Right Care Initiative

William Bommer
April 13, 2020
Coronaviruses (CoVs)

- Positive-strand RNA viruses with large genomes (≥27,000 bases).
- Both alpha and beta types cause disease in humans.
- Account for 10-30% of cases of the common cold (Pubmed 31971553).
- Very stable for an RNA virus – CoV OC43 isolates from 1960s and 2001 had only 2 amino acid differences (Pubmed 15280490).
- Easily hops between species
  - MERS-CoV hopped from camels to humans
  - SARS-CoV hopped from bats to humans and civets
  - SARS-CoV-2 hopped from bats to humans
  - Easily hops between species
- SARS-CoV-2 is 80% identical to SARS-CoV-1, the 2003 SARS virus

SARS-CoV-1/2 life cycle

1. Spike protein (S) binds to ACE2.
2. The transmembrane protease TMPRSS or endosomal cathepsin L cleaves S to activate membrane fusion.
3. Cellular ribosomes translate a nonstructural polyprotein from the positive-strand RNA.
4. Embedded viral proteases process the polyprotein to create the replicase.
5. The replicase produces full-length copies of both strands and subgenomic mRNAs.
6. Ribosomes translate the subgenomic mRNAs to produce structural proteins.
7. Structural proteins package the positive-strand RNA and bud off into exocytic vehicles.
SARS-CoV-1/2 environmental sensitivity

- Enveloped virus (with a plasma membrane), disrupted by surfactants/detergents, 60-80% alcohol, bleach.

- Sensitive to UV
  - 2–3x more sensitive than influenza virus to UV (Pubmed 17880524, 16254359).
  - Estimated 10-fold survival decrease after 2–3h direct sunlight

- Sensitive to temperature
  - 10-fold survival decrease with 5°C temperature increase (Pubmed 22312351)
  - Killed by 30min 75°C heat (Pubmed 14631830).
Survival of SARS-CoV-2 depends on the surface (Pubmed 32182409)
- Drop of virus applied, allowed to dry. 1mL cell-culture media applied and tested.
- On steel and plastic, 10-fold survival decrease in ~12h. On cardboard (porosity/type unclear), 10-fold survival decrease in 4–8h.
- On absorbent material like a power towel, survival should be similar to cardboard or lower, and virus should be more effectively trapped.
COVID-19 virus (SARS-CoV-2) key facts

- Within the beta-coronavirus family
- Highly similar to 2003 SARS virus, SARS-CoV-1
- Uses ACE2 as receptor, extracellular/endosomal proteases as activators
- As an enveloped virus, is relatively fragile
- Sensitive to heat, detergents, and solvents
Part 2
- Headache 14%
- Nasal congestion 5%
- Sore throat 14%
- Dry cough 68%
- Productive cough 33%
- Dyspnea 19%
- Nausea/emesis 5%
- Diarrhea 4-14%
- Myalgias 15%
SARS-CoV
SARS from 2002-2003
&
SARS-CoV-2
COVID-19

Attachment protein “spike”

The spike protein of SARS-CoV-2 is primed by TMPRSS2

SARS-CoV-2 uses the ACE2 receptor for host cell entry

TMPRSS2

Angiotensin converting enzyme (ACE2)

Host cell
Testing Window and Workflow – PHASE III-A PLAN (April 1, 2020)

CDC-Based Assay x2
80 tests/day

Roche cobas 6800 EUA + LDT
188 tests/day

Sample Accrual

TODAY

TOMORROW
Testing Window and Workflow – PHASE III-C PLAN (April 15, 2020)

Lab-Based High Throughput Testing
Non-High-Risk Cases Per Current Testing Plan

Random Access Testing (no batched testing):
90 tests/hour for IgM and IgG Serology

1,180 tests/day

720 tests/day

TODAY

Anti-SARS-CoV-2 IgM and IgG Serology Testing
Patient and Employee Screening
Testing Window and Workflow – **PHASE IV PLAN (April 2020)**

Secondary 6800 for increased throughput and back-up

Random Access Testing (no batched testing): 90 tests/hour for IgM and IgG Serology

**Complete Clinical Molecular and Serology Solutions** → 2 people per shift

**TODAY**
Other Barriers and Solutions: Banking of Specimens

- Biobank activated to support banking of ALL COVID-19 positive samples
- Coordination with institution to provide stewardship.
- Several IRBs established jointly between Pathology, Infectious Diseases, and Pulmonary Critical Care.
- Committee established to review and approve study request.
Connecting with Research......It takes a village....

