INO-4800: One SARS-CoV-2 Vaccine, One Decade of Innovation

Cell & Gene Therapy Products, June 8, 2020
Robert J. Juba Jr.
Presentation Outline

• INOVIO Technology – DNA Medicines Powering Potent Antigen-Specific Immune Responses
• Designing INO-4800 (with a little help from MERS)
• Preclinical Evaluation of INO-4800
• GMP Manufacturing – A Proven Platform
• Stability Advantages of a DNA Plasmid Drug Product
• Proven Smart Delivery System and Clinical Safety Profile
• Regulatory Strategies for Rapid Response
• Phase 1 Clinical Study Progress
• Looking Forward
Powering a New Decade of DNA Medicines

Precisely Designed Plasmids Delivered Through Proprietary Smart Device

Safe and Robust Immune Responses in More Than 2,000 Patients

In Vivo Immune Responses for “Off-the-Shelf” Speed, Efficiency

Extensive Patent Portfolio Protecting Technology Platform

FIRST DNA Medicine in Phase 3 Clinical Trials (VGX-3100) for Precancerous Cervical Dysplasia

FIRST to Show Clearance of High-Risk HPV 16/18 in Phase 2b Trial (VGX-3100)

FIRST to Show Complete Response in Phase 1 w/2 PD-1s for Head and Neck Cancer (MEDI0457)

FIRST dMAb™ plasmid in Phase 1 for Zika (INO-A002)
1. Identify diverse strains/variants of a target virus or cancer

2. Assess gene sequence of selected antigen(s) from chosen strains/variants of the virus or cancer

3. Create optimal Consensus Sequence for the selected antigen

4. Insert SynCon sequence for each selected antigen into a separate precisely designed plasmid

5. Manufacture DNA medicine and deliver into muscle or skin using CELLECTRA® proprietary smart device

6. Protective antibodies and killer T cells produced by immune system against diverse strains of a virus or cancer
INO-4800: Synthetic DNA vaccine targeting SARS-CoV-2 Spike Glycoprotein

Rapid design of INO-4800

Isolation of virus

Zhu, N et al. 2020 NEJM

Virus sequence published

INO-4800 instructs expression of Spike protein

INO-4800: Synthetic DNA vaccine targeting SARS-CoV-2 Spike Glycoprotein

Spike protein is the main target of neutralizing antibodies
- Considered a key component for vaccines
- Codon and RNA optimized

Gene Optimization Algorithm

Cloned into expression vector

Control
INO-4800
INOVIO Response to Novel Coronavirus COVID-19 Outbreak Builds Upon Prior Experience in Developing a MERS Vaccine

We designed our COVID-19 vaccine candidate, named INO-4800, based upon studies targeting the MERS coronavirus family members.

**Track Record of Success with MERS DNA Vaccine – Preclinical**
- 100% protection from clinical disease in primate model after 2 immunizations
- 75% protection after a single immunization
- Strong cellular and humoral responses after 1 or 2 doses (NHP, camels and mice)

**Track Record of Success with MERS DNA Vaccine – Clinical**
- Phase 1 (US) and Phase 2 (Korea) data generated
- 76% seroconversion after single immunization
- Over 80% seroconversion after two immunizations
- Strong and broad cellular responses noted at all time points

Spike protein is the main target of neutralizing antibodies
- Considered a key component for vaccines
  - Codon and RNA optimized
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<th>Binding antibody Responses</th>
<th>ACE2/Spike blocking</th>
<th>Biodistribution</th>
<th>Pseudovirus neut.</th>
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INOVIO INO-4800 Preclinical Rapid Response Timeline

First Subject Dosed in Phase 1 Trial – April 6th, 2020

Species
- Mouse
- G. Pig (ID delivery)
- Rabbit (full human dose)
- NHP (immunogenicity/challenge)
- Ferret (challenge)

Feb 4th
In vitro expression data


ACE2/Spike blocking
Biodistribution
Pseudovirus neut.
Live virus neut.

