COVID-19 Conversations

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COVID19Conversations.org
#COVID19Conversations
Developing Therapeutics During a Pandemic

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http://globalhealth.unc.edu
Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)

**Source Candidates**
- Publicly Available Data
- Submission from Investigators
- Survey Responses

**Clinical Agents**
- Antivirals
- Host Targeted / Immunomodulators
- Symptomatic / Supportive
- Neutralizing mAbs

**Prioritization Activities**
- Score Candidates based on Pre-defined Criteria
- Assess Supply and Other Logistical Needs
- Develop Minimum Entry Criteria

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FNIH
An Orally Bioavailable Broad-Spectrum Antiviral Inhibits SARS-CoV-2 in Human Airway Epithelial Cell Cultures and Multiple Coronaviruses in Mice

An Orally Bioavailable Broad-Spectrum Antiviral Inhibits SARS-CoV-2 in Human Airway Epithelial Cell Cultures and Multiple Coronaviruses in Mice (*EID-2801*)

Fig. 6 Prophylactic and therapeutic EIDD-2801 reduces SARS-CoV replication and pathogenesis.
A Phase IIa Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Tolerability and Efficacy of EID-2801 to Eliminate Infectious Virus Detection in Persons with COVID-19

DESIGN  
This is a phase IIa, double-blind, placebo-controlled, randomized trial, designed to compare the safety, tolerability, and antiviral activity of EID-2801 versus placebo as measured by infectious virus detection in symptomatic adult outpatients with COVID-19.

DURATION  
29 days. Treatment will be for 5 days with 24 days of follow-up.

SAMPLE SIZE  
52 participants who start study treatment; approximately 26 participants in each of two treatment arms (A and B). Participants who are randomized but do not start study treatment will be replaced.

POPULATION  
Symptomatic, outpatient (at baseline), adults (≥18 years) with SARS-CoV-2 infection as evidenced by RNA detection in a nasopharyngeal specimen within 4 days of symptom onset.

REGIMEN  
Participants will be randomized 1:1 to receive active/placebo study treatment as follows: EID-2801 100 mg twice daily (BID) for five days.

ClinicalTrials.gov Identifier: NCT04405570, UNC-Chapel Hill
Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model

Fig. 1 SARS-CoV-2 neutralizing antibody isolation strategy.

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Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model


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Isolation of potent SARS-CoV-2 neutralizing antibodies and protection from disease in a small animal model

Fig. 5 A potent SARS-CoV-2 RBD-specific neutralizing mAb protects against weight loss and lung viral replication in Syrian hamsters.
COVID-19 mAb Applications: PX and TX

Monoclonal Abs (mAbs):

- Offer immediate protection for those exposed or unvaccinated in high risk settings
- Can be provided to people unlikely to respond to a vaccine, or allergic
- They could stop viral replication and block progression of disease
- Can help predict requirements for a vaccine by identifying required titers of neutralizing antibodies

Target Populations for mAbs:

- Nursing homes, both residents and attendants
- High incidence workplaces (e.g. meat packing plants)
- Index case contacts (e.g. household contacts)

**Environment(s) drive exposure; biologic factors promote disease progression:**

*mAb might provide solutions?*
## SARS-CoV-2 Spike Protein mAbs

<table>
<thead>
<tr>
<th>Company</th>
<th>mAbs</th>
<th>First in Human</th>
<th>Notes</th>
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<tbody>
<tr>
<td><strong>Lilly</strong></td>
<td>LY-CoV-555, high affinity neutralizing antibody against RBD, isolated from a recovered SARS-CoV-2 patient Lilly in collaboration with AbCellera.</td>
<td>May 2020</td>
<td>First in human in hospitalized patients, May 2020.</td>
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<tr>
<td><strong>Regeneron</strong></td>
<td>Two SARS-CoV-2 spike directed mAbs from their humanized Ab mouse platform and isolated from human convalescent serum</td>
<td>June 2020</td>
<td>First in human hospitalized patients, June 2020.</td>
</tr>
<tr>
<td><strong>Vir</strong></td>
<td>Vir mAb, S309, isolated from a SARS-CoV patient that is cross-reactive with SARS-CoV-2,</td>
<td>July 2020</td>
<td></td>
</tr>
<tr>
<td><strong>AstraZeneca</strong></td>
<td>AZ has selected a 2 mAb combination against the SARS-CoV-2 spike protein (AZD7442)</td>
<td>July 2020</td>
<td>Plan Phase I single dose escalation study in normal volunteers, August 2020 (DARPA)</td>
</tr>
<tr>
<td><strong>Michel Nussenzweig</strong></td>
<td>Michel Nussenzweig developed cocktail of two mAbs isolated from convalescent plasma, target two non-overlapping epitopes of the receptor binding domain</td>
<td>July 2020</td>
<td></td>
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<td></td>
<td>Bristol Myers Squibb will manufacture antibodies</td>
<td>Fall 2020</td>
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*Note: The mAbs listed are examples of antibodies targeting the SARS-CoV-2 spike protein, which is a key target for neutralizing the virus.*
One-Third of All U.S. Coronavirus Deaths Are Nursing Home Residents or Workers

Covid-19 deaths in long-term care facilities: 35%

All other Covid-19 deaths in the U.S.
Skilled Nursing Home RCT Strategy

Approach

• A “peri-exposure” prophylaxis study
• Enroll and randomize asymptomatic staff and residents
• mAb given IV monthly over 3 months, with 3 months follow-up
• Detection of infection weekly with nasal swab (PCR test)
• Daily evaluation of signs and symptoms of COVID-19
• Measurement of the ability of mAbs to prevent infection itself, or progression of early unrecognized infection(s)
Further Evaluation of mAbs to alter COVID-19

*With Detection of SARS-CoV-2 by RNA-PCR:*

- Quantitate nasal viral copy number, and perhaps in saliva
- Quantitate duration of viral shedding
- Quantitate subgenomic RNA (as a measure or replication)
- Measure SARS-CoV-2 replication competence directly
- Measure seroconversion, realizing a mAb could delay or disrupt seroconversion
Mapping COVID-19 Incidence and NIAID Sites
Combination prevention for COVID-19

The coronavirus disease 2019 (COVID-19) pandemic has produced the fear and disorder inevitably provoked by emerging pathogens. As such, it should also inspire consideration of our experience with HIV over the past 40 years. As with HIV, the need to reduce infections with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2, the cause of COVID-19), and attendant morbidity and mortality, requires medical and nonmedical strategies. The most important lesson learned from tackling HIV is to use a combination of prevention strategies.

The first step to stopping the spread of SARS-CoV-2 has already been taken—behavioral changes. This reflects a rapid but imperfect understanding of the transmission of this virus. At the beginning of the AIDS epidemic, changes in sexual behavior, condom promotion, and government interventions (closing “hotspots” of HIV transmission such as brothels) made a difference. For SARS-CoV-2, masks and gloves, hand hygiene, and “shelter in place” mandates have already demonstrated benefits. More efficient behavioral intervention requires better understanding of the rules governing SARS-CoV-2 transmission. What are the risks from exposure to respiratory droplets, airborne virus, and surface contamination? What concentration of SARS-CoV-2 is required for transmission? Evidence suggests that SARS-CoV-2 transmission is greatest early in infection prior to development of symptoms—the same lesson learned from HIV. Given this rule, combination medical prevention strategies that will require large trials with thousands of participants is moving...
THANK YOU!