



The Promise of DNA Vaccines:

**A new approach to vaccine design, drug delivery
and disease prevention**

By:

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This document contains certain forward-looking statements relating to our plans to develop electroporation-based drug and gene delivery technologies and DNA vaccines. Actual events or results may differ from the expectations set forth herein as a result of a number of factors, including uncertainties inherent in pre-clinical studies, clinical trials and product development programs (including, but not limited to, the fact that pre-clinical and clinical results referenced in this release may not be indicative of results achievable in other trials or for other indications, that results from one study may not necessarily be reflected or supported by the results of other similar studies and that results from an animal study may not be indicative of results achievable in human studies), the availability of funding to support continuing research and studies in an effort to prove safety and efficacy of electroporation technology as a delivery mechanism or develop viable DNA vaccines, the availability or potential availability of alternative therapies or treatments for the conditions targeted by the company or its collaborators, including alternatives that may be more efficacious or cost-effective than any therapy or treatment that the company and its collaborators hope to develop, evaluation of potential opportunities, issues involving patents and whether they or licenses to them will provide the company with meaningful protection from others using the covered technologies, whether such proprietary rights are enforceable or defensible or infringe or allegedly infringe on rights of others or can withstand claims of invalidity and whether the company can finance or devote other significant resources that may be necessary to prosecute, protect or defend them, the level of corporate expenditures, assessments of the company's combined technology by potential corporate or other partners or collaborators, capital market conditions, our ability to successfully integrate Inovio and VGX Pharmaceuticals, the impact of government healthcare proposals and other factors set forth in our Annual Report on Form 10-K for the year ended December 31, 2008, our Form 10-Q for the six months ended June 30, 2009, and other regulatory filings from time to time. There can be no assurance that any product in Inovio's pipeline will be successfully developed or manufactured, that final results of clinical studies will be supportive of regulatory approvals required to market licensed products, or that any of the forward-looking information provided herein will be proven accurate.

Good morning and thank you for that kind introduction.

As a member of the TR100 in 2002 (MIT course 10 and 14 grad), it is my true pleasure to speak to you this morning about the exciting progress we are making at Inovio Biomedical in our universal vaccine programs.

That's the focus of my remarks to you this morning. Vaccines . . . how far vaccines have taken us in preventing disease . . . and the promise of a new technology, called DNA vaccines.

Let me bring one statistic to your attention that's not top-of-mind to most people. Vaccines have saved more lives and prevented more human suffering than any other human invention. As they say in sports, you can look it up.

Even as recently as a century ago, infectious diseases were the main cause of death worldwide, even in the most developed countries. For instance, the Spanish flu pandemic of 1918 killed more people than all the bullets and bombs did during the Great War.

Today, there is a vast range of vaccines available to protect against more than two dozen infectious diseases, especially for kids. As a father of three young kids under six, I really appreciate the work of other people who came before us. Our society has found that the only way to control or even eliminate diseases is consistent, wide-spread use of vaccines.

While the vaccine industry recently went through a couple of relatively stagnant decades, improvements in business models have helped turn the vaccine market into a hot growth business. The global vaccine market is greater than US \$20 billion this year and is growing at 15-20% annually, with expectations to double in size in less than four years, far outpacing most other pharmaceutical sectors.

Yet, while there's new hope, there are old challenges.

First, many of the most menacing infectious diseases in the world, such as TB and malaria, continue to elude conventional vaccine approaches, as they have for decades. New infectious disease-causing agents such as HIV, pandemic flu, and Chikungunya viruses are still claiming millions of lives annually and have the potential to wreak even greater havoc globally.

Overall, it seems that most of the lower-hanging fruit has been picked from the "tree of diseases" using the traditional approaches. So, it became clear, like in other industries, we have to change our approach to meet new circumstances . . . in this case that means fighting new diseases.

The conventional vaccines we've depended upon simply employed weakened or killed viruses or different parts of the viruses as vaccines. They were and are still grown in eggs or cells and harvested over weeks of time with a very inefficient manufacturing process. To step beyond this decades-old approach, we are now pushing the frontiers with a new generation of vaccines, called DNA vaccines, with a completely new approach to vaccine design, formulation, manufacturing, and delivery using the best of modern science.

This novel field was launched in the early 90's by academic scientists like David Weiner of the University of Pennsylvania and industry researchers like Margaret Liu of Merck. These early pioneers found that immunizing animals with a small circular string of DNA called a plasmid, which encodes for a specific antigen or vaccine target, was a simple, yet elegant new method to generate vaccine responses.

