NVX-CoV2373 Vaccine for COVID-19

Dr. Gregory Glenn, World Vaccine Congress Webcast

13 May 2020
Executive summary

- Novavax has a prefusion, stable recombinant SARS-CoV-2 Spike protein nanoparticle vaccine candidate (NVX-CoV2373) that has been highly immunogenic in mice and nonhuman primates
- Novavax is employing a mature vaccine platform to address the current COVID-19 pandemic
- Novavax is initiating a single protocol (Phase 1 and 2) this month with key data delivered Q3 and into Q4
- NVX-CoV2373 can be scaled up rapidly to produce up to 100M doses by year end and continue to scale throughout 2021
- NVX-CoV2373 could potentially be deployed under emergency use authorization by the end of 2020 pending positive safety and immune data
Novavax vaccine pipeline

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<tr>
<th>PROGRAM DESCRIPTION</th>
<th>PRECLINICAL</th>
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<td><strong>Matrix-M</strong> NanoFlu™ – Nanoparticle Seasonal Influenza Vaccine - Older Adults (65+ yrs)</td>
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<td><strong>Matrix-M</strong> NVX-CoV2373 – Coronavirus vaccine candidate¹</td>
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<td><strong>Matrix-M</strong> ResVax™ - RSV F Vaccine - Infants via Maternal Immunization²</td>
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<td><strong>Matrix-M</strong> RSV F Vaccine - Older Adults (60+ yrs)</td>
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<td><strong>Matrix-M</strong> RSV F Vaccine - Pediatrics (6 mos – 5 yrs)</td>
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<td><strong>Matrix-M</strong> Combination Influenza/RSV F Vaccine - Older Adults (60+ yrs)</td>
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<td><strong>Matrix-M</strong> Ebola GP Vaccine</td>
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¹Supported by grant from CEPI of up to $388 million
²Supported by the $89.1 million grant from the Bill and Melinda Gates Foundation.

Completed Phase 3, March 2020. Successfully achieved all primary endpoints and achieved statistical significance in key secondary endpoints.
Recombinant Protein Nanoparticles

Platform technology: previous experience allows directional confidence in early development

Experience with RSV, Seasonal Influenza and Ebola instructive

Highlights From Seasonal Influenza NanoFlu Nanoparticle Vaccine (qNIV)

Novavax qNIV released primary results from their P3 pivotal trial in March 2020 in adults older than 65 years. The trial remains ongoing for long term safety.

Recombinant adjuvanted vaccine addresses drift, egg adaptation and immune senescence.

Robust antibody and T cell responses.

Nanoparticle and Matrix M™ adjuvant share many similarities with NVX-CoV237.

In mice, Ebola glycoprotein (EBOV GP) nanoparticle vaccine, administered with Matrix-M, induced potent polyfunctional CD4+ and CD8+ T cell responses. 

Matrix-M adjuvant enhances antibody, cellular and protective immune responses of a Zaire Ebola/Makona virus glycoprotein (GP) nanoparticle vaccine in mice.

In mice, EBOV GP nanoparticle vaccine, administered with Matrix-M, induced potent neutralizing antibody responses, with dose sparing, and protection from lethal challenge.

Matrix-M adjuvant enhances antibody, cellular and protective immune responses of a Zaire Ebola/Makona virus glycoprotein (GP)nanoparticle vaccine in mice

Bengtsson et al.
Vaccine 34 (2016) 1927–1935
In baboons, EBOV GP nanoparticle vaccine with Matrix-M adjuvant was predictive of immunogenicity in humans

- Robust antibody and T cells
- Key role of adjuvant
- Dose sparing with Matrix-M
- Persistence of immunity
- Value of prime - boost

Fries, et al. Ebolavirus glycoprotein subunit vaccine with saponin Matrix-M™ adjuvant is highly protective against virulent human ebolavirus Zaire in Macaca fascicularis: An alternative to virus vector-based vaccines; in preparation.
In humans, EBOV GP nanoparticle vaccine, administered with Matrix-M, in a 2 dose schedule, induced potent and durable ELISA and neutralizing antibody responses over a year, with dose sparing.

