RAPID COVID-19 VACCINE DEVELOPMENT ENABLED BY PROTOTYPE PATHOGEN PREPAREDNESS

AVAC eSeminar
August 25, 2020

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NIAID Vaccine Research Center

Commencement Address by President Clinton at Morgan State University, Baltimore, May 18, 1997

"If America complains to find an AID vaccine and we entail others in our cause, we will do it... Today I'm pleased to announce the National Institutes of Health will establish a new AIDS vaccine research center dedicated to this crusade."

Basic Research
Process Development

- AIDS/HIV
- Influenza
- Ebola/Marburg
- RSV
- Malaria
- Tuberculosis
- EID
  - West Nile virus, Zika
  - Chikungunya
  - W/E/V equine encephalitis viruses
  - MERS-CoV, SARS, and other CoV
  - Nipah and other paramyxoviruses
  - EV-D68 and other picornaviruses
  - Smallpox

GLP Analysis
Nucleic acid
Vectors
VLPs
Proteins and nanoparticles
Monoclonal antibodies
Clinical Trials
Vaccine Development Strategies for Pandemic Preparedness

- Platform approach
  - Plug-and-play
- Priority-pathogen
  - Selected pathogens of concern
- Prototype-pathogen
  - Systematic preparedness
  - All virus families of concern

Novel Vaccine Technologies Essential Components of an Adequate Response to Emerging Viral Diseases
BS Graham, JR Mascola, AS Fauci
MO Health, CO Production and AS. Fauci

New Technologies are Transforming Vaccinology

- Structure-based vaccine design
- Single-cell sorting, sequencing, and bioinformatics
  - Rapid isolation of human mAbs
  - Definition of antibody lineages
  - Analysis of immune responses
- Protein engineering of self-assembling nanoparticles
- Rapid DNA synthesis
- Recombinant DNA and genetic engineering technology
  - Rapid cell line development
  - Animal model development
- Nucleic acid and vector-based delivery of vaccine antigen
Preserving Apical Epitopes Improves Immunogenicity

Summary

- Solving atomic structure of prefusion RSV F revealed a new target of vulnerability.

- Stabilized RSV pre-F candidate trimeric subunit vaccine (DS-Cav1) provides a clinical proof-of-concept for structure-based vaccine design by preserving neutralization-sensitive epitopes on the vaccine antigen.

- The concept of stabilizing the prefusion conformation of class I fusion proteins can be generalized across other virus families.
**Structure-guided Stabilization of HKU1 CoV Spike**

![Image of a human coronavirus spike protein structure](image)

**Stabilized CoV Spike Protein Improve Expression**

**A**

- NTD: N-terminal domain
- CTD: C-terminal domain
- S1/S2: S1 and S2 subunits
- S2': S2' subunit
- 767: Residue 767
- 1276: Residue 1276
- 1351: Residue 1351

**B**

- Asn1067
- Leu1068

**C**

- MERS S-WT
- MERS S-2P
- SARS S-WT
- SARS S-2P

**D**

- Prefusion S
- Postfusion S

MERS S-2P has 50-fold greater expression than wild-type sequence.

S-2P maintains prefusion structure preserving NT-sensitive epitopes.
Coronavirus Origins and Phylogeny


Drosten et al Adv Viral Research 2018 and adapted from Ralph Baric

mRNA immunization strategy
**mRNA immunization strategy**

Protein expression affected by mRNA chemistry and manufacturing process

Nelson et al. Sci Adv 2020

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**MERS S-2P protects against mouse-adapted MERS CoV challenge in hDPP4 transgenic mice**

Week 0 1 2 3 4 5 6 7

Lung Viral Load

Day 3

Lung Hemorrhage Score

Day 3

Weight Loss

1 µg MERS S-2P mRNA

0.1 µg MERS S-2P mRNA

0.01 µg MERS S-2P mRNA

PBS

% Body Weight

Day Post-challenge

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Summary

- **Proline** mutations in S from multiple CoV strains *stabilizes prefusion S*

- Stabilized *prefusion S trimers are more immunogenic* and protective than WT trimers or monomeric subunits

