Biomedical Prevention for COVID-19: Vaccines, MABs and Lessons from HIV

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This activity is jointly provided by Physicians’ Research Network and the Medical Society of the State of New York.
Help find a vaccine for COVID-19!

We're looking for:
- Adults aged 18 and older
- People who are more likely to be exposed to COVID-19, including:
  - People with underlying medical conditions
  - People with greater chances of exposure at their job
  - People who live or work in elder-care facilities
  - People over age 65
  - People who work in jails or prisons
  - People from racial and ethnic groups that have been impacted in greater numbers by the epidemic, such as African Americans, Latinx, and Native Americans

If you decide to join a COVID-19 prevention study, you will be compensated for your time.

You CANNOT get infected with SARS-CoV-2 or get COVID-19 illness from the study vaccine.

www.CoronavirusPreventionNetwork.org
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BIOMEDICAL PREVENTION FOR COVID-19: VACCINES, MABS AND LESSONS FROM HIV

Mark J. Mulligan, MD, FIDSA
Director, NYU Langone Vaccine Center

PRN WEBINAR, July 22, 2020
Outline

• Potential conflicts of interest
• Learning objectives
• Immunity
• Vaccine Trials
• MAB, Rx
• Acknowledgements

Not: convalescent plasma
Potential Conflicts of Interest – USG-funded work

• HHS/NIH/NIAID RESEARCH GRANT FUNDING
  – VACCINE AND TREATMENT EVALUATION UNIT (VTEU)
  – ASTRAZENECA (OXFORD) COVID-19 VACCINE TRIAL
  – LILLY SARS-COV-2 MAB EFFICACY TRIAL, Px IN NURS HOMES
  – REGENERON SARS-COV-2 MAB EFFICACY TRIAL, PROPHYLAXIS IN HOUSEHOLDS

• HHS/BARDA FUNDING
  – COVID SPECIMENS FOR MEDICAL COUNTERMEASURES
Potential Conflicts of Interest – Industry Collaborations

- PFIZER RESEARCH FUNDING
  - PHASE 1-2 COVID-19 MRNA VACCINE TRIAL
- LILLY RESEARCH FUNDING
  - SARS-COV-2 MAB NEUTRALIZATION POTENCY VS LIVE SARS-COV-2
  - SARS-COV-2 MAB PHASE 1 SAFETY AND EFFICACY TRIAL
- SANOFI RESEARCH FUNDING
  - VERO CELL-GROWN YELLOW FEVER VIRUS VACCINE CLINICAL TRIAL
- MEISSNA VACCINES, INC SCIENTIFIC ADVISORY BOARD GUEST,
Objectives

• Gain an appreciation of the progress on COVID-19 vaccines, and how the vaccine platforms compare to those being evaluated for HIV.

• Understand the potential uses of monoclonal antibodies (MABs) against SARS-CoV-2, and parallels to HIV MAB work.

• Be aware of COVID-19 vaccine trials in the NYC area.

• Learn the latest about natural immunity to COVID-19.
The Virus
SARS-CoV-2

Immune response

- Infected cells destroyed
- Antibodies produced
- Memory B cells and T cells created

1. Virus enters oral + respiratory cells
2. Virus enters epithelium
3. Virus fuses with vesicle and its RNA is released
4. Virus assembly
5. Virus release
6. Virus ingested by antigen-presenting cell (APC)
Immunity - Acute Ab response, 2 patients, first 3 weeks

SARS-CoV-2 S1-specific antibody by isotype in ELISA

Immunity – duration of binding Ab

13 Convalescent Patients – first six weeks

SARS-CoV-2 S1-specific antibody by isotype in ELISA

Immunity – duration of binding Ab

13 Convalescent Patients – next six weeks

SARS-CoV-2 S1-specific antibody by isotype in ELISA

Immunity – functional antibody

**Live virus neutralization assay**

48 hr neutralization assay
SARS-CoV-2 mNeon green (Xie et al., *Cell Host & Microbe*, 2020)