SARS-CoV-2 Viral Culturing: Cultured sample from index case to for studies and also control material for UCDH Clinical Laboratory

Non-Human Primates: Pulled SARS-CoV-2 virus from UCD index case to begin non-human primate studies including evaluating the benefit of convalescent serum and help produce a serology assay for clinical testing.

Convalescent Serum: Planning phases now and collaboration between Transfusion Medicine (Pathology) and Infectious Diseases. Also joint collaboration with CIID and Primate Center.
Connecting with Research......It takes a village....

**GMP Facility:** Preliminary work to produce viral transport media for anticipated shortages. The media is used for COVID-19 testing as well as other viral diseases including respiratory viral panel testing.
Connecting with Research......It takes a village....

**3D Printing of Swabs:** Development of in-house swabs to offset supply chain issues.

**Machine Learning:** Prediction of COVID-19 severity in hospitalized patients and augmentation of molecular SARS-CoV-2 testing results.

**Serology:** Health personnel and community screening for COVID-19 immunity. Also study comparing different IgM and IgG assays.
COVID-19 clinical trials UC Davis SOM
Research Workgroup Townhall meeting 4/3 2020
Angela Haczku and Maya Juarez
# CURRENTLY ENROLLING TRIALS

<table>
<thead>
<tr>
<th>Drug Name</th>
<th>Remdesivir</th>
<th>Sarilumab</th>
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</thead>
<tbody>
<tr>
<td><strong>Sponsor</strong></td>
<td></td>
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<tr>
<td><strong>Coordinating Division</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>PI</strong></td>
<td></td>
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<tr>
<td><strong>Contact</strong></td>
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<table>
<thead>
<tr>
<th><strong>Dose / Regimen</strong></th>
<th>1:1</th>
<th>2:2:1</th>
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</thead>
<tbody>
<tr>
<td>Placebo : 200mg IV day 1</td>
<td>200mg : 400mg : placebo</td>
<td></td>
</tr>
<tr>
<td>100mg IV days 2-10 or (or discharge)</td>
<td>1 time IV dose</td>
<td></td>
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</tbody>
</table>

| **Target / Mechanism** | Selective Inhibitor of Nuclear Export (SINE) | IL6R (monoclonal antibody) |

