Some Considerations on Developing COVID-19 Vaccines

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Disclaimer

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Topics

• The science
• Regulatory pathway
• Clinical plan and design considerations
Coronaviruses and the novel SARS-CoV-2 that causes COVID-19

Common human coronaviruses (account for 15 to 30% of common colds)*
- 229E (alpha coronavirus)
- NL63 (alpha coronavirus)
- OC43 (beta coronavirus)
- HKU1 (beta coronavirus)

Other human coronaviruses
- MERS-CoV
- SARS-CoV
- SARS-CoV-2 (novel coronavirus causing COVID-19)

http://sdcity.edu/about/communications/covid19/

https://www.cdc.gov/coronavirus/types.html
SARS-CoV-2: key genomic differences from other coronaviruses that cause less severe disease

Regions (red) that might code for lethal differences in the virus that causes COVID-19 as well as SARS and MERS.

These differences could be targets for testing or treatments.

Gussow et al, PNAS June 30, 2020 117 (26) 15193-15199
Could prior exposure to common cold coronaviruses provide cross-protection for severe COVID-19?

• Isolated immune cells stimulated by segment of SARS-CoV-2 'spike proteins'
  • Overlap between common cold coronaviruses and SARS-CoV-2: C-terminal domain > N-term

• Results
  • As expected, high 85% (15/18) of patients had re-activated CD4+ T cells to C-term
  • Surprisingly, 35% (24/68) healthy individuals also activated to SARS-CoV-2 C-term

• Implications for the design and analysis of upcoming COVID-19 vaccine trials?

https://doi.org/10.1038/s41586-020-2598-9
<table>
<thead>
<tr>
<th>Vaccine category</th>
<th>Safety</th>
<th>Speed and ease of production</th>
<th>Logistics of global distribution</th>
<th>Potential for NAb induction</th>
<th>Potential for cell-mediated immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live attenuated virus</td>
<td>Substantial concerns</td>
<td>N/A</td>
<td>N/A</td>
<td>Probably high</td>
<td>Probably Good</td>
</tr>
<tr>
<td>Inactivated virus</td>
<td>Some concerns</td>
<td>Intermediate</td>
<td>Feasible</td>
<td>Moderate</td>
<td>Poor</td>
</tr>
<tr>
<td>Non-replicating virus vector (recombinant DNA virus)</td>
<td>High</td>
<td>High</td>
<td>Feasible</td>
<td>Weak</td>
<td>Probably good</td>
</tr>
<tr>
<td>DNA plasmid given by electroporation mRNA</td>
<td>High</td>
<td>High</td>
<td>Some concerns</td>
<td>Very weak</td>
<td>Probably good</td>
</tr>
<tr>
<td>Soluble or nanoparticle S- or RBD-protein, with adjuvant</td>
<td>High</td>
<td>Low</td>
<td>Feasible</td>
<td>High</td>
<td>Poor</td>
</tr>
</tbody>
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1 full list on WHO website.
2 Safety indicates the likelihood the vaccine will be tolerated without serious adverse effects in the absence of infection.
3 Most emphasis has been placed on the induction of NAbs, although some data on cellular immune responses are emerging from animal studies and more will be obtained in human trials.
4 N/A, not applicable. There are no known plans to produce this type of vaccine.
5 For a killed virus vaccine to be safe, the pathogen must be fully inactivated. Historically, inactivation has sometimes been incomplete (e.g., with polio vaccines).
6 Delivering DNA vaccines into muscles via electroporation is a relatively complex procedure compared to direct injection via needles or oral delivery.
7 The ease with which mRNA vaccines can be formulated and distributed has not been widely discussed. However, if these vaccines turn out to be unstable at ambient temperatures it will be challenging to distribute frozen or chilled stocks.
8 General experience suggests that producing a stable cell line and using it to make large stocks of recombinant proteins under Good Manufacturing Process conditions can take 1-2 years.