<table>
<thead>
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<th>Dilution</th>
<th>1/20</th>
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<th>1/80</th>
<th>1/160</th>
<th>1/320</th>
<th>1/640</th>
<th>1/1280</th>
<th>1/2560</th>
<th>1/5120</th>
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<td>NLV-1 V1</td>
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<td>Positive control</td>
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</tbody>
</table>

Mock and Uninfected

**ELISA Binding Ab vs S1**

<table>
<thead>
<tr>
<th></th>
<th>NLV-</th>
<th>DPO</th>
<th>IgM</th>
<th>IgG</th>
<th>IgA</th>
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<tr>
<td>2 - V1</td>
<td>28</td>
<td>1817</td>
<td>12786</td>
<td>3209</td>
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<tr>
<td>2 - V2</td>
<td>53</td>
<td>723</td>
<td>13890</td>
<td>1762</td>
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</tbody>
</table>

Unpublished

NYU Grossman School of Medicine
Target of Ab

Spike Protein, S

Amanat et al., *Nat Med*, 2020
Immunity – development of long-lasting memory

Memory B cell Responses

- COVID-19 Covalescent
- COVID-19 Asymptomatic
- Healthy Controls
- Influenza Patients
Measuring immunity to SARS-CoV-2 is key for understanding COVID-19 and vaccine development.

Epitope pools detect CD4+ and CD8+ T cells in 100% and 70% of convalescent COVID patients.

T cell responses are focused not only on spike but also on M, N, and other ORFs.

Grifoni et al., *Cell*, 2020, June 25, 2020
Pre-existing immunity

- T cell reactivity against SARS-CoV-2 was observed in 20-50% of unexposed people
  - Non-spike > spike; CD4 > CD8
- It is speculated that this reflects T cell memory to circulating ‘common cold’ coronaviruses.
  - HCoV-OC43, HCoV-HKU1, HCoV-NL63 and HCoV-229E

Grifoni et al., Cell, 2020; Sette and Crotty, Nat Rev Imm, 2020; 3 preprints
Deep immune profiling of COVID-19 patients reveals distinct immunotypes with therapeutic implications

Divij Mathew1,2,*, Josephine R. Giles1,2,*, Amy E. Baxter1,2,*, Derek A. Oldridge1,4,*, Allison R. Greenplate1,2,*, Jennifer E. Wu1,2,*, Cécile Alanio1,2,*, Leticia Kuri-Cervantes1,5, M. Betina Pampena1,5, Kurt D’Andrea6, Sasikanth Manne1,2, Zeyu Chen1,2, Yinhui Jane Huang1,2, John P. Reilly7, Ariel R. Weisman7, Caroline A. G. Ittner7, Oliva Kuthuru1,2, Jeanette Dougherty1,2, Kito Nzingha1,2, Nicholas Han1,2, Justin Kim1,2, Ajinkya Pattekar1,8, Eileen C. Goodwin1,5, Elizabeth M. Anderson1,5, Madison E. Weirick1,5, Sigrid Gouma1,5, Claudia P. Arevalo1,5, Marcus J. Bolton1,5, Fang Chen9, Simon F. Lacey9,10, Holly Ramage11, Sara Cherry1,4, Scott E. Hensley1,5, Sokratis A. Apostolidis1,12, Alexander C. Huang1,3,13, Laura A. Vella1,14, The UPenn COVID Processing Unit†, Michael R. Betts1,5,‡, Nuala J. Meyer15,‡, E. John Wherry1,2,3,‡

• Analyzed 125 COVID-19 patients, and compared recovered to healthy individuals using high dimensional cytometry.
• A subgroup of patients had T cell activation characteristic of acute viral infection and plasmablast responses reaching >30% of circulating B cells.
• However, another subgroup had lymphocyte activation comparable to uninfected subjects.
SKETCHPAD

PHASE TWO

By Jason Adam Katzenstein
Over 100 Vaccine Candidates in Development

A Vaccine Platforms

- DNA
  - Coronavirus spike gene
  - Viral genes (some inactive)
  - Viral vector (non-replicating)
- RNA (+ LNP)
  - Coronavirus spike gene
  - Viral genes (some inactive)
  - Viral vector (replicating)
- Protein-based (e.g. Spike)
  - Virus (inactivated)
  - Virus (attenuated)

