws, including the civil False Claims Act, which prohibit, among other things, individuals or entities from knowingly presenting, or causing to be presented, claims for payment from Medicare, Medicaid, or other third-party payors that are false or fraudulent;
- the federal Health Insurance Portability and Accountability Act of 1996, or HIPAA, which prohibits, among other things, executing a scheme to defraud any healthcare benefit program or making false statements relating to healthcare matters;
- HIPAA, as amended by the Health Information Technology for Economic and Clinical Health Act, and their implementing regulations, which imposes certain requirements relating to the privacy, security and transmission of individually identifiable health information on certain individuals and entities;
- the Physician Payments Sunshine Act, created under the ACA, which requires pharmaceutical companies to record any transfers of value made to doctors and teaching hospitals, as well as ownership and investment interests held by physicians and their immediate family members, and to annually report such data to CMS;
- the Federal Food, Drug, and Cosmetic Act, which among other things, strictly regulates drug product marketing, prohibits manufacturers from marketing drug products for off-label use and regulates the distribution of drug samples;
- the U.S. Foreign Corrupt Practices Act, which, among other things, prohibits companies issuing stock in the U.S. from bribing foreign officials for government contracts and other business; and
- state law equivalents of each of the above federal laws, such as anti-kickback and false claims laws which may apply to items or services reimbursed by any third-party payor, including commercial insurers, state and local laws requiring the registration of pharmaceutical sales and medical representatives, and state laws governing the privacy and security of health information in certain circumstances, many of which differ from each other in significant ways and often are

not preempted by HIPAA, thus complicating compliance efforts; and

- additional state and local laws such as laws in California and Massachusetts, which mandate implementation of compliance programs, compliance with industry ethics codes, and spending limits, and other state and local laws, such as laws in Vermont, Maine, and Minnesota which require reporting to state governments of gifts, compensation, and other remuneration to physicians.

A pharmaceutical company will need to spend substantial time and money to ensure that its business arrangements with third parties comply with applicable healthcare laws and regulations. Because of the breadth of these laws and the narrowness of the statutory exceptions and regulatory safe harbors available, which require strict compliance in order to offer protection, it is possible that governmental authorities may conclude that its business practices do not comply with current or future statutes, regulations, agency guidance or case law involving applicable healthcare laws. If a pharmaceutical company's operations are found to be in violation of any of the laws described above or any other governmental regulations that apply to it, it may be subject to significant penalties, including administrative, civil and criminal penalties, damages, fines, disgorgement, possible exclusion from participation in Medicare, Medicaid and other federal healthcare programs, imprisonment, integrity and/or other oversight obligations, contractual damages, reputational harm and the curtailment or restructuring of operations.

Other Regulations

We also are subject to various federal, state and local laws, regulations, and recommendations relating to safe working conditions, laboratory and manufacturing practices, the experimental use of animals, and the use and disposal of hazardous or potentially hazardous substances, including radioactive compounds and infectious disease agents, used in connection with our research. The extent of government regulation that might result from any future legislation or administrative action cannot be accurately predicted.

Commercialization and Manufacturing

Because of the broad potential applications of our technologies, we intend to develop and commercialize products both on our own and through our collaborators and licensees. We intend to develop and commercialize products in well-defined specialty markets, such as infectious diseases and cancer. Where appropriate, we intend to rely on strategic marketing and distribution alliances.

We believe our plasmids can be produced in commercial quantities through uniform methods of fermentation and processing that are applicable to all plasmids. We believe we will be able to obtain sufficient supplies of plasmids for all foreseeable clinical investigations.

Relationship with GeneOne

We acquired an equity interest in GeneOne in 2005. As of December 31, 2018, we owned 7.8% of the outstanding capital stock of GeneOne and GeneOne owned 73,590 shares of our common stock. To our knowledge, none of our current officers, directors, or key employees beneficially owns, directly or indirectly, any securities of GeneOne.

In 2008, we sold our manufacturing operations (including patent rights to certain manufacturing technology) to VGXI, Inc., a wholly-owned United States subsidiary of GeneOne. In connection with this transfer we entered into a Supply Agreement pursuant to which VGXI, Inc., a cGMP contract manufacturer, produces and supplies the DNA plasmids for all of our research and early clinical trials. The price of the plasmids we purchase from VGXI, Inc. is determined by us and GeneOne at the time of order placement or, with respect to product supplied in connection with a grant contract, based on the contracted bid provided by the applicable agency. We agreed to treat GeneOne and its subsidiary as our most favored supplier for DNA plasmids and GeneOne and its subsidiary agreed to treat us as their most favored customer. Before we can manufacture DNA plasmids on our own behalf or engage a third party other than GeneOne or its subsidiary to manufacture DNA plasmids for us, we must first offer such manufacturing work to GeneOne or its subsidiary.

In 2014, we entered into a Collaborative Development Agreement with GeneOne to co-develop an Ebola vaccine through Phase 1 clinical trials. In 2015, we amended the agreement to provide that we would have control over the development program, in return for the payment of certain development fees.

In 2015, we entered into a Collaborative Development Agreement with GeneOne to co-develop a DNA vaccine for MERS through Phase 1 clinical trials. Under the terms of the agreement, GeneOne will be responsible for funding all preclinical and clinical studies through Phase 1. In return, GeneOne will receive up to 35% milestone-based ownership interest in the MERS immunotherapy upon achievement of the last milestone event of completion of the

Phase 1 safety and immunogenicity study. The collaborative research program will terminate upon the completion of activities under the development plan, unless sooner terminated.