By better mimicking the effects of natural viral infections, DNA vaccines have the ability to generate more powerful and broad immune responses than conventional vaccines. But, unlike live-attenuated viral vaccines, DNA vaccines pose zero threat for reversion of the vaccine to a virulent form. They cannot replicate or cause disease.

On the scientific side, the game-changing potential of this new technology caught my interest during my early career and I devoted myself to helping advance this field as part of my doctoral research in Dave Weiner's lab at Penn. We have since co-published over 75 papers on DNA vaccines.

On the business side, similar to what many of you in the audience have done, I left my comfortable position at Merck to start VGX Pharmaceuticals in 2000 with David Weiner to advance this new vaccine strategy. (I might add here that I have also received great advice from Bob Langer from our company's inception.)

Now, while DNA vaccines have great promise, we've also seen a great barrier to their effectiveness. In test after test in human trials, it became abundantly clear there was one glaring shortcoming of this new vaccine technology...that was delivery of DNA plasmids into cells.

However, we, and others in the field, have found an important technique to overcome this. Back in the 1970s, scientists discovered that applying electrical pulses to a cell in a petri dish enabled dramatically increased uptake of a biological material into the cell. And, while this phenomenon, called "electroporation," was widely used as a laboratory technique, it wasn't until the 1990s that the first research was undertaken to investigate potential direct applications of electroporation to humans in vivo.

Over the past several years, Inovio Biomedical has been a pioneer in developing in vivo electroporation delivery and commands a dominant intellectual property position in this field. It is this precise reason that we chose to merge VGX with Inovio Biomedical earlier this year.

Let me explain how electroporation assists the uptake of useful molecules such as a DNA vaccine into a cell. After a DNA vaccine is injected into the target tissue, a brief, controlled electrical pulse is applied directly to that tissue. Just milliseconds of electroporation pulses temporarily open pores in the cell membrane, allowing a significant quantity of the previously injected DNA vaccine to enter the cells.

After a short period of time the pores reseal, leaving the cells undamaged. By some measurements as much as 10 -100 fold more DNA plasmids enter the cells by this method, leading to a 100-1000 fold greater immune response. Our recent data presentation at a vaccine conference led a prominent researcher from the NIH to publicly exclaim, "Inovio now holds the world's record in generating T cell responses in monkeys."

Indeed, these and many other experimental data support the idea that in vivo electroporation may be the key enabling technology to finally make DNA vaccination clinically and commercially viable. The dramatic improvements to DNA vaccine delivery and potency that we are achieving allows us to reach for the "Holy Grail" of vaccine developer, designing vaccines that can protect against a broader range of evolving strains of a disease. This includes protecting against rapidly changing strains of a disease such as influenza and HIV, and against pathogen strains to which a vaccine is not specifically matched.

Let me briefly describe our novel approach to accomplish this. It is actually a marriage of medicine, science, computer programming, some luck and hard work. At its core, our SynCon™, or synthetic consensus vaccine approach starts with aligning a selected set of sequences for a given antigen and identifies the most conserved amino acids at each position. The conserved amino acids are then pieced together to yield a consensus immunogen. In theory, the consensus immunogen should contain the most conserved features of the component viruses, while at the same time introducing some variability unique to the component sequences. By design, SynCon™ immunogens should yield related, but unmatched vaccines to the targeted virus strains. This may be an important feature for targeting viruses that show high genetic diversity or high mutation frequencies as they pass from host to host.

Let me focus on one great example of our novel SynCon™ approach and that is our universal flu vaccine program. Each year hundreds of millions of flu vaccine doses are produced to address the seasonal flu problems. These vaccines are newly formulated each year based on strains of the disease that are expected to be most prevalent. Influenza viruses are classified H1N1, H2N2, H5N1, etcetera, based on which combination of one of 16 HA and one of 9 NA proteins they possess. Even within a subtype, there

are dozens of virus strains isolated from humans and the strains change each year because the virus mutates, making vaccines based on the previous sequences less effective.

Today and for many years past, at the beginning of each year flu experts around the world gather to determine which three strains of influenza to combine for the next annual season flu vaccine. Using technologies developed before some of us in this room were even born, traditional flu vaccine makers then rely on the growth of an influenza strain in eggs or cells, and the subsequent harvesting and inactivation of that virus for injectable administration. These vaccines cannot be stockpiled if they go unused, nor stored without refrigeration.

At Inovio, we felt that there should be a better way.

Instead of targeting a specific strain or strains, we developed a universal vaccine strategy to deal with ever-changing flu threats. As a part of our universal flu vaccine program, starting in 2007 we designed SynCon™ DNA vaccine constructs for H1 HA, H2 HA, and H3 HA. To this combination we also added H5 avian flu HA.

