COVID-19 Conversations

Myron Cohen

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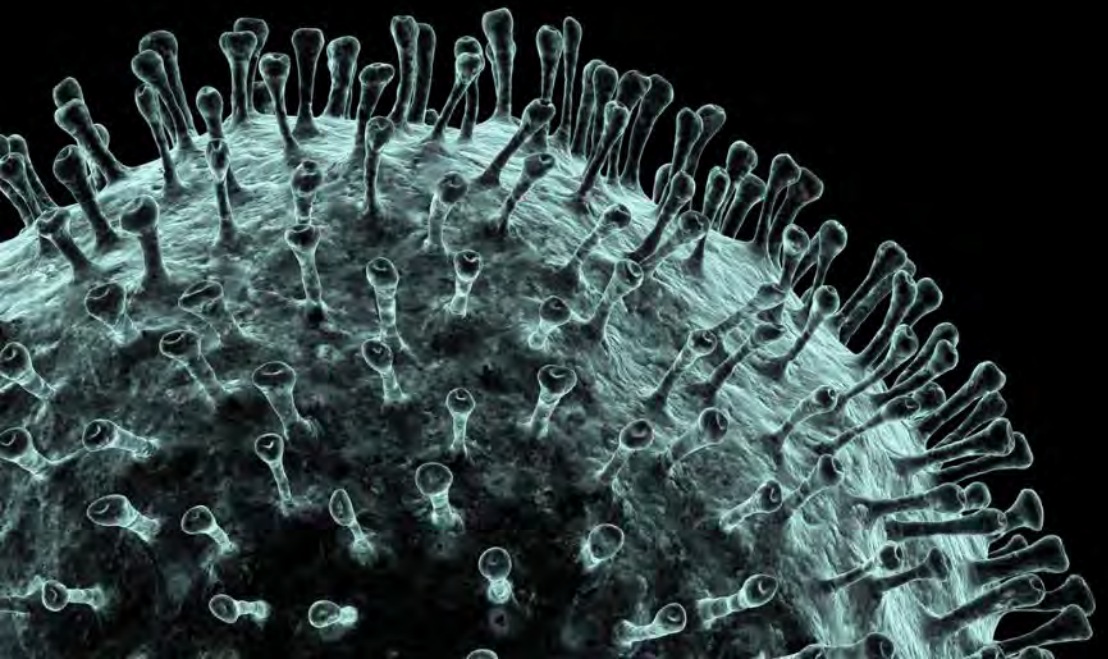

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Developing Therapeutics During a Pandemic

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Accelerating COVID-19 Therapeutic Interventions and Vaccines (ACTIV)

Source Candidates

- Publicly Available Data
- Submission from Investigators
- Survey Responses

Clinical Agents

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

FNIH

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

Timothy P Sheahan, Amy C Sims, Shuntai Zhou, Rachel L Graham, Andrea J Pruijssers, Maria L Agostini, Sarah R Leist, Alexandra Schäfer, Kenneth H Dinnon 3rd, Laura J Stevens, James D Chappell, Xiaotao Lu, Tia M Hughes, Amelia S George, Collin S Hill, Stephanie A Montgomery, Ariane J Brown, Gregory R Bluemling, Michael G Natchus, Manohar Saindane, Alexander A Kolykhalov, George Painter, Jennifer Harcourt, Azaibi Tamin, Natalie J Thornburg, Ronald Swanstrom, Mark R Denison, Ralph S Baric

. Sci Transl Med. 2020 Apr 29;12(541)