In January 2016, we and GeneOne expanded the collaboration agreement to test and advance our DNA-based vaccine for preventing and treating Zika virus. GeneOne will be responsible for funding all preclinical and clinical studies through Phase 1. In return, GeneOne will receive up to a 35% milestone-based ownership interest in the Zika immunotherapy upon achievement of the last milestone event of the completion of the Phase 1 safety and immunogenicity study.

In December 2017, we completed the sale of certain assets related to our compound VGX-1027 to GeneOne for $1.0 million.

Revenue recognized from GeneOne consists of licensing and other fees from the influenza and Zika collaborations. For the years ended December 31, 2018 and 2017, we recognized revenue from GeneOne of $342,000 and $551,000, respectively. Operating expenses recorded from transactions with GeneOne relate primarily to biologics manufacturing. These operating expenses for the years ended December 31, 2018 and 2017 were $7.0 million and $2.3 million, respectively. At December 31, 2018 and 2017, we had an accounts payable and accrued liability balance of $372,000 and $107,000, respectively, related to GeneOne and its subsidiaries. At December 31, 2018 and 2017, $381,000 and $331,000, respectively, of prepayments made to GeneOne were classified as long-term other assets on our consolidated balance sheet.

Intellectual Property

Patents and other proprietary rights are essential to our business. We file patent applications to protect our technologies, inventions and improvements to our inventions that we consider important to the development of our business. We file for patent registration extensively in the United States and in key foreign markets. Although our patent filings include claims covering various features of our products and product candidates, including composition, methods of manufacture and use, our patents do not provide us with complete protection, or guarantee, against the development of competing products. In addition, some of our know-how and technology are not patentable. We thus also rely upon trade secrets, know-how, continuing technological innovations and licensing opportunities to develop and maintain our competitive position. We also require employees, consultants, advisors and collaborators to enter into confidentiality agreements, but such agreements may provide limited protection for our trade secrets, know-how or other proprietary information.

Our intellectual property portfolio covers our proprietary technologies, including CELLECTRA® delivery and vaccine related technologies. As of December 31, 2018, our patent portfolio included over 113 issued United States patents and 593 issued foreign counterpart patents.

If we fail to protect our intellectual property rights adequately our competitors might gain access to our technology and our business would thus be harmed. In addition, defending our intellectual property rights might entail significant expense. Any of our intellectual property rights may be challenged by others or invalidated through administrative processes or litigation through the courts. In addition, our patents, or any other patents that may be issued to us in the future, may not provide us with any competitive advantages, or may be challenged by third parties. Furthermore, legal standards relating to the validity, enforceability and scope of protection of intellectual property rights are uncertain. Effective patent, trademark, copyright and trade secret protection may not be available to us in each country where we operate. The laws of some foreign countries may not be as protective of intellectual property rights as those in the United States, and domestic and international mechanisms for enforcement of intellectual property rights in those countries may be inadequate. Accordingly, despite our efforts, we may be unable to prevent third parties from infringing upon or misappropriating our intellectual property or otherwise gaining access to our technology. We may be required to expend significant resources to monitor and protect our intellectual property rights. We may initiate claims or litigation against third parties for infringement of our proprietary rights or to establish the validity of our proprietary rights. Any such litigation, whether or not it is ultimately resolved in our favor, would result in significant expense to us and divert the efforts of our technical and management personnel.

There may be rights we are not aware of, including applications that have been filed but not published that, when issued, could be asserted against us. These third-parties could bring claims against us, and that would cause us to incur substantial expenses and, if successful against us, could cause us to pay substantial damages. Further, if a patent infringement suit were brought against us, we could be forced to stop or delay research, development, manufacturing or sales of the product or biologic drug candidate that is the subject of the suit. As a result of patent infringement

claims, or in order to avoid potential claims, we may choose or be required to seek a license from the third-party. These licenses may not be available on acceptable terms, or at all. Even if we are able to obtain a license, the license would likely obligate us to pay license fees or royalties or both, and the rights granted to us might be non-exclusive, which could result in our competitors gaining access to the same intellectual property. Ultimately, we could be prevented from commercializing a product, or be forced to cease some aspect of our business operations, if, as a result of actual or threatened patent infringement claims, we are unable to enter into licenses on acceptable terms. All of the issues

described above could also impact our collaborators, which would also impact the success of the collaboration and therefore us.

Important legal issues remain to be resolved as to the extent and scope of available patent protection for biologic products, including vaccines, and processes in the United States and other important markets outside the United States, such as Europe and Japan. Foreign markets may not provide the same level of patent protection as provided under the United States patent system. We recognize that litigation or administrative proceedings may be necessary to determine the validity and scope of certain of our and others' proprietary rights. Any such litigation or proceeding may result in a significant commitment of resources in the future and could force us to interrupt our operations, redesign our products or processes, or negotiate a license agreement, all of which would adversely affect our revenue. Furthermore, changes in, or different interpretations of, patent laws in the United States and other countries may result in patent laws that allow others to use our discoveries or develop and commercialize our products.

We cannot guarantee that the patents we obtain or the unpatented technology we hold will afford us significant commercial protection.

Significant Customers and Research and Development

During the year ended December 31, 2018, we derived 75% of our revenue from ApolloBio and 23% of our revenue from AstraZeneca. During the years ended December 31, 2017 and 2016, we derived 53% and 4% of our revenue from AstraZeneca, 24% and 75% of our revenue from DARPA, and 14% and 14% of our revenue from Roche, respectively. Since our inception, virtually all of our activities have consisted of research and development efforts related to developing our electroporation technologies and immunotherapies. Research and development expense consists of expenses incurred in performing research and development activities including salaries and benefits, facilities and other overhead expenses, clinical trials, contract services and other outside expenses. Our research and development expense was $95.3 million in 2018, $98.6 million in 2017 and $88.7 million in 2016.

Geographic Information

All of our revenue for the years ended December 31, 2018, 2017 and 2016 was earned in the United States. All of our long-lived assets are located in the United States.