Published
Submitted
INO-4800 was manufactured for human clinical use using INOVIO’s Platform MFG Process

- Process is established in a Platform Master File with FDA – 20 Drug Substances, 12 Drug Products
- Process has received Advanced Therapy Medicinal Products (ATMP) certification for quality for manufacture of VGX-3100 (HPV 16/18 precancerous dysplasia)
- Identical critical processing parameters (CPPs) and critical quality attributes (CQAs) for upstream and downstream drug substance manufacture and drug product fill/finish

Accelerated timeline from plasmid construction to release for human use

- 31-Jan (plasmid received by CMO) to 03-Apr (release for human use)
Stability Advantages of a DNA Plasmid Drug Product

• VGX-3100 stability assessed at multiple storage conditions
  ➢ Real-time 5°C
  ➢ Accelerated 25°C (Room Temp)
  ➢ Stressed 37°C

• Supercoiled % is most applicable measure of plasmid stability

• Only first order degradation of supercoiled to open circular form (single nicked strand)
  ➢ 2% loss over 54 months at 5°C
  ➢ 85% supercoiled after 12 months at 25°C
  ➢ Total circular forms maintained at 99-100% at all stability conditions – no formation of linearized plasmid
Clinical Safety and Success of the CELLECTRA® Platform

CELECTRA® 2000 EP Technology – Track record of success in the clinic

- >2000 Human Subjects and approx. 6000 Doses
- CELECTRA® 5PSP Device Developed to support Phase 3 and Commercial Launch
- Phase 2 Efficacy Data combining DNA vaccine and EP
- Global - Regulatory Approval for studies in 6 continents (including Central & Sub-Saharan Africa). Both devices CE marked in Europe.
INO-4800: Regulatory Strategy - Leveraging the Power of A Platform Technology to Rapidly Advance a COVID-19 Vaccine Candidate to Phase 1 testing in the United States

• INO-4800 Release Data
• Standard plasmid construction and platform manufacturing process
• 20 drug substances and 12 drug products in a platform master file

The Power of a Platform Technology

• INO-4800 Preclinical Study Data
• Supportive preclinical and clinical data from similarly designed plasmids

US IND was given authorization to proceed on April 2nd, First subject dosed on April 6th 2020

• INO-4800 is the 16th program since 2008 to utilize this same regulatory approach for rapid advancement into Phase 1 testing

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<th>FDA</th>
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<th>Ministry of Food: Drug Safety</th>
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<td><strong>Resounding support for platform technology approach</strong>&lt;br&gt;• Facilitation of IND Review&lt;br&gt;• Preliminary information on Emergency Use Authorization (EUA) for future consideration&lt;br&gt;• Assess theoretical risk of vaccine-enhanced disease</td>
<td><strong>Open and receptive to future discussions; specifically rapid Scientific Advice</strong>&lt;br&gt;Assess theoretical risk for vaccine-enhanced disease</td>
<td><strong>Highly motivated to rapidly advance to Phase 1 testing in Korea</strong>&lt;br&gt;• Will consider waiver of GLP toxicology and biodistribution study requirement&lt;br&gt;• Assess theoretical risk of vaccine-enhanced disease</td>
<td><strong>Willing to evaluate platform data from similarly designed plasmids</strong>&lt;br&gt;Facilitation of IND Review&lt;br&gt;Assess theoretical risk of vaccine-enhanced disease</td>
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INO-4800 US Phase 1 Progress

- An open label **study design** in a small sample size – 40 healthy volunteers - to gain preliminary assessment on safety, tolerability and immunogenicity
- Utilize **historical experience** with clinical trial sites to quickly complete start-up activities
- **Front load preparatory** activities at the operational level for subjects to be dosed as soon as the clinical investigational product is available
- **Motivated** study sites and volunteers
- **Supportive** DSMB members to make rapid decision

**Unprecedented speed** in starting the study (83 days from plasmid design to clinical testing) and completing enrollment (17 working days)
### INO-4800 Looking Forward

#### JUNE – JULY 2020

- In June, U.S. Phase 1 trial and animal challenge results to be announced
- Phase 2/3 trial to evaluate vaccine efficacy in humans is expected to begin
- Human clinical trials expected to begin in China and South Korea*

#### ONGOING

- Scale-up INO-4800 COVID-19 vaccine production to target one million doses by the end of 2020, and 100's million doses by the end of 2021, for potential use under emergency authorization.*

* Pending appropriate regulatory guidance and external funding
Rob Juba, VP, Biological Manufacturing & Clinical Supply Management
Rob.Juba@Inovio.com