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

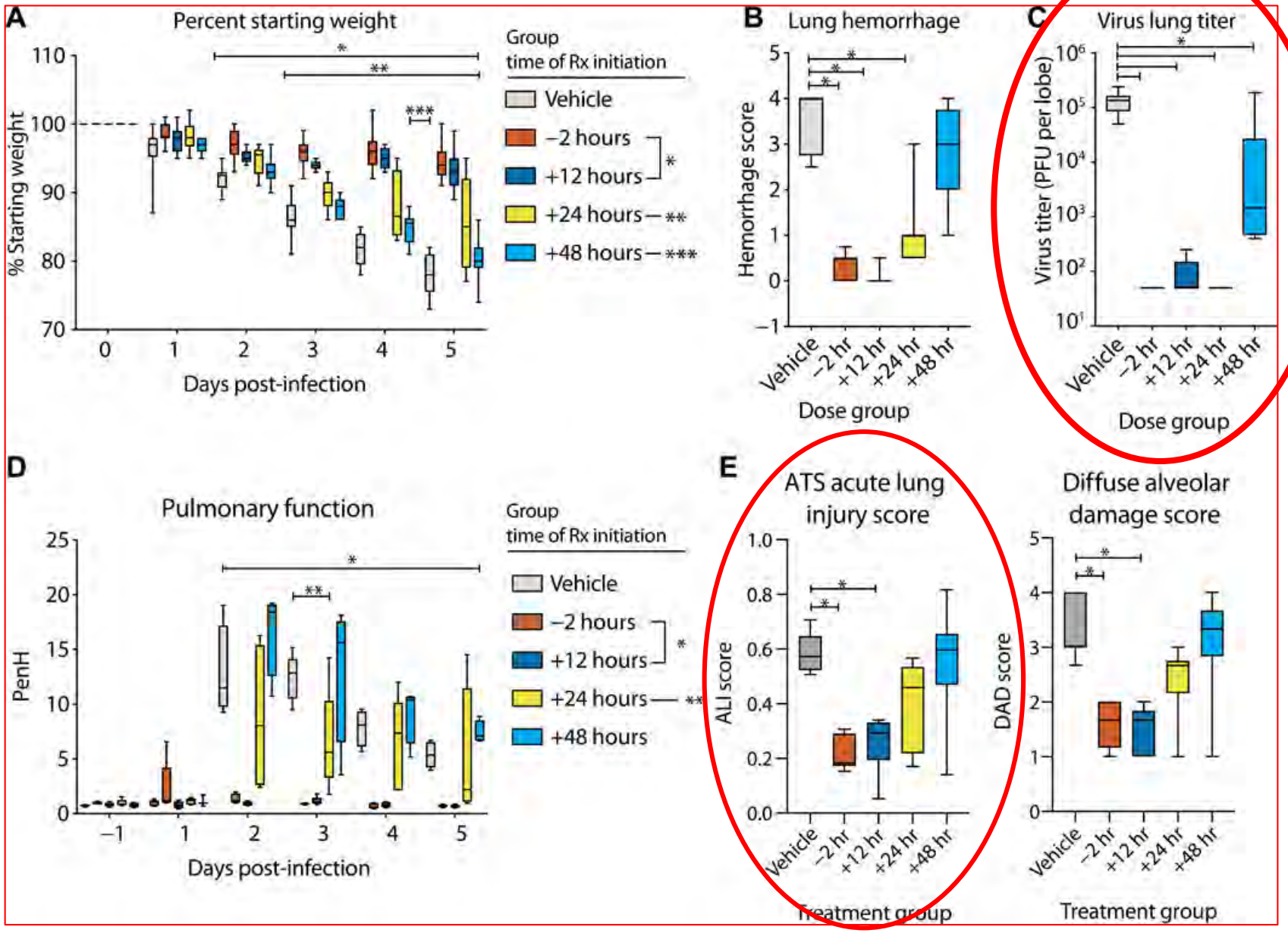


Fig. 6 Prophylactic and therapeutic EIDD-2801 reduces SARS-CoV replication and pathogenesis.

. Sci Transl Med. 2020 Apr 29;12(541)

A Phase IIa Randomized, Double-Blind, Placebo-Controlled Trial to Evaluate the Safety, Tolerability and Efficacy of EIDD-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 EIDD-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: EIDD-2801 100 mg twice daily (BID) for five days.