B Vaccine Candidates

- Other
- DNA
  - Viral vector (replicating)
  - SARS-CoV-2 live attenuated
- RNA
  - Viral vector (non-replicating)
  - SARS-CoV-2 inactivated
- Protein-based

Funk at al., Front. Pharmacol., 19 June 2020
HVTN 702, Uhambo, Phase 2B/3 trial – no protection

- 2/20: DSMB found during an interim review - did not prevent HIV
- ALVAC-HIV + gp120/MF59, Prime-boost, sub-type C, based on RV144
- No safety concern
- Began 2016, S Africa, enrolled 5,407 sexually active men & women
- 129 HIV infections in vaccine ppts, and 123 HIV infections in placebo
- two other late-stage, multinational vaccine trials, Imbokodo and Mosaico, ongoing
- AMP trials are testing an IV MAB for preventing HIV
HVTN 705/HPX2008: THE IMBOKOUDO STUDY

• Efficacy study testing a combination of two experimental vaccines to prevent HIV
• The study vaccines are:
  – Ad26.Mos4.HIV (Ad26 vaccine; mosaic immunogens)
  – Clade C gp140 (protein vaccine) + alum adjuvant
• 2600 HIV-negative women in sub-Saharan Africa
• Janssen, J&J + NIAID HVTN
• Ongoing
**Mosaico, HPX3002/HVTN 706**

- Phase 3 HIV vaccine efficacy trial - ongoing
- Ad26.Mos4.HIV and aluminum phosphate-adjuvanted Clade C gp140 and Mosaic gp140
- Mosaico study will enroll 3,800 participants across 8 countries, including Argentina, Italy, Mexico, Poland and the United States.
- 3800 transgender individuals and in men who have sex with men - communities disproportionately affected by HIV
rAd-5 viral vector, Spike, single IM injection, 3 dose levels - $5 \times 10^{10}$, $1 \times 10^{11}$, $1.5 \times 10^{11}$ viral particles

<table>
<thead>
<tr>
<th>Day 14</th>
<th>Low dose group (n=36)</th>
<th>Middle dose group (n=36)</th>
<th>High dose group (n=36)</th>
<th>p value</th>
<th>Day 28</th>
<th>Low dose group (n=36)</th>
<th>Middle dose group (n=36)</th>
<th>High dose group (n=36)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA antibodies to the receptor binding domain</td>
<td></td>
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</tr>
<tr>
<td>GMT</td>
<td>7.5 (4.3–13.2)</td>
<td>91.2 (55.9–148.7)</td>
<td>132.6 (80.7–218.0)</td>
<td>0.29</td>
<td>615.8 (405.4–935.5)</td>
<td>806.0 (528.2–1229.9)</td>
<td>1445.8 (935.5–2234.5)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>≥4-fold increase</td>
<td>16 (44%)</td>
<td>18 (50%)</td>
<td>22 (61%)</td>
<td>0.35</td>
<td>35 (97%)</td>
<td>34 (94%)</td>
<td>36 (100%)</td>
<td>0.77</td>
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<tr>
<td>Neutralising antibodies to live SARS-CoV-2</td>
<td></td>
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<tr>
<td>GMT</td>
<td>8.2 (5.8–11.5)</td>
<td>9.6 (6.6–14.1)</td>
<td>12.7 (8.5–19.0)</td>
<td>0.24</td>
<td>14.5 (9.6–21.8)</td>
<td>16.2 (10.4–25.2)</td>
<td>34.0 (22.6–50.1)</td>
<td>0.0082</td>
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</tr>
<tr>
<td>≥4-fold increase</td>
<td>10 (28%)</td>
<td>11 (31%)</td>
<td>15 (42%)</td>
<td>0.42</td>
<td>18 (50%)</td>
<td>18 (50%)</td>
<td>27 (75%)</td>
<td>0.046</td>
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</table>

Data are mean (95% CI) or n (%). The p values are the result of comparison across the three dose groups. If the difference was significant across the three groups, the differences between groups were estimated with 95% CIs. SARS-CoV-2—severe acute respiratory syndrome coronavirus 2. GMT = geometric mean titre.