- May be a *general solution for beta-CoV* vaccine antigen design

- mRNA suitable delivery approach and *rapid manufacturing* platform

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**Coronavirus Disease 2019 (COVID-19) (December 2019 – Present)**

- **COVID-19** is the name of the disease caused by the novel coronavirus **SARS-CoV-2**
COVID-19 VACCINE DEVELOPMENT

SARS-CoV-2 Outbreak

- Dec 31, 2019: 1st report of respiratory virus outbreak in Wuhan, China
- Jan 10, 2020: 2019-nCoV sequences published
- Jan 23, 2020: DMID initiates clinical and regulatory process
- Jan 11, 2020: VRC decides on vaccine sequence with Moderna
- Jan 14, 2020: UT-Austin solves spike structure
- Jan 16, 2020: Moderna receives sequence for GMP production
- Jan 31, 2020: VRC makes nCoV spike protein
- Feb 1, 2020: First nCoV spike ELISA for cross-reactivity
- Feb 3, 2020: Immunogenicity confirmed in mice
- Feb 4, 2020: VRC vaccinates mice
- Feb 18, 2020: Immunogenicity confirmed in mice
- Feb 20, 2020: DMID submits IND
- Feb 21, 2020: Moderna ships vaccine to DMID
- March 2, 2020: FDA safe-to-proceed
- March 16, 2020: Phase 1 Clinical trial starts
- March 16, 2020: Phase 2 clinical trial starts
- July 27, 2020: Phase 3 Clinical trial starts

CORONAVIRUS BIOLOGY AND NOMENCLATURE

Spike Protein

Viral membrane

Corona = crown or circle of light

High Quality Protein is the Basis for Next Steps

Isolation of monoclonal antibodies

Assay development

Vaccines

Global COVID-19 Vaccine Landscape

28 Vaccine Candidates in Clinical Evaluation

Nucleic acid
DNA
mRNA
Whole-inactivated virus
Recombinant Adenovirus Vectors
Recombinant proteins or subdomains

139 Vaccine Candidates in Pre-clinical Evaluation

Nanoparticle display of structurally defined proteins
live attenuated virus
Recombinant Vectors
Recombinant or chimeric viruses
Virus-like particles
Peptides

Source: WHO 7 July 2020
mRNA-1273 mouse immunogenicity and protection

Week

Week

1x10⁶ pfu challenge dose

Days

weight

weight

weight

weight

PFU lung

PFU lung

PFU nose

PFU nose

Cytokines lung

Cytokines lung

Pathology lung

Pathology lung

Corbett et al BioRxiv 2020

mRNA-1273 is immunogenic and protective

Post prime and post-boost serology

Viral Load day 2

2-dose

1-dose

2-dose

1-dose

ELISA

NT

Lung

N/A

Nose

Corbett et al BioRxiv 2020
mRNA-1273 protects up to 13 weeks post-boost without immunopathology

Lung

Nose

Breakthrough Pathology

Corbett et al BioRxiv 2020

Immunization of Aged Mice with ERD Controls

<table>
<thead>
<tr>
<th>Group</th>
<th>Animal #</th>
<th>Vaccine</th>
<th>Week 0 Immunization</th>
<th>Week 3 Immunization</th>
<th>Week 7 Challenge</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>Control mRNA</td>
<td>04/20/20</td>
<td>05/11/20</td>
<td>MA10 $10^3$ pfu</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>mRNA-1273</td>
<td>1 µg</td>
<td>1 µg</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>mRNA-1273</td>
<td>0.1 µg</td>
<td>0.1 µg</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>DIV SARS-CoV-1 in alum</td>
<td>10µl</td>
<td>10µl</td>
<td></td>
</tr>
</tbody>
</table>

DIV SARS-CoV-1
double-inactivated
Formalin/UV
SARS-1 virus in alum historically associated with VAERD in mice

mRNA-1273
Stabilized spike – S-2P

MA10 SARS-CoV-2
RBD-modified
10 serial passages
Virulent in mice

Confidential to NIAID/VRC - unpublished
mRNA-1273 in NHP - Experimental Design

- **Immunizations W0/W4:**
  - PBS
  - 10 µg mRNA-1273
  - 100 µg mRNA-1273

- **Post-challenge sampling:**
  - Blood: Days 0, 2, 4 and 7
  - Nasal swabs: Days 1, 2, 4 and 7
  - Bronchoalveolar lavage: Days 2, 4 and 7