ClinicalTrials.gov Identifier: NCT04405570, UNC-Chapel Hill

Science

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

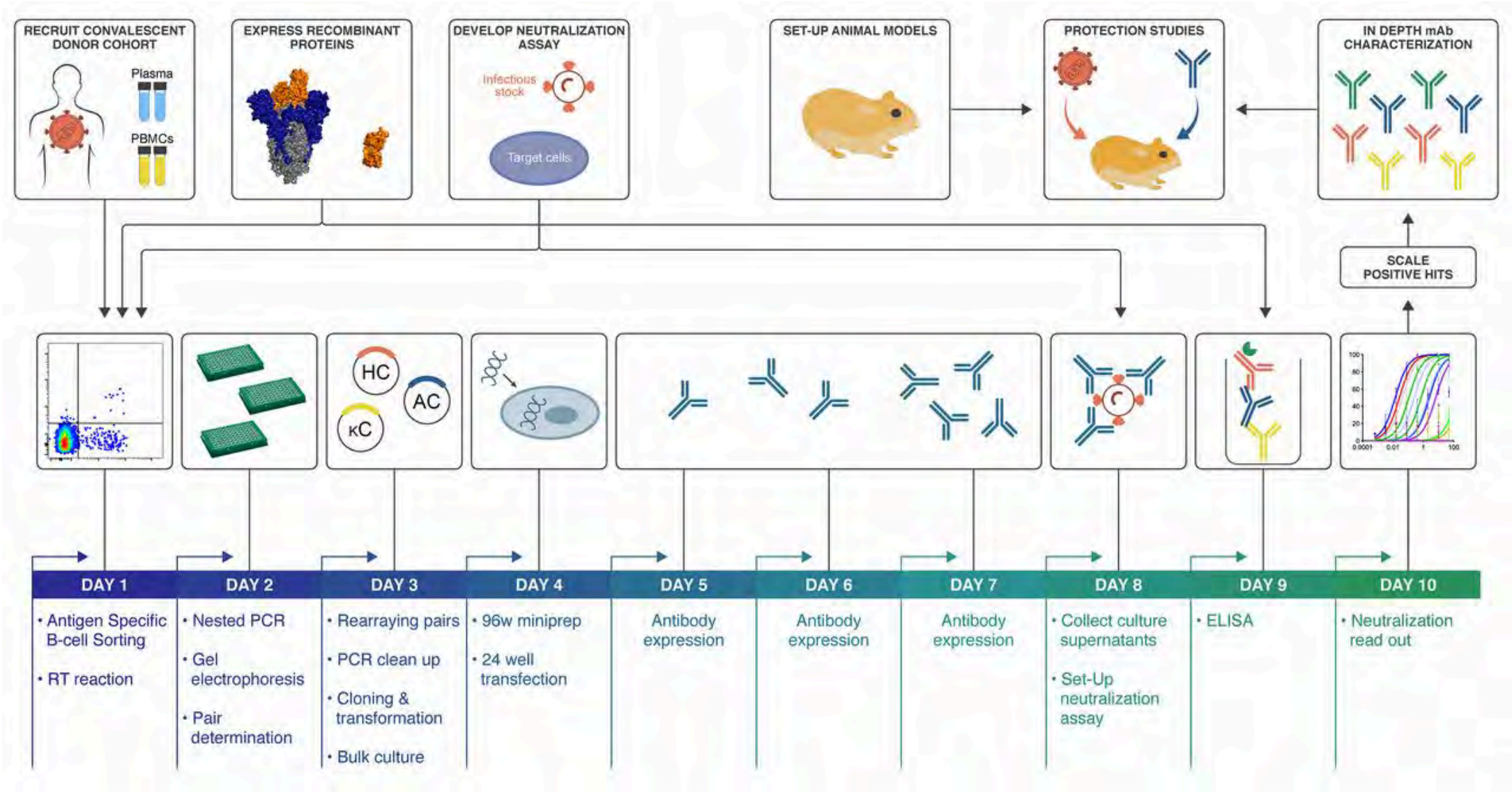
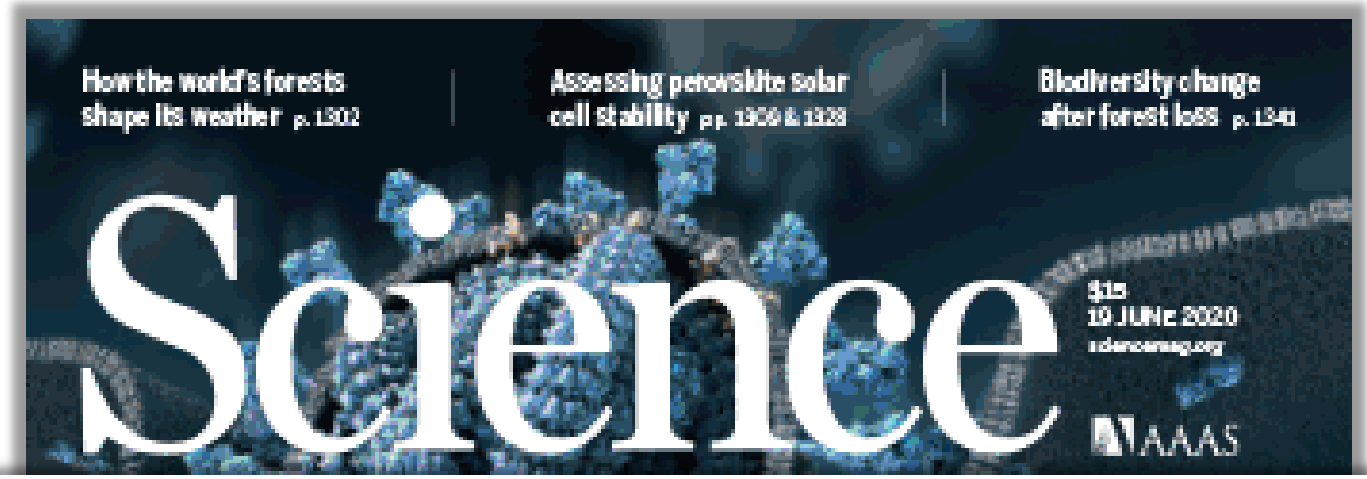