If we are correct, the potential of this approach is staggering. In theory, these consensus HA vaccine constructs delivered as a single shot with our electroporation device could protect vaccinated subjects from 90-95% of all human seasonal and pandemic influenza concerns.

Moreover, the vaccines might not even have to be administered annually after the first few priming sessions. Rather, the same combination could be used to boost our immune system every few years. Perhaps most importantly, we might not have to play “catch up” every time there is a new pandemic flare-up.

In the last two years we have been testing these ambitious goals systematically to prove the potency and breadth of each of our HA SynCon™ vaccines against each of the influenza virus families. For our first step, we completed an extensive set of proof-of-concept animal studies in mice, rabbits, ferrets, pigs, and monkeys. These data showed that our SynCon™ H5N1 vaccine generated cross-protective immune responses against a divergent set of unmatched H5N1 viruses. This was true against clade 1 to clade 2.3 viruses, showing strong cross-clade protection.

Moving to our second of the four HA components, we have also demonstrated that our SynCon™ H1N1 vaccine generated protective antibody responses in animals against unmatched H1N1 viruses. In perhaps our most dramatic virus challenge and protection study, vaccinated animals were injected with the deadly H1N1 flu virus that caused the 1918 Spanish flu, which killed over 40 million people. Inovio's

vaccine candidate completely protected animals from an unmatched challenge using the 1918 Spanish-flu virus, while all animals died in the unvaccinated group.

Most recently, we found that this consensus H1N1 vaccine, which was designed and constructed several years before the dramatic appearance of the currently circulating H1N1 swine flu, was able to generate sufficient protective antibody responses against the currently circulating virus strain.

Fast forwarding to today, we are working diligently to move our universal flu vaccine program into human clinical testing, with the first of the trials to begin in early 2010 with the H5 component. We plan to add H1 and other HA components in a strategic fashion to properly test our universal consensus flu strategy. We are very excited to arrive at the stage where we can test this strategy in humans.

However, we're not targeting just influenza. Beyond our universal flu vaccine program, we have applied the SynCon™ strategy to develop novel vaccine candidates against HIV, hepatitis C virus, and HPV for cervical cancer therapy.

HIV and cervical cancer programs are currently in Phase I clinical trials, with important clinical data expected during the next six to 12 months. We have also utilized our SynCon™ approach to develop a universal vaccine for dengue virus, where simultaneously generating immune responses against all four sub-types of the dengue virus has been a difficult task. In preclinical studies, we found that this universal vaccine induced cross-protective neutralizing antibody responses against all four dengue subtypes. We look forward to moving this program into clinical evaluation.

Furthermore, in a partnership with PATH Malaria Vaccine Initiative, a Gates Foundation-funded NGO, Inovio is applying its state-of-the-art technology to develop a new generation of SynCon™ DNA vaccines for malaria. I'm pleased to report we are making important progress in this area.

To sum up, this is an important "transitional" period for Inovio, for vaccines, for DNA vaccines delivered with our electroporation technology, and for diseases we hope to prevent. The recent swine-flu outbreak does not at this time appear likely to become one of the world's most devastating influenza pandemics. But the fact that this new strain of influenza has spread quickly and been designated by WHO as a pandemic has dramatically captured the world's attention. This outbreak has highlighted the unmet need for vaccines with protective capability against evolving strains of this disease and others yet to be identified.

At Inovio, we have taken important steps to bring us to this transitional time - from decades-old vaccine technology to an important new generation of vaccines. As part of our business strategy, Inovio has

added important components of our DNA vaccine development platform by merging with and acquiring organizations. We have consolidated technologies and strengthened patents, and we have secured the financial resources to advance our programs. We have demonstrated countless proof-of-concept studies in preclinical testing and we expect to report on more definitive human data in the next several months.

In closing, there can be no doubt that vaccines have been the single most effective tool developed by man to reduce infant mortality and extend human life-span. This was primarily accomplished using the conventional approaches for vaccine development and production. Yet there are still important public health challenges ahead of us that have not been addressed with conventional vaccines.

Inovio is in the thick of this pivotal challenge to advance technologies to provide important new developments in vaccines: These developments are:

- to increase the breadth of strain coverage
- to increase potency
- and to improve manufacturing methods for the next generation of vaccines.

This next generation of vaccines must also:

- decrease development costs
- improve vaccine affordability for global coverage
- and shorten response time to cope with emerging pandemics.

These are all themes driving Inovio. These are the reasons my colleagues and I come to work every day and the progress toward these goals continues to build the hope for better vaccines tomorrow.

Thank you.