Corporate History and Headquarters

We have been a leader in advancing the capabilities of DNA-based immunotherapies to treat infectious diseases and cancers going back to the original incorporation of Viral Genomix, Inc. under the laws of Delaware on April 17, 2000. We were renamed VGX Pharmaceuticals, Inc. on May 31, 2006. On February 21, 2007, VGX Pharmaceuticals acquired Advisys, Inc., a company possessing DNA and electroporation technology, through an asset purchase agreement. On April 14, 2007, VGX Pharmaceuticals entered into an exclusive license agreement with the Trustees of the University of Pennsylvania related to therapeutic and prophylactic DNA vaccines developed by Professor David B. Weiner at the University of Pennsylvania School of Medicine.

Recognizing the value of electroporation delivery technology, devices, and patents in advancing DNA-based immunotherapy products, on June 1, 2009, VGX Pharmaceuticals completed a merger with Inovio Biomedical Corporation, a publicly listed company focused on electroporation delivery technology.

Inovio Biomedical Corporation started as Biotechnologies & Experimental Research, Inc. and was incorporated on June 29, 1983 in California to create products for the research marketplace. The company changed its corporate name to BTX, Inc. on December 10, 1991, and to Genetronics, Inc. on February 8, 1994. On April 14, 1994, Genetronics, Inc. became a public company through a share exchange agreement with Consolidated United Safety Technologies, Inc., a company listed on the Vancouver Stock Exchange under the laws of British Columbia, Canada. The company changed its name to Genetronics Biomedical Ltd. on September 29, 1994. Genetronics, Inc. remained as a wholly owned operating subsidiary. On September 2, 1997, the company listed on the Toronto Stock Exchange. On December 8, 1998, the company listed on the American Stock Exchange (now NYSE MKT) and voluntarily de-listed from the Toronto Stock Exchange on January 17, 2003. On June 15, 2001, Genetronics Biomedical Ltd. completed a change in jurisdiction of incorporation from British Columbia, Canada, to the state of Delaware and became Genetronics Biomedical Corporation. On January 25, 2005, Genetronics Biomedical Corporation acquired Inovio AS, a gene delivery technology company located in Norway. On March 31, 2005, Genetronics Biomedical Corporation was renamed Inovio Biomedical Corporation.

The merger between VGX Pharmaceuticals and Inovio Biomedical Corporation was effected pursuant to the terms of an Amended and Restated Agreement and Plan of Merger dated December 5, 2008, as further amended on March 31, 2009. On May 14, 2010, the combined entity changed its corporate name to Inovio Pharmaceuticals, Inc. We conduct our business through our United States wholly-owned subsidiaries, VGX Pharmaceuticals, LLC and Genetronics, Inc.

Our corporate headquarters are located at 660 W. Germantown Pike, Suite 110, Plymouth Meeting, Pennsylvania 19462, and our telephone number is (267) 440-4200.

Available Information

Our Internet website address is www.inovio.com. In addition to the information contained in this Annual Report, information about us can be found on our website. Our website and information included in or linked to our website are not part of this Annual Report.

We make our annual report on Form 10-K, quarterly reports on Form 10-Q, current reports on Form 8-K and amendments to those reports filed or furnished pursuant to Section 13(a) or 15(d) of the Securities Exchange Act of 1934, or the Exchange Act, available free of charge on our website as soon as reasonably practicable after we electronically file such material with, or furnish it to, the Securities and Exchange Commission, or the SEC. The SEC maintains an Internet site (www.sec.gov) that contains reports, proxy and information statements, and other information regarding issuers that file electronically with the SEC, including us.

Information regarding our corporate governance, including the charters of our audit committee, our nomination and corporate governance committee and our compensation committee, our Code of Business Conduct and Ethics, our Corporate Governance Guidelines, our Corporate Governance Policy and information for contacting our board of directors is available on our website.

Our Code of Business Conduct and Ethics includes our Code of Ethics applicable to our Chief Executive Officer and Chief Financial Officer, who also serves as our principal accounting officer. Any amendments to or waivers of the Code of Ethics will be promptly posted on our website or in a report on Form 8-K, as required by applicable law.

Employees

As of February 28, 2019, we employed 281 people on a full-time basis and 7 people under consulting and project employment agreements. Of the combined total, 231 were in product research, which includes research and development, quality assurance, clinical, engineering, and manufacturing, and 57 were in general and administrative functions, which includes corporate development, information technology, legal, investor relations, finance and corporate administration. None of our employees are subject to collective bargaining agreements.

ITEM 1A. RISK FACTORS

You should carefully consider the following factors regarding information included in this Annual Report. The risks and uncertainties described below are not the only ones we face. Additional risks and uncertainties not presently known to us or that we currently deem immaterial also may impair our business operations. If any of the following risks actually occur, our business, financial condition and operating results could be materially adversely affected.

Risks Related to Our Business and Industry

We have incurred losses since inception, expect to incur significant net losses in the foreseeable future and may never become profitable.

We have experienced significant operating losses to date. As of December 31, 2018 our accumulated deficit was approximately $620.4 million. We have generated limited revenues, primarily consisting of license revenue, grant funding and interest income. We expect to continue to incur substantial additional operating losses for at least the next several years as we advance our clinical trials and research and development activities. We may never successfully commercialize our vaccine product candidates or electroporation-based synthetic vaccine delivery technology and thus may never have any significant future revenues or achieve and sustain profitability.

We have limited sources of revenue and our success is dependent on our ability to develop our vaccine and immunotherapies and other product candidates and electroporation equipment.