clinical data available (Aug, 2020)
### Current COVID-19 Vaccine Candidates

<table>
<thead>
<tr>
<th>Vaccine Technique</th>
<th>Vaccine Candidate Company</th>
<th>2020</th>
<th>2021</th>
</tr>
</thead>
<tbody>
<tr>
<td>mRNA</td>
<td>Moderna</td>
<td>Ph1</td>
<td>Ph3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph2</td>
<td></td>
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<tr>
<td></td>
<td>Pfizer/BioNTech</td>
<td>Ph1/2</td>
<td>Ph2b/3</td>
</tr>
<tr>
<td>Protein based</td>
<td>Novavax</td>
<td>Ph1/2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sanofi Pasteur</td>
<td>Ph1/2</td>
<td>Ph3</td>
</tr>
<tr>
<td>Viral vector</td>
<td>AstraZeneca/Oxford</td>
<td>Ph1</td>
<td>Ph3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph2</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Cansino</td>
<td>Ph1</td>
<td>Ph3</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ph2</td>
<td></td>
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<tr>
<td></td>
<td>Merck/Themis</td>
<td>Ph1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Janssen</td>
<td>Ph1/2</td>
<td>Ph3</td>
</tr>
</tbody>
</table>

Latest update: August 10, 2020
Sanofi Pasteur: two approaches for COVID vaccines

1 - Baculovirus recombinant vaccine approach
- Cell Culture
- Protein Antigens
- Adjuvants
- Licensed platform
- Safety experience
- BARDA collaboration
- Existing large scale manufacturing capacity

2 - Translate Bio mRNA vaccine approach
- In Vitro Transcription
- mRNA
- Delivery System
- mRNA Formulation
- Different MoA
- Adds manufacturing capacity
- Building on current collaboration
- R&D synergies
Protein based, Baculovirus recombinant platform established and well-understood

Licensed vaccine against flu

Early work in SARS

Flublok® Quadrivalent Influenza Vaccine

Proven to prevent more cases of influenza in adults 50+.

Flublok® Quadrivalent Vaccine: Proven to prevent more cases of influenza in adults 50+.

Compared with a standard-dose quadrivalent inactivated influenza vaccine.

A recombinant baculovirus-expressed S glycoprotein vaccine elicits high titers of SARS-associated coronavirus (SARS-CoV) neutralizing antibodies in mice.

Zhimin Zhou, Penny Post, Rick Chubet, Katherine Holtz, Clifton McPherson, Martin Petrie, Manon Cox

Traditional vs Pandemic Paradigm
Challenges and Opportunities for Vaccine Development

Opportunities for pandemics
1. Accelerated regulatory pathway
2. Shortened discovery and pre-clinical
3. Streamlined clinical development
4. At-risk manufacturing scale-up

“There is no accelerated pathway for COVID-19 or any other emerging infectious disease”
Regulatory path options

**Regular Approval**
- Clinical efficacy demonstrated

**Accelerated Approval**
- A surrogate "reasonably likely" to predict benefit

**Emergency Use Authorization**
- "May have benefit"

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**FDA Guidance, June 2020**
- EUA+ (Emergency Use Authorization, plus), September 2020

**Reuters**

Sinovac's coronavirus vaccine candidate approved for emergency use in China – source
AUGUST 28, 2020. BEIJING (Reuters) - Sinovac Biotech Ltd's coronavirus vaccine candidate CoronaVac was approved for emergency use as part of a programme in China to vaccinate high-risk groups such as medical staff, a person familiar with the matter said.

**ABC News**

Russia's approval of virus vaccine greeted with some alarm
Russia has become the first country to approve a coronavirus vaccine for use among tens of thousands of its citizens
By VLADIMIR ISACHENKOV and Darya Litvinova Associated Press
August 11, 2020, 9:27 AM • 6 min read
FDA guidance

Development and Licensure of Vaccines to Prevent COVID-19
Guidance for Industry

Key points:

• Traditional approval paradigm: efficacy demonstration required
  • no accepted surrogate
  • EUA possible

• Acceleration of pre-clinical safety evaluation for established platforms

• Use of adaptive and seamless designs

• Inclusion of diverse populations

• Randomized, placebo-controlled Ph3 efficacy trial
  • “COVID-19 disease” and “infection” endpoints
  • vaccine efficacy LB 30%, point estimate 50%+

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
June 2020
COVID-19 Vaccines Likely Available Through “EUA-Plus” Pathway, FDA’s Marks Says; More Guidance Coming On Emergency Use Standards