<table>
<thead>
<tr>
<th><strong>Key Inclusion Criteria</strong></th>
<th>Hospitalized adult (or planned to admit) with COVID-19 (patients whose confirmation is pending can be screened)</th>
<th>Radioactive evidence of pneumonia AND/OR</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>- Radiographic evidence of pneumonia AND/OR</td>
<td>- Radiographic evidence of pneumonia AND/OR</td>
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<tr>
<td></td>
<td>- Rales/crackles on auscultation AND</td>
<td>- Rales/crackles on auscultation AND</td>
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<tr>
<td></td>
<td>- Requiring suppl O2 (including mechanically ventilated) AND</td>
<td>- Requiring suppl O2 (including mechanically ventilated) AND</td>
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<td></td>
<td>- has multi-organ system dysfunction AND/OR</td>
<td>- has multi-organ system dysfunction AND/OR</td>
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<tr>
<td></td>
<td>- on vasopressors/ECMO/renal replacement AND/OR</td>
<td>- on vasopressors/ECMO/renal replacement AND/OR</td>
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<tr>
<td></td>
<td>- in ICU</td>
<td>- in ICU</td>
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<tr>
<td><strong>Key Exclusion Criteria</strong></td>
<td>EGFR ≥ 50</td>
<td>ALT or AST &gt; 5 x ULN</td>
</tr>
<tr>
<td></td>
<td>- ALT or AST &gt; 5 x ULN</td>
<td>Chronic use of corticosteroids (&gt;10mg/day) for non-COVID condition</td>
</tr>
<tr>
<td></td>
<td>- Current use of corticosteroids (&gt;10mg/day) for non-COVID condition (can be stopped during study)</td>
<td>- Significant neutropenia or thrombocytopenia</td>
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<tr>
<td></td>
<td>- Requiring dialysis</td>
<td>- Recent treatment with the select DMARDs/Immunosuppressive agents</td>
</tr>
<tr>
<td></td>
<td>- Recent treatment with the select antivirals and</td>
<td>Note: concomitant HCQ treatment is disallowed</td>
</tr>
<tr>
<td></td>
<td>- Participating in other experimental antiviral agents or experimental treatments.</td>
<td>- Immunosuppressive therapy within 5 months</td>
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<td></td>
<td></td>
<td>- Concurrent use of another investigational agent in a blinded (placebo controlled) fashion</td>
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<td></td>
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<td>- Current autoimmune or inflammatory disease other than rheumatoid arthritis</td>
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<table>
<thead>
<tr>
<th><strong>Comments:</strong></th>
<th>Cannot be used with concomitant hydrochloroquine</th>
<th>MTX, cyclosporine, mycophenolate, tacrolimus, gold, penicillamine, or sulfasalazine</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Patients who do not require supplemental O2 accepted</td>
<td>Azathioprine or cyclophosphamide</td>
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<td></td>
<td></td>
<td>Leflunomide</td>
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<thead>
<tr>
<th><strong>Prohibited meds once enrolled</strong></th>
<th>acetaminophen, any other experimental drug</th>
<th>Patients with poor kidney function accepted</th>
</tr>
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<tbody>
<tr>
<td>Status</td>
<td>Drug/agent</td>
<td>Sponsor</td>
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<tr>
<td>--------------</td>
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</tr>
<tr>
<td>Feasibility Evaluation</td>
<td>Allogeneic bone-marrow derived MSCs and MSC exosomes</td>
<td>Brainstorm / CIRM</td>
</tr>
<tr>
<td>Placenta derived stem cells and microvesicles</td>
<td>Capricor / Cedars</td>
<td>Pulm/Surgery</td>
</tr>
<tr>
<td>hydroxychloroquine</td>
<td>NIH PETAL</td>
<td>Pulm/CC</td>
</tr>
<tr>
<td>Vitamin C / Acetaminophen</td>
<td>NIH PETAL</td>
<td>Pulm/CC</td>
</tr>
<tr>
<td>ID moving forward to IRB</td>
<td>Verdinexor</td>
<td>Karyopharma</td>
</tr>
<tr>
<td>Pulm moving forward to IRB</td>
<td>inhaled NO</td>
<td>Bellerophon</td>
</tr>
<tr>
<td>Feasibility Evaluation</td>
<td>COVID-19 vaccine as yet unkn</td>
<td>NIAID DMID</td>
</tr>
<tr>
<td>recombinant ACE-2</td>
<td>GSK</td>
<td>Pulm/CC</td>
</tr>
<tr>
<td>clazakizumab</td>
<td>Vitaeris?</td>
<td>Pulm/CC/VA</td>
</tr>
<tr>
<td>anti-IL-33 mAb</td>
<td>NIH/Regeneron</td>
<td>Pulm/CC</td>
</tr>
<tr>
<td>Status</td>
<td>Project title</td>
<td>Sponsor</td>
</tr>
<tr>
<td>-------------------------------</td>
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</tr>
<tr>
<td>IRB approved, initiating collection</td>
<td>Respiratory Infection Biorepository (RIB)</td>
<td>none</td>
</tr>
<tr>
<td>IRB pending</td>
<td>Biomarkers and diagnostic test development of COVID-19</td>
<td>none</td>
</tr>
<tr>
<td>IRB pending/unclear</td>
<td>Convalescent blood from COVID-19 recovering patients</td>
<td>none</td>
</tr>
<tr>
<td>IRB pending</td>
<td>Mitigation of COVID-19 diagnostic swab shortage</td>
<td>none</td>
</tr>
<tr>
<td>IRB pending</td>
<td>Registry: Study of the Treatments and Outcomes of critically ill Patients with COVID-19</td>
<td>David Leaf / Brigham and Women's (unfunded)</td>
</tr>
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Historic vaccine research strengths

- Discovery of feline immunodeficiency virus enabled later vaccine development (Niels Pedersen, Janet Yamamoto)
- Development of SIV model & study of innumerable HIV vaccine concepts at CNPRC (Murray Gardner, Chris Miller, many others)
- Salmonella vaccines: antigen identification and human serum responses (McSorley)
- Development of cytomegalovirus vector for HIV prophylaxis (Peter Barry)
- Active and passive vaccination strategies for Zika virus (Van Rompay, Coffey)
Outstanding questions and UC Davis strengths

- Outstanding questions about current SARS-CoV-2 vaccine candidates
  - Efficacy? Mechanism?
  - Escape via mutation?
  - Antibody-dependent enhancement?
  - Season-to-season durability?
  - Efficacy in older or infirm populations?

- UC Davis strengths
  - Animal modeling
  - Advanced vaccine concepts stimulating host T cells (i.e., those applicable to HIV)
  - SVM, SOM, OHI, Biological Sciences, others
  - Translational strength from CTSC and engaged clinicians
Ongoing effort to develop vaccines on a relevant time scale

- Combined T- and B-cell vaccines designed to place protective cells in the lung (Hartigan-O’Connor, Iyer, Miller, Van Rompay)
  - CD4:CD8 balanced
  - Localized to airways
  - Extraordinarily durable
- Definition of the protective immune repertoire (Keller, Maverakis)
- Pediatric vaccines (with Duke, UNC)
- Delivery methods