We do not sell any products and may not have any other products commercially available for several years, if at all. Our ability to generate future revenues depends heavily on our success in:

- developing and securing United States and/or foreign regulatory approvals for our product candidates, including securing regulatory approval for conducting clinical trials with product candidates;
- developing our electroporation-based DNA delivery technology; and
- commercializing any products for which we receive approval from the FDA and foreign regulatory authorities.

Our electroporation equipment and product candidates will require extensive additional clinical study and evaluation, regulatory approval in multiple jurisdictions, substantial investment and significant marketing efforts before we generate any revenues from product sales. We are not permitted to market or promote our electroporation equipment and product candidates before we receive regulatory approval from the FDA or comparable foreign regulatory authorities. If we do not receive regulatory approval for and successfully commercialize any products, we will not generate any revenues from sales of electroporation equipment and products, and we may not be able to continue our operations.

None of our human vaccine and immunotherapy product candidates have been approved for sale, and we may not develop commercially successful vaccine products.

Our human vaccine and immunotherapy programs are in the early stages of research and development, and currently include product candidates in discovery, preclinical studies and Phase 1, 2 and 3 clinical trials. There are limited data regarding the efficacy of synthetic vaccine and immunotherapy candidates compared with conventional vaccines, and we must conduct a substantial amount of additional research and development before any regulatory authority will approve any of our vaccine product candidates. The success of our efforts to develop and commercialize our product candidates could fail for a number of reasons. For example, we could experience delays in product development and clinical trials. Our product candidates could be found to be ineffective or unsafe, or otherwise fail to receive necessary regulatory clearances. The products, if safe and effective, could be difficult to manufacture on a large scale or uneconomical to market, or our competitors could develop superior products more quickly and efficiently or more effectively market their competing products.

In addition, adverse events, or the perception of adverse events, relating to vaccine and immunotherapy candidates and delivery technologies may negatively impact our ability to develop commercially successful products. For example, pharmaceutical companies have been subject to claims that the use of some pediatric vaccines has caused personal injuries, including brain damage, central nervous system damage and autism. These and other claims may influence public perception of the use of vaccine and immunotherapy products and could result in greater governmental regulation, stricter labeling requirements and potential regulatory delays in the testing or approval of our potential products.

Our indebtedness and liabilities could limit the cash flow available for our operations, expose us to risks that could adversely affect our business, financial condition and results of operations.

To date, we have sold $70.0 million aggregate principal amount of 6.50% convertible senior notes due 2024 (the "Notes"). We may also incur additional indebtedness to meet future financing needs. Our indebtedness could have significant

negative consequences for our security holders and our business, results of operations and financial condition by, among other things:

- increasing our vulnerability to adverse economic and industry conditions;
- limiting our ability to obtain additional financing;
- requiring the dedication of a substantial portion of our cash flow from operations to service our indebtedness, which will reduce the amount of cash available for other purposes;
- limiting our flexibility to plan for, or react to, changes in our business;
- diluting the interests of our existing stockholders as a result of issuing shares of our common stock upon conversion of the Notes; and
- placing us at a possible competitive disadvantage with competitors that are less leveraged than us or have better access to capital.

Our business may not generate sufficient funds, and we may otherwise be unable to maintain sufficient cash reserves, to pay amounts due under the Notes and any additional indebtedness that we may incur. In addition, our cash needs may increase in the future. In addition, any future indebtedness that we may incur may contain financial and other restrictive covenants that limit our ability to operate our business, raise capital or make payments under our other indebtedness. If we fail to comply with these covenants or to make payments under our indebtedness when due, then we would be in default under that indebtedness, which could, in turn, result in that and our other indebtedness becoming immediately payable in full.

The conditional conversion feature of the Notes, if triggered, may adversely affect our financial condition, operating results, or liquidity.

In the event the conditional conversion feature of the Notes is triggered, holders of Notes will be entitled to convert their Notes at any time during specified periods at their option. If one or more of the holders of the Notes elects to convert their notes, unless we satisfy our conversion obligation by delivering only shares of our common stock, we would be required to settle all or a portion of our conversion obligation through the payment of cash, which could adversely affect our liquidity. The conditional convertibility of the Notes will be monitored at each quarterly reporting date and analyzed dependent upon market prices of our common stock during the prescribed measurement periods.

We will need substantial additional capital to develop our synthetic vaccine and immunotherapy programs and electroporation delivery technology.

Conducting the costly and time-consuming research, pre-clinical and clinical testing necessary to obtain regulatory approvals and bring our product candidates and delivery technology to market will require a commitment of substantial funds in excess of our current capital. Our future capital requirements will depend on many factors, including, among others:

- the progress of our current and new product development programs;
- the progress, scope and results of our pre-clinical and clinical testing;
- the time and cost involved in obtaining regulatory approvals;
- the cost of manufacturing our products and product candidates;
- the cost of prosecuting, enforcing and defending against patent infringement claims and other intellectual property rights;
- debt service obligations on the Notes;
- competing technological and market developments; and
- our ability and costs to establish and maintain collaborative and other arrangements with third parties to assist in potentially bringing our products to market.

Additional financing may not be available on acceptable terms, or at all. Domestic and international capital markets have from time to time experienced heightened volatility and turmoil, making it more difficult to raise capital through the issuance of equity securities. Volatility in the capital markets can also negatively impact the cost and availability of credit, creating illiquid credit markets and wider credit spreads. Concern about the stability of the markets generally and the strength of counterparties specifically has led many lenders and institutional investors to reduce, and in some cases cease to provide, funding to borrowers. To the extent we are able to raise additional capital through the sale of equity securities or we issue securities in connection with another transaction, the ownership position of existing stockholders could be substantially diluted. If additional funds are raised through the issuance of preferred stock or

debt securities, these securities are likely to have rights, preferences and privileges senior to our common stock and may involve significant fees, interest expense, restrictive covenants and the

granting of security interests in our assets. Fluctuating interest rates could also increase the costs of any debt financing we may obtain. Raising capital through a licensing or other transaction involving our intellectual property could require us to relinquish valuable intellectual property rights and thereby sacrifice long-term value for short-term liquidity.