Table 3: Specific antibody responses to the receptor binding domain, and neutralising antibodies to live SARS-CoV-2

Appeared safe, dose-dependent vaccine reactions, generally well tolerated. A.E.s: fever, fatigue, headache, and muscle pain.

*Lancet* 2020; 395: 1845–54
CanSino Biologics – Phase 1

ICS Assay for Peptide-specific CD4+ or CD8+ T cells

Appeared safe, dose-dependent vaccine reactions, generally well tolerated. A.E.s: fever, fatigue, headache, and muscle pain.

- Limitations of this Interim report
  - Short follow up: ? duration
  - Pre-existing immunity, dampens
  - Likely need for a booster
    - Response magnitudes low?
    - Relative to convalescent patients?
  - Choice of rAd5: HIV vaccine experience

*Lancet* 2020; 395: 1845–54
Immunogenicity and safety of a recombinant adenovirus type-5-vectored COVID-19 vaccine in healthy adults aged 18 years or older: a randomised, double-blind, placebo-controlled, phase 2 trial

Feng-Cai Zhu *, Xu-Hua Guan *, Yu-Hua Li, Jian-Ying Huang, Tao Jiang, Li-Hua Hou, Jing-Xin Li, Bei-Fang Yang, Ling Wang, Wen-Juan Wang, Shi-Po Wu, Zhao Wang, Xiao-Hong Wu, Jun-Jie Xu, Zhe Zhang, Si-Yue Jia, Bu-Sen Wang, Yi Hu, Jing-Jing Liu, Jun Zhang, Xiao-Ai Qian, Qiong Li, Hong-Xing Pan, Hu-Dachun Jiang, Peng Deng, Jin-Bo Guo, Xue-Wen Wang, Xing-Huan Wang, Wei Chen

The Lancet, published online July 20, 2020

CanSino Biologics Phase 2
Phase 1/2 Study to Describe the Safety and Immunogenicity of a COVID-19 RNA Vaccine Candidate (BNT162b1) in Adults 18 to 55 Years of Age: Interim Report

Mark J. Mulligan¹*, Kirsten E. Lyke²*, Nicholas Kitchin³,a, Judith Absalon³,b, Alejandra Gurtman³,b, Stephen Lockhart³,a, Kathleen Neuzil², Vanessa Raabe¹, Ruth Bailey³,a, Kena A. Swanson³,b, Ping Li³,c, Kenneth Koury³,b, Warren Kalina³,b, David Cooper³,b, Camila Fontes-Garfias⁶,Pei-Yong Shi⁶, Özlem Türeci⁷, Kristin R. Tompkins³,b, Edward E. Walsh⁴, Robert Frenck⁵, Ann R. Falsey⁴, Philip R. Dormitzer³,b, William C. Gruber³,b, Uğur Şahin⁷, and Kathrin U. Jansen³,b

- FIH, phase 1 randomized, double-blinded clinical trial
- Nucleoside-modified mRNA
- Immunogen: RBD trimer
- Healthy adults, 18-55 y.o., 2 vaccinations days 1, 21
Systemic events and medication use within 7 days of vaccination

First dose
10, 30, 100 mcg

Second dose
10, 30 mcg

Pfizer + BioNTech
• FIH phase 1 clinical trial
• lipid nanoparticle–encapsulated, nucleoside-modified messenger RNA
• Immunogen: a stabilized prefusion spike protein
• dose-escalation, 25 µg, 100 µg, or 250 µg
• open-label trial including 45 healthy adults
• Healthy adults, 18 to 55 years, 2 vaccinations days 1, 28
Genetic vaccination: Messenger RNA

• The vaccine: a lipid nanoparticle capsule composed of four lipids and formulated in a fixed ratio of mRNA and lipid

• The immunogen: SARS-CoV-2 glycoprotein with a transmembrane anchor and an intact S1–S2 cleavage site.
  – Stabilized in its prefusion conformation by 2 P subs
Demographics, tolerability, safety