- Design\(^1\): phase 1 (off IND), placebo-controlled, dose-escalation trial conducted in 230 healthy adults (18-50 years) randomized to 1 of 13 arms to evaluate 4 EBOV GP antigen doses as single- or 2-dose regimens with or without adjuvant. Safety and immunogenicity were assessed through 1-year post-dosing.
- Unadjuvanted 2-dose regimens show modest response by day 35 (approx. 5-fold over placebo background);
- 1-dose adjuvanted regimens show **10-fold** enhancement over 2-dose unadjuvanted regimens, reach plateau at 21 days;
- 2-dose adjuvanted regimens show responses >**100-fold** above unadjuvanted vaccine;
- No antigen dose response in any group; 6.5µg is a good as 50.

1. Fries L, 2019
EBOV GP nanoparticle vaccine Phase 1 human immunogenicity

Human EBOV GP Phase 1 immune responses in the FANG ELISA compared to vectored vaccines

EBOV GP nanoparticle vaccine responses in NHP ≥ median ELISA values\(^1\) in subjects immunized with vectored vaccines and showed protection in the field\(^2\)

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\(^1\)Logue, et al. JVM. 2018
\(^2\)Henai-Restrepo, et al. Lancet 2017
Recombinant Protein Nanoparticles

Platform technology: previous experience allows directional confidence in early development

Engineered for immunogenicity, stability and productivity

SARS-CoV-2 Spike protein structure critical for protection, characterization tools well developed

Novavax NVX-CoV2373 Vaccine Approach

- Developed from a gene sequence to phase 1 in ~90 days nanoparticle vaccines against Ebola GP and influenza A/H7N9 HA with Matrix=M adjuvant
- SARS CoV-2 Spike (S) gene synthesized by GenScript and delivered Jan 20
- Engineered >20 constructs
- Screened for hACE2-binding, stability, productivity, immunogenicity
- NVX-CoV2373 selected a stabilized, prefusion, hACE2-binding, candidate
NVX-CoV2373 and Matrix-M™
Critical partners for immunogenicity

CoV2373 Antigen
hACE2 receptor
SARS-CoV-2 trimer

Novavax, Inc. (U.S.)

Matrix-M

Novavax AB (Sweden)
The 2373 rSpike protein in the Nanoparticle Vaccine is in the prefusion state, its native structure.

The native structure is deemed critical for inducing protective immune responses.

Together with PS80 forms a detergent/protein nanoparticle.

- 2D class average overlay with recently solved cryoEM of SARS-CoV-2 trimeric spike protein (EMD ID 21374)
NVX-CoV2373 binds with high affinity to hACE2 receptor

Binding is an indication of the correct prefusion structure, predicts induction of functional antibodies that will block infection
NVX-CoV-2 construct stability

NVX-COV2373 SARS-CoV-2 prefusion S ACE2 binding 48 hr stress conditions

Balb/C Mice: NVX-CoV2373 10µg + Matrix-M
Anti-S IgG, hACE2 receptor inhibition, SARS-CoV-2 Neutralization

NVX-CoV2373 anti-S IgG  hACE2 Receptor Inhibition  Neutralization*

*Matt Frieman, UMD School of Medicine BSL3 SARS-CoV-2 virus infection Vero E6 cell CPE (50%) assay.
Balb/C Mice: NVX-CoV2373 vaccine 10ng - 10µg dose-ranging hACE2 receptor inhibition (50%)

- Functional immunity induced at 10ng dose NVX-CoV2373
- Matrix improves immune responses
- Second vaccination improves immune responses
Baboons: NVX-CoV2373+Matrix-M
Anti-S IgG, hACE2 receptor inhibition, and Neutralization

NVX-CoV2373 anti-S IgG

Neutralization*

*Matt Frieman, UMD School of Medicine BSL3 SARS-CoV-2 virus infection Vero E6 cell CPE (50%) assay.
Baboons: ELISPOT IFN-γ and IL-4 responses PBMCs Day 28