Our failure to successfully address ongoing liquidity requirements would have a substantially negative impact on our business. If we are unable to obtain additional capital on acceptable terms when needed, we may need to take actions that adversely affect our business, our stock price and our ability to achieve cash flow in the future, including possibly surrendering our rights to some technologies or product opportunities, delaying our clinical trials or curtailing or ceasing operations.

We depend upon key personnel who may terminate their employment with us at any time and we may need to hire additional qualified personnel in order to obtain financing, pursue collaborations or develop or market our product candidates.

The success of our business strategy will depend to a significant degree upon the continued services of key management, technical and scientific personnel and our ability to attract and retain additional qualified personnel and managers, including personnel with expertise in clinical trials, government regulation, manufacturing, marketing and other areas. Competition for qualified personnel is intense among companies, academic institutions and other organizations. If we are unable to attract and retain key personnel and advisors, it may negatively affect our ability to successfully develop, test, commercialize and market our products and product candidates.

We face intense and increasing competition and many of our competitors have significantly greater resources and experience.

If any of our competitors develop products with efficacy or safety profiles significantly better than our products, we may not be able to commercialize our products, and sales of any of our commercialized products could be harmed. Some of our competitors and potential competitors have substantially greater product development capabilities and financial, scientific, marketing and human resources than we do. Competitors may develop products earlier, obtain FDA approvals for products more rapidly, or develop products that are more effective than those under development by us. We will seek to expand our technological capabilities to remain competitive; however, research and development by others may render our technologies or products obsolete or noncompetitive, or result in treatments or cures superior to ours.

Many other companies are pursuing other forms of treatment or prevention for diseases that we target. For example, many of our competitors are working on developing and testing cancer vaccines and immunotherapies and several products such as the CAR-Ts developed by our competitors have been approved for human use. Our competitors and potential competitors include large pharmaceutical and more established biotechnology companies. These companies have significantly greater financial and other resources and greater expertise than us in research and development, securing government contracts and grants to support research and development efforts, manufacturing, pre-clinical and clinical testing, obtaining regulatory approvals and marketing. This may make it easier for them to respond more quickly than us to new or changing opportunities, technologies or market needs. Many of these competitors operate large, well-funded research and development programs and have significant products approved or in development. Small companies may also prove to be significant competitors, particularly through collaborative arrangements with large pharmaceutical companies or through acquisition or development of intellectual property rights. Our potential competitors also include academic institutions, governmental agencies and other public and private research organizations that conduct research, seek patent protection and establish collaborative arrangements for product and clinical development and marketing. Research and development by others may seek to render our technologies or products obsolete or noncompetitive.

If we lose or are unable to secure collaborators or partners, or if our collaborators or partners do not apply adequate resources to their relationships with us, our product development and potential for profitability will suffer.

We have entered into, or may enter into, distribution, co-promotion, partnership, sponsored research and other arrangements for development, manufacturing, sales, marketing and other commercialization activities relating to our products. For example, in the past we have entered into license and collaboration agreements. The amount and timing of resources applied by our collaborators are largely outside of our control.

If any of our current or future collaborators breaches or terminates our agreements, or fails to conduct our collaborative activities in a timely manner, our commercialization of products could be diminished or blocked completely. We may not receive any event-based payments, milestone payments or royalty payments under our collaborative agreements if our collaborative partners fail to develop products in a timely manner or at all. It is possible that collaborators will change their strategic focus, pursue alternative technologies or develop alternative products, either on their own or in collaboration with others. Further, we may be forced to fund programs that were previously funded by our collaborators, and we may not have, or be able to access, the necessary funding. The effectiveness of our partners, if any, in marketing our products will also affect our revenues and earnings.

We desire to enter into new collaborative agreements. However, we may not be able to successfully negotiate any additional collaborative arrangements and, if established, these relationships may not be scientifically or commercially successful. Our success in the future depends in part on our ability to enter into agreements with other highly-regarded organizations. This can be difficult due to internal and external constraints placed on these organizations. Some organizations may have insufficient administrative and related infrastructure to enable collaborations with many companies at once, which can extend the time it takes to develop, negotiate and implement a collaboration. Once news of discussions regarding possible collaborations are known in the medical community, regardless of whether the news is accurate, failure to announce a collaborative agreement or the entity's announcement of a collaboration with another entity may result in adverse speculation about us, resulting in harm to our reputation and our business.

Disputes could also arise between us and our existing or future collaborators, as to a variety of matters, including financial and intellectual property matters or other obligations under our agreements. These disputes could be both expensive and time-consuming and may result in delays in the development and commercialization of our products or could damage our relationship with a collaborator.

A small number of licensing partners and government contracts account for a substantial portion of our revenue.

We currently derive, and in the past we have derived, a significant portion of our revenue from a limited number of licensing partners and government grants and contracts. Revenue can fluctuate significantly depending on the timing of upfront and event-based payments and work performed. If we fail to sign additional future contracts with major licensing partners and the government, if a contract is delayed or deferred, or if an existing contract expires or is canceled and we fail to replace the contract with new business, our revenue would be adversely affected.

We have agreements with government agencies, which are subject to termination and uncertain future funding.

We have entered into agreements with government agencies, such as the NIAID and DARPA, and we intend to continue entering into these agreements in the future. Our business is partially dependent on the continued performance by these government agencies of their responsibilities under these agreements, including adequate continued funding of the agencies and their programs. We have no control over the resources and funding that government agencies may devote to these agreements, which may be subject to annual renewal and which generally may be terminated by the government agencies at any time.