FDA is re-framing the likely regulatory pathway for the first vaccines against the SARS-CoV-2 virus as “Emergency Use Authorization-plus” — by which vaccines would meet a higher standard than a traditional EUA but would not check all the boxes required for a full Biologics Licence Application.
A typical combined Phase 1 / 2 study

• A small safety sentinel cohort (in 10s) followed by a larger dose ranging study (usually in 100s to allow Go/No-Go and dose selection for Phase 3)

• Dose formulations to be studied
  • Lower and upper range of dose level
  • 1- vs 2-injection
  • Adjuvant for antigen-sparing, due to limited manufacturing capacity

• Keep in mind: data rollout and criteria for faster & robust Go/No-Go decision and dose selection
Dose, Dose, Dose

• Biomarkers
  • binding and neutralizing antibody titers, and their relevance?
  • T cell responses and their role in fighting the virus?
• Use of adjuvant for antigen-sparing
  • For pandemic: 5µg/adj vs 25µg can “increase” manufacturing capacity by 5-fold
• Criteria
  • Maximum Tolerable Dose (MTD) – efficacy
  • Minimum Effective Dose (MED) – safety & capacity
  • Reference: convalescent samples – similar? 2-fold higher? 5-fold?
• Other considerations
  • At risk populations (likely early adopters): e.g. elderly, likely lower immune responses & safety concern

Push for higher titers than natural infection?


Our results indicate that antiviral antibodies against SARS-CoV-2 did not decline within 4 months after diagnosis.
Randomization Ratio: Equal vs Unequal?
Unequal ratio could increase the chance of observing imbalance in rare, serious safety events, with bias against larger arm.

Prob. include 0 events on control and >3 for vaccine.
Sample size nv and nc for vaccine and control, respectively

Real Example: In a late phase trial, there were 10 cardiovascular events on vaccine and 1 on control. The randomization ratio was 3:1 (nv=1668 vaccine, and nc=554 on control).
Diverse populations

• Inclusion of diverse populations recommended (or, required?)
  • At-risk populations (healthcare workers, comorbidities)
  • Demographics (age/elderly, racial and ethnic minorities, country, etc.)
  • Immuno-compromised populations (e.g., HIV)
  • Sero-negative and sero-positive populations

• However, expectation to demonstrate efficacy in each sub-population not realistic
  • Consistency, correlate of protection, biomarker extrapolation: opportunity for statistical contributions

• Also note possible differences in benefit/risk threshold for sub-populations
  • Children: lower risk, higher requirement for safety … well established platform?
Alpha-spending function for interim efficacy analysis: speed vs power

- Pocock spending functions spend more alpha for early interim analyses
- Linear spending?
- O’Brien-Fleming spending function spends more for late analyses
Unchartered situation, requiring vigilance and adaptation

• What if case accrual not as fast as hoped?
• What if leading vaccines not highly effective as hoped?
• What if first approvals make it challenging to use placebo in subsequent trials?
• What if much worse “2nd wave” as happened during the 1918 flu pandemic?
• What if ...

Harvard Data Science Review

Bayesian Adaptive Clinical Trials for Anti-Infective Therapeutics During Epidemic Outbreaks

Shomesh Chaudhuri, Andrew W. Lo, Danying Xiao, Qingyang Xu

Published on: May 14, 2020

... Our results illustrate the importance of adapting the clinical trial design and the regulatory approval process to the specific parameters and stage of the epidemic.
For example: what if slow case accrual?

• **Manageable**
  • Enrolling & running multiple Ph3 studies, each with 30K-60K healthy subjects
  • Sizable safety database

• **Unpredictable**
  • Accrual of COVID cases, for multiple studies
  • Pandemic landscape: when, where, who?

Alternative approaches for timely decisions?

Where to find shrimp?
And be lucky 10 days in a row?
Concluding remarks

• Our science about the novel SARS-CoV-2 virus and COVID-19 disease is evolving at daily basis

• Race against the virus to develop safe and effective vaccines needs consideration of both speed and risk
  • In this global pandemic, safety of the COVID vaccines is paramount for use in millions of otherwise healthy people

• Given the unique challenges in this global pandemic, one-size-fit-all vs “adaptive” approach as science & knowledge advance

• Opportunities for quantitative scientists to guide the development of COVID vaccines in this unchartered water