- 89% white, 87% non-hispanic
- Solicited systemic adverse events were more common after the second vaccination
- Solicited local adverse events were mostly mild to moderate
- Reported in >50%: fever, fatigue, chills, headache, myalgia, and pain at the injection site
- No concerns: clinicalsafety labs, unsolicited AEs
Binding Ab to Spike protein: ELISA

RBD antigen ELISA result was similar
Virus neutralizing Activity of Serum

C PsVNA

D PRNT

Study Day

25 µg 100 µg 250 µg Convalescent

Study Day

25 µg 100 µg Convalescent
SARS-CoV-2-specific T Cell Responses

• The 25-µg and 100-µg doses elicited CD4+ T-cell responses biased toward expression of Th1 cytokines (tumor necrosis factor α > interleukin 2 > interferon γ)

• Minimal type 2 helper T-cell (Th2) cytokine expression (interleukin 4 and interleukin 13)

• CD8+ T-cell responses to S-2P were detected at low levels after the second vaccination in the 100-µg dose group
Safety and immunogenicity of the ChAdOx1 nCoV-19 vaccine against SARS-CoV-2: a preliminary report of a phase 1/2, single-blind, randomised controlled trial


- Developed at Oxford University’s Jenner Institute and licensed to AstraZeneca
- Non-replicating chimpanzee adenovirus expressing the spike
- Preclinical: protected macaques against lung disease - Single dose – 6 vaccinated c/w 3 controls; nasal no change (preprint)
  - In pigs, NAB boosted with second dose
ChAdOx1 COVID-19 Vaccine – phase 1-2 Ab responses

Binding Ab (ELISA) – single vaccination
ChAdOx1 COVID-19 Vaccine – phase 1-2 Ab responses

Neutralizing Ab – Boosting effect
Pregnant women, children

• Use of COVID-19 preventive vaccines in pregnancy and in women of childbearing potential will be an important consideration for vaccination programs.

• FDA encourages data to support inclusion of pregnant women and women of childbearing potential who are not actively avoiding pregnancy.

• It is important for developers of COVID-19 vaccines to plan for pediatric assessments of safety and effectiveness.
Operation Warp Speed

• A partnership led by US HHS to invest in and coordinate the development of COVID-19 diagnostics, therapeutics and vaccines.

• **COVID Prevention Network (CoVPN)** – NIH press release 7/8/20, a functional unit of Operation Warp Speed
  – will use a harmonized vaccine protocol
  – NIAID networks clinical trials infrastructure
  – HVTN, HPTN, IDCRC, ACTG + many other trial sites (> 100 US and international)
  – Vaccines and MAB
Timeline

- July: NIAID+Moderna mRNA – S – phase 3, 30,000 participants (>\$500M)
  - 90-100 trial sites
- July: Pfizer (industry funded)
  - Phase 2/3 launch
- August: AstraZeneca (Oxford) ChAdOx1 – S - phase 3, 30,000 participants – (\$1.2B)
- Soon after:
  - Janssen (Johnson & Johnson) – Ad26 - S
  - NovaVax: subunit protein S + adjuvant – (\$1.6B)
  - Sanofi/GSK subunit protein S + adjuvant
  - Inovio
  - others
Community engagement

• Particularly with the communities most vulnerable to COVID-19 severe outcomes, will be critical to the success of this research endeavor.

• CoVPN website:  
  https://www.coronaviruspreventionnetwork.org
  – clinical trial participant registry: customized data collection platform to securely identify potential trial participants
Help find a vaccine for COVID-19!

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You CANNOT get infected with SARS-CoV-2 or get COVID-19 illness from the study vaccine.

www.CoronavirusPreventionNetwork.org
COVID-19 Vaccine - NYC area trial sites

https://www.coronaviruspreventionnetwork.org

- Moderna – mRNA in LNP – S - July
  - Weill Cornell Uptown, NYC
  - Weill Cornell Chelsea, NYC
  - Meridian Clinical Research, Bronx, NYC
  - other

- AstraZeneca – Oxford – ChAdOx1 – S - August
  - U Rochester (A Falsey, national study PI)
  - NY Blood Center, Manhattan
  - Bronx Prevention Research, NYC
  - Columbia (M Sobieszczyk, national study PI)
  - NYU Langone Vaccine Center
    - Up to 5 vaccination locations:
      - Tisch – midtown Manhattan, NYC
      - Bellevue Med Center - midtown Manhattan, NYC
      - NYU Langone Health – Brooklyn, NYC
      - NYU Winthrop - Mineola, Long Island
      - VA Medical Center, midtown Manhattan, NYC
  - other
MAB