Government agencies may fail to perform their responsibilities under these agreements, which may cause them to be terminated by the government agencies. In addition, we may fail to perform our responsibilities under these agreements. Many of our government agreements are subject to audits, which may occur several years after the period to which the audit relates. If an audit identifies significant unallowable costs, we could incur a material charge to our earnings or reduction in our cash position. As a result, we may be unsuccessful entering, or ineligible to enter, into future government agreements.

Our quarterly operating results may fluctuate significantly.

We expect our operating results to be subject to quarterly fluctuations. Our net loss and other operating results will be affected by numerous factors, including:

- variations in the level of expenses related to our electroporation equipment, product candidates or future development programs;
- expenses related to corporate transactions, including ones not fully completed;
- addition or termination of clinical trials or funding support;
- any intellectual property infringement lawsuit in which we may become involved;
- any legal claims that may be asserted against us or any of our officers;
- regulatory developments affecting our electroporation equipment and product candidates or those of our competitors;
- debt service obligations on the Notes;
- our execution of any collaborative, licensing or similar arrangements, and the timing of payments we may make or receive under these arrangements; and
- if any of our products receives regulatory approval, the levels of underlying demand for our products.

If our quarterly operating results fall below the expectations of investors or securities analysts, the price of our common stock could decline substantially. Furthermore, any quarterly fluctuations in our operating results may, in turn, cause the price of our stock to fluctuate substantially. We believe that quarterly comparisons of our financial results are not necessarily meaningful and should not be relied upon as an indication of our future performance.

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If we are unable to obtain FDA approval of our products, we will not be able to commercialize them in the United States.

We need FDA approval prior to marketing our electroporation equipment and products in the United States. If we fail to obtain FDA approval to market our electroporation equipment and product candidates, we will be unable to sell our products in the United States, which will significantly impair our ability to generate any revenues.

This regulatory review and approval process, which includes evaluation of pre-clinical studies and clinical trials of our products as well as the evaluation of our manufacturing processes and our third-party contract manufacturers' facilities, is lengthy, expensive and uncertain. To receive approval, we must, among other things, demonstrate with substantial evidence from well-controlled clinical trials that our electroporation equipment and product candidates are both safe and effective for each indication for which approval is sought. Satisfaction of the approval requirements typically takes several years and the time needed to satisfy them may vary substantially, based on the type, complexity and novelty of the product. We do not know if or when we might receive regulatory approvals for our electroporation equipment and any of our product candidates currently under development. Moreover, any approvals that we obtain may not cover all of the clinical indications for which we are seeking approval, or could contain significant limitations in the form of narrow indications, warnings, precautions or contra-indications with respect to conditions of use. In such event, our ability to generate revenues from such products would be greatly reduced and our business would be harmed.

The FDA has substantial discretion in the approval process and may either refuse to consider our application for substantive review or may form the opinion after review of our data that our application is insufficient to allow approval of our electroporation equipment and product candidates. If the FDA does not consider or approve our application, it may require that we conduct additional clinical, pre-clinical or manufacturing validation studies and submit that data before it will reconsider our application. Depending on the extent of these or any other studies, approval of any applications that we submit may be delayed by several years, or may require us to expend more resources than we have available. It is also possible that additional studies, if performed and completed, may not be successful or considered sufficient by the FDA for approval or even to make our applications approvable. If any of these outcomes occur, we may be forced to abandon one or more of our applications for approval, which might significantly harm our business and prospects.

It is possible that none of our products or any product we may seek to develop in the future will ever obtain the appropriate regulatory approvals necessary for us or our collaborators to commence product sales. Any delay in obtaining, or an inability to obtain, applicable regulatory approvals would prevent us from commercializing our products, generating revenues and achieving and sustaining profitability.

Clinical trials involve a lengthy and expensive process with an uncertain outcome, and results of earlier studies and trials may not be predictive of future trial results.

Clinical testing is expensive and can take many years to complete, and its outcome is uncertain. Failure can occur at any time during the clinical trial process. The results of pre-clinical studies and early clinical trials of our products may not be predictive of the results of later-stage clinical trials. Results from one study may not be reflected or supported by the results of similar studies. Results of an animal study may not be indicative of results achievable in human studies. Human-use equipment and product candidates in later stages of clinical trials may fail to show the desired safety and efficacy traits despite having progressed through pre-clinical studies and initial clinical testing. The time required to obtain approval by the FDA and similar foreign authorities is unpredictable but typically takes many years following the commencement of clinical trials, depending upon numerous factors. In addition, approval policies, regulations, or the type and amount of clinical data necessary to gain approval may change. We have not obtained regulatory approval for any human-use products.

Our products could fail to complete the clinical trial process for many reasons, including the following:

- we may be unable to demonstrate to the satisfaction of the FDA or comparable foreign regulatory authorities that our electroporation equipment and a product candidate are safe and effective for any indication;
- the results of clinical trials may not meet the level of statistical significance required by the FDA or comparable foreign regulatory authorities for approval;
-

the FDA or comparable foreign regulatory authorities may disagree with the design or implementation of our clinical trials;

- we may not be successful in enrolling a sufficient number of participants in clinical trials;
- we may be unable to demonstrate that our electroporation equipment and a product candidate's clinical and other benefits outweigh its safety risks;
- we may be unable to demonstrate that our electroporation equipment and a product candidate presents an advantage over existing therapies, or over placebo in any indications for which the FDA requires a placebo-controlled trial;

- the FDA or comparable foreign regulatory authorities may disagree with our interpretation of data from pre-clinical studies or clinical trials;
- the data collected from clinical trials of our product candidates may not be sufficient to support the submission of a new drug application or other submission or to obtain regulatory approval in the United States or elsewhere;
- the FDA or comparable foreign regulatory authorities may fail to approve the manufacturing processes or facilities of us or third-party manufacturers with which we or our collaborators contract for clinical and commercial supplies; and
- the approval policies or regulations of the FDA or comparable foreign regulatory authorities may significantly change in a manner rendering our clinical data insufficient for approval.