**Week 0**
- Immunization

**Week 4**
- Immunization

**Week 8**
- **Challenge**
- Lung Pathology

**Day 0**
**Day 7/8**

**Challenge Lung Pathology**

**Immunizations W0/W4:**
- PBS
- 10 µg mRNA-1273
- 100 µg mRNA-1273

**Post-challenge sampling:**
- Blood: Days 0, 2, 4 and 7
- Nasal swabs: Days 1, 2, 4 and 7
- Bronchoalveolar lavage: Days 2, 4 and 7

**Binding Antibody Responses to Spike Protein**

**Binding IgG**

- 10 µg mRNA-1273
- 100 µg mRNA-1273

**RBD-specific Binding**
- 4 Weeks Post-boost

**S1_NTD-specific Binding**
- 4 Weeks Post-boost

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Corbett et al. NEJM July 28

Kizzmekia Corbett
Bob Seder
Mario Roederer
Nancy Sullivan
Kathy Foulds
Tracey Ruckwardt
Ian Moore
Martha Nason
JP Todd

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23

24

Kizzmekia Corbett
Barbara Flynn
Joe Francica
Functional Antibody Responses

ACE2 Binding Inhibition
4 Weeks Post-boost

Live Virus Neutralization
4 Weeks Post-boost

mRNA-1273 Elicits Th1-biased Responses and Tfh

Corbett et al. NEJM July 28
Rapid Clearance of SARS-CoV-2 in Upper and Lower Airways

Day 7 Pathology Post-Challenge

Corbett et al. NEJM July 28

Corbett et al. NEJM July 28
Correlations with Virus Clearance

Corbett et al. NEJM July 28

mRNA-1273 Phase 1

<table>
<thead>
<tr>
<th>Age</th>
<th>Dose (µg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>18-55</td>
<td>25, 100, 250</td>
</tr>
<tr>
<td>56-70</td>
<td>50, 100</td>
</tr>
<tr>
<td>≥71</td>
<td></td>
</tr>
</tbody>
</table>
Dose effect and reactions greater after 2nd dose. 3/14 severe

No serious adverse events and no pre-specified study halting rules were met through Day 43

Solicited systemic and local adverse events in >50% included fatigue, chills, headache, myalgia, and pain at the injection site

Dose effect and reactions greater after 2nd dose. 3/14 severe

Spike- and RBD-specific IgG

18-55
N=15/dose group

18-55
N=15/dose group

Confidential to NIAID/VRC

Jackson et al. NEJM 2020

Confidential to NIAID/VRC
Neutralizing Activity

Pseudovirus ID50 NT

PRNT 80

T Cell Analysis – mRNA-1273

CD4

CD8

Confidential to NIAID/VRC

Jackson et al. NEJM 2020
U.S. SARS-CoV-2 Vaccine Candidates
Operation Warp Speed (OWS)

- Overall lead (Moncef Slaoui)
- COO (General Gustave Perna)

Vaccines (Hepburn)

Diagnostics (Tromberg)

Therapeutics (Woodcock)

Vaccine Development

Supply & Manufacturing

Delivery & Admin.

NIH

BARDA

CDC

- Preclinical animal models
- Immune assay development and standardization
- Phase 3 Clinical Trials

COVID-19 Prevention Network

www.Coronaviruspreventionnetwork.org

Predictive Analytics: Essential Facilities and Trial Sites
Summary

- Product development and clinical evaluation started in record time
  - Prior fundamental basic and translational research
  - Precision vaccinology and new technologies
  - Prototype pathogen preparedness planning
  - Pre-established public-private partnership

- mRNA-1273 is immunogenic and well-tolerated in mice, NHP, and humans
  - Protective in mice and NHP in upper and lower airway
  - Immunogenic in older age groups
  - Phase 3 trial started July 27