• Highly potent neutralizing antibody(ies)
• Passive immunization – for prophylaxis
  – Household contacts
  – Nursing homes
• Treatment
• IV, IM, or SC
• Long half-life
• Single dose
• In comparison to HVTN/HPTN AMP study: HIV-specific MAB
Adherence

- Non-pharmaceutical interventions
  - Effective
- As a country we can do better against this virus.
- Individual responsibility, behavior
- Leadership responsibility, policy
- Principle, to stay healthy & protect others
  - Is it essential?

- Identifying a safe and effective COVID-19 vaccine is essential.
- In the meantime, stay NY strong, and…
Thank You Team!

I would like to sincerely thank the research team working on the COVID-19 Vaccine Studies Initiative at the NYU Langone Vaccine Center: Faculty, Staff, and Trainees.

I would like to thank the research participants in the COVID-19 Vaccine Studies Initiative.

**Research Funding:** NIAID, BARDA, Pfizer, Lilly, NYU Grossman School of Medicine

Vanessa Raabe
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Mary Olson
Elisabeth Cohen
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Bo Shopsin
Purvi Parikh
Lalitha Parameswaran
Ellie Carmody
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…and others

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Laura Frye
Heekoung Youn
Jane Fran
Kanika Ballani
Natalie Veling
Juanita Erb
Mahnoor Ali
Lisa Zhao
Stephanie Rettig
Hibah Khan
Susan Lucaj
Harry Lambert
Kelly Hu
Jonathan Hyde
…and others

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Platforms, Immunogens, moving fast

SARC-CoV-2 RNA sequence
Published 1/10/20

• PLATFORMS
  • Genetic – flexible, rapid, scalable
    – RNA – 1) 3/16/20 first vaccination → press release, 5/18/20 → NEJM, in press 7/10/20; 2) 5/4/20 → 7/1 preprint; Revision submitted
    – DNA – 4/3/20 → press release June
  • Recombinant viral vector
    – Adenovirus – non-replicating
      • Chimpanzee Ad
      • Ad26
      • Ad5 – 3/16/20 first vaccination → Lancet 5/22/20; E1 and E3 deleted
    – VSV; RSV; replicating
  • Subunit protein + Adjuvant
  • Whole killed viral vaccine – chemically inactivated viral particles – Sinovac, Science, 5/5/20, 3 doses in macaques

• IMMUNOGENS
  – S, full-length spike (S1 + S2)
  – RBD, receptor-binding domain of spike – NAB target
  – other
Modern – NIAID mRNA - S

- stabilized spike protein – pre-fusion
- a genetic platform called mRNA (messenger RNA)
- Lipid nanoparticle
- Although RNA-based vaccines are easy to develop, none has ever been licensed.
- Has shown promise in animal model
  - prevented viral replication in the lungs of mice challenged with SARS-CoV-2
- 3/16/20 first vaccination (L Jackson, KPWRHI, Seattle; VTEU, IDCRC)
- 2 IM injections, D1 and D29
  - 25, 100, or 250 mcg

- **Phase 1:** press release 5/18/20
  - With 2 doses of 25 or 100 mcg, all ppts made binding Ab; 8/8 made NAB
    - Magnitudes similar to convalescent patients
    - At D43, two weeks post second dose
    - At 250mcg, 3 severe reactions (of 12 ppts)
      - Post second dose

- **Phase 2:** fully enrolled, 300 younger and 300 older adults (press release 7/8/20)
  - two vaccinations of mRNA-1273 given 28 days apart. Each participant is receiving placebo, a 50 µg or a 100 µg dose at both vaccinations.

- **Phase 3:** start in July expected; manufacturing completed; 30,000 ppts, 100mcg, 1:1 randomization with placebo
Thank You for Your Attendance!
For tonight’s CME and MOC quiz please visit:
www.prn.org