Our product candidates are combination products regulated under both the biologic and device regulations of the Public Health Service Act and Federal Food, Drug, and Cosmetic Act. Third-party manufacturers may not be able to comply with current good manufacturing practices, or cGMP, regulations, regulations applicable to biologic/device combination products, including applicable provisions of the FDA's drug cGMP regulations, device cGMP requirements embodied in the Quality System Regulation, or QSR, or similar regulatory requirements outside the United States. Our failure, or the failure of our third-party manufacturers, to comply with applicable regulations could result in sanctions being imposed on us, including clinical holds, fines, injunctions, civil penalties, delays, suspension or withdrawal of approvals, license revocation, seizures or recalls of product candidates, operating restrictions and criminal prosecutions, any of which could significantly affect supplies of our product candidates.

Delays in the commencement or completion of clinical testing could result in increased costs to us and delay or limit our ability to generate revenues.

Delays in the commencement or completion of clinical testing could significantly affect our product development costs. We do not know whether planned clinical trials will begin on time or be completed on schedule, if at all. In addition, ongoing clinical trials may not be completed on schedule, or at all, and could be placed on a hold by the regulators for various reasons. The commencement and completion of clinical trials can be delayed for a number of reasons, including delays related to:

- obtaining regulatory approval to commence a clinical trial;
- adverse results from third party clinical trials involving gene based therapies and the regulatory response thereto;
- reaching agreement on acceptable terms with prospective CROs and trial sites, the terms of which can be subject to extensive negotiation and may vary significantly among different CROs and trial sites;
- future bans or stricter standards imposed on gene based therapy clinical trials;
- manufacturing sufficient quantities of our electroporation equipment and product candidates for use in clinical trials;
- obtaining institutional review board, or IRB, approval to conduct a clinical trial at a prospective site;
- slower than expected recruitment and enrollment of patients to participate in clinical trials for a variety of reasons, including competition from other clinical trial programs for similar indications;
- conducting clinical trials with sites internationally due to regulatory approvals and meeting international standards;
- retaining patients who have initiated a clinical trial but may be prone to withdraw due to side effects from the therapy, lack of efficacy or personal issues, or who are lost to further follow-up;
- collecting, reviewing and analyzing our clinical trial data; and
- global unrest, terrorist activities, and economic and other external factors.

Clinical trials may also be delayed as a result of ambiguous or negative interim results. In addition, a clinical trial may be suspended or terminated by us, the FDA, the IRB overseeing the clinical trial at issue, any of our clinical trial sites with respect to that site, or other regulatory authorities due to a number of factors, including:

- failure to conduct the clinical trial in accordance with regulatory requirements or our clinical protocols;
- inspection of the clinical trial operations or trial sites by the FDA or other regulatory authorities resulting in the imposition of a clinical hold;
- unforeseen safety issues; and
- lack of adequate funding to continue the clinical trial.

If we experience delays in completion of, or if we terminate, any of our clinical trials, the commercial prospects for our electroporation equipment and our product candidates may be harmed and our ability to generate product revenues will be delayed. In addition, many of the factors that cause, or lead to, a delay in the commencement or completion of clinical trials may also ultimately lead to the denial of regulatory approval of a product candidate. Further, delays in the commencement or completion of clinical trials may adversely affect the trading price of our common stock.

We and our collaborators rely on third parties to conduct our clinical trials. If these third parties do not successfully carry out their contractual duties or meet expected deadlines, we and our collaborators may not be able to obtain regulatory approval for or commercialize our product candidates.

We and our collaborators have entered into agreements with CROs to provide monitors for and to manage data for our on-going clinical programs. We and the CROs conducting clinical trials for our electroporation equipment and product candidates are required to comply with current good clinical practices, or GCPs, regulations and guidelines enforced by the FDA for all of our products in clinical development. The FDA enforces GCPs through periodic inspections of trial sponsors, principal investigators and trial sites. If we or the CROs conducting clinical trials of our product candidates fail to comply with applicable GCPs, the clinical data generated in the clinical trials may be deemed unreliable and the FDA may require additional clinical trials before approving any marketing applications.

If any relationships with CROs terminate, we or our collaborators may not be able to enter into arrangements with alternative CROs. In addition, these third-party CROs are not our employees, and we cannot control whether or not they devote sufficient time and resources to our on-going clinical programs or perform trials efficiently. These CROs may also have relationships with other commercial entities, including our competitors, for whom they may also be conducting clinical studies or other drug development activities, which could harm our competitive position. If CROs do not successfully carry out their contractual duties or obligations or meet expected deadlines, if they need to be replaced, or if the quality or accuracy of the clinical data they obtain is compromised due to the failure to adhere to our clinical protocols, regulatory requirements, or for other reasons, our clinical trials may be extended, delayed or terminated, and we may not be able to obtain regulatory approval for or successfully commercialize our product candidates. As a result, our financial results and the commercial prospects for our product candidates would be harmed, our costs could increase and our ability to generate revenues could be delayed. Cost overruns by or disputes with our CROs may significantly increase our expenses.

Even if our products receive regulatory approval, they may still face future development and regulatory difficulties.

Even if United States regulatory approval is obtained, the FDA may still impose significant restrictions on a product's indicated uses or marketing or impose ongoing requirements for potentially costly post-approval studies. This governmental oversight may be particularly strict with respect to gene based therapies. Our products will also be subject to ongoing FDA requirements governing the labeling, packaging, storage, advertising, promotion, record keeping and submission of safety and other post-market information. For example, the FDA strictly regulates the promotional claims that may be made about medical products. In particular, a product may not be promoted for uses that are not approved by the FDA as reflected in the product’s approved labeling. However, companies may in certain circumstances share truthful and not misleading information that is otherwise consistent with the product’s FDA approved labeling. In addition, manufacturers of drug products and their facilities are subject to continual review and periodic inspections by the FDA and other regulatory authorities for compliance with current good manufacturing practices, or cGMP, regulations. If we or a regulatory agency discover previously unknown problems with a product, such as adverse events of unanticipated severity or frequency, or problems with the facility where the product is manufactured, a regulatory agency may impose restrictions on that product, the manufacturer or us, including requiring withdrawal of the product from the market or suspension of manufacturing. If we, our product candidates or the manufacturing facilities for our product candidates fail to comply with applicable regulatory requirements, a regulatory agency may:

- issue Warning Letters or untitled letters;
- impose civil or criminal penalties;
- suspend regulatory approval;
- suspend any ongoing clinical trials;
- refuse to approve pending applications or supplements to applications filed by us;
- impose restrictions on operations, including costly new manufacturing requirements; or

- seize or detain products or require us to initiate a product recall.

Even if our products receive regulatory approval in the United States, we may never receive approval or commercialize our products outside of the United States.

In order to market any electroporation equipment and product candidates outside of the United States, we must establish and comply with numerous and varying regulatory requirements of other countries regarding safety and efficacy. Approval procedures vary among countries and can involve additional product testing and additional administrative review periods. The time required to obtain approval in other countries might differ from that required to obtain FDA approval. The regulatory approval process in other countries may include all of the risks detailed above regarding FDA approval in the United States as well as other risks. Regulatory approval in one country does not ensure regulatory approval in another, but a failure or delay in obtaining regulatory approval in one country may have a negative effect on the regulatory process in others. Failure to obtain regulatory approval in other countries or any delay or setback in obtaining such approval could have the same adverse effects detailed above regarding FDA approval in the United States. Such effects include the risks that our product candidates may not be approved for all indications requested, which could limit the uses of our product candidates and have an adverse effect on their commercial potential or require costly, post-marketing follow-up studies.

We face potential product liability exposure and, if successful claims are brought against us, we may incur substantial liability.

The use of our electroporation equipment and synthetic vaccine candidates in clinical trials and the sale of any products for which we obtain marketing approval expose us to the risk of product liability claims. Product liability claims might be brought against us by consumers, healthcare providers, pharmaceutical companies or others selling or otherwise coming into contact with our products. For example, pharmaceutical companies have been subject to claims that the use of some pediatric vaccines has caused personal injuries, including brain damage, central nervous system damage and autism, and these companies have incurred material costs to defend these claims. If we cannot successfully defend ourselves against product liability claims, we could incur substantial liabilities. In addition, regardless of merit or eventual outcome, product liability claims may result in:

- decreased demand for our product candidates;
- impairment of our business reputation;
- withdrawal of clinical trial participants;
- costs of related litigation;
- distraction of management's attention from our primary business;
- substantial monetary awards to patients or other claimants;
- loss of revenues; and
- inability to commercialize our products.

We have obtained product liability insurance coverage for our clinical trials, but our insurance coverage may not be sufficient to reimburse us for any expenses or losses we may suffer. Moreover, insurance coverage is becoming increasingly expensive, and, in the future, we may not be able to maintain insurance coverage at a reasonable cost or in sufficient amounts to protect us against losses due to liability. On occasion, large judgments have been awarded in class action lawsuits based on products that had unanticipated side effects. A successful product liability claim or series of claims brought against us could cause our stock price to decline and, if judgments exceed our insurance coverage, could adversely affect our business.

We currently have no marketing and sales organization. If we are unable to establish marketing and sales capabilities or enter into agreements with third parties to market and sell our products, we may not be able to generate product revenues.

We currently do not have a sales organization for the marketing, sales and distribution of our electroporation equipment and product candidates. In order to commercialize any products, we must build our marketing, sales, distribution, managerial and other non-technical capabilities or make arrangements with third parties to perform these services. We contemplate establishing our own sales force or seeking third-party partners to sell our products. The establishment and development of our own sales force to market any products we may develop will be expensive and time consuming and could delay any product launch, and we may not be able to successfully develop this capability. We will also have to compete with other pharmaceutical and biotechnology companies to recruit, hire, train and retain marketing and sales personnel. To the extent we rely on third parties to commercialize our approved products, if any, we will receive lower revenues than if we commercialized these products ourselves. In addition, we may have little or

no control over the sales efforts of third parties involved in our commercialization efforts. In the event we are unable to develop our own marketing and sales force or collaborate with a third-party marketing and sales organization, we would not be able to commercialize our product candidates which would negatively impact our ability to generate product revenues.

If any of our products for which we receive regulatory approval does not achieve broad market acceptance, the revenues that we generate from their sales will be limited.

The commercial success of our electroporation equipment and product candidates for which we obtain marketing approval from the FDA or other regulatory authorities will depend upon the acceptance of these products by both the medical community and patient population. Coverage and reimbursement of our product candidates by third-party payors, including government payors, generally is also necessary for optimal commercial success. The degree of market acceptance of any of our approved products will depend on a number of factors, including:

- our ability to provide acceptable evidence of safety and efficacy;
- the relative convenience and ease of administration;
- the prevalence and severity of any actual or perceived adverse side effects;
- limitations or warnings contained in a product's FDA-approved labeling, including, for example, potential “black box” warnings
- availability of alternative treatments;