*Stimulation IFN-γ production was 0.01% treated with medium only, however IFN-γ animal No.609 (5µg group) was 1.07% (100 folds higher) stimulated with medium only, thus was not included in the analysis.
Baboons: Intracellular Cytokine Staining (IFN-γ, IL-2, TNF-α) Multifunctional Ag-Specific CD4 T-cells day 28

**Double cytokine+ CD4 T cells**

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<th>25µg</th>
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<th>5 µg</th>
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<td>+Matrix M</td>
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**Triple cytokine+ CD4 T cells**

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Baboon/human: Anti-CoV2373 S IgG Responses

NVX-CoV2373 Immunized Baboons

COVID-19 Convalescent Serum (Individual Subjects)
Baboon/human: hACE2 Receptor Inhibition Responses

NVX-CoV2373 Immunized Baboons

COVID-19 Convalescent Serum (Individual Subjects)
Preclinical Testing NVX-CoV2373 Vaccine for Enhanced Disease

• Mechanism of enhancement reported for SARS and MERS-CoV
  • Mice: Th2 dominance associated with eosinophils in lung lesions.
  • NHP: Virus-antibody immune complexes and cytokine storm associated with enhanced lung inflammation; not associated with antibody-mediated enhancement of viral replication (ADE).

• Rodent models for Th2 dominance
  • Balb/C mice – IgG subclass and IL-4/IFN-γ ELISPOT
  • ACE2-transgenic mice – CoV-2 challenge/histopathology
  • Syrian golden hamsters – CoV-2 challenge/histopathology

• Non-human primates for cytokine storm – lung pathology
  • Cynomolgus – CoV-2 challenge/histopathology
  • Rhesus – CoV-2 challenge/histopathology
NVX-CoV2373: Clinical Plan
NVX-CoV2373 phase 1 clinical trial
With or without 50 mg Matrix-M™ adjuvant

- Single protocol Phase 1/Phase 2
- Phase 1 – 130 subjects, 18-59 years of age
  - Data to be filed to US IND for Phase 2 initiation
  - Key Immune measurements:
    - ELISA
    - Receptor Binding Inhibition
    - Neutralization
    - CMI – Th1/Th2
- Key Safety
  - Reactogenicity
  - Safety labs pre/post vaccination
  - Pause rules with SMC in place
  - AE (SNMC, SAE, AESI)
- Key Data – Currently recruiting, Data July

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<th>Treatment Group</th>
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<th>Day 21</th>
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<td>Matrix-M Adjuvant</td>
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<td>E</td>
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NVX-CoV2373 phase 2B clinical trial

- Single protocol Phase 1/Phase 2
- Phase 2 proposed to follow closely on day 35 Phase 1 results
  - ~2200 Subjects, 1000 > Older Adults
  - US and Australia
  - Placebo controlled
  - Considerations 1 vs 2 doses, Fractional dosing
- COVID-19 disease endpoints – PCR confirmed
  - Multiple severities
- Trigger for Phase 3 (or potential EUA)
- Other parallel trials in other geographies and populations under development
CEPI $388M Funding for NVX-CoV2373 COVID-19 Vaccine Development and Manufacturing; May 11, 2020

- Richard Hatchett, CEO of CEPI: “The expansion of our partnership with Novavax represents CEPI’s single biggest investment to date.”
- Support clinical development NVX-CoV2373 vaccine candidate through Phase 2
- Support rapid scale-up of vaccine manufacturing
- Allows for increased production of Matrix-M adjuvant
- Reserves global large-scale manufacturing capacity

Novavax Dr. Sonia Maciejewski and Dr. Nita Patel, Director of Antibody Discovery and Vaccine Development
Summary

- Novavax has selected a prefusion, hACE2-binding, stable, immunogenic, SARS-CoV-2 spike nanoparticle vaccine with Matrix-M adjuvant
- GMP manufacturing of the NVX-CoV2373 and Matrix-M are being scaled up to 100M doses by the end of 2020 and > 1B doses in 2021
- Clinical evaluation is underway with a goal to be able to deploy the vaccine prior to or by the end of the year working with the regulatory authorities under emergency conditions
Thank you to the Novavax Team, CEPI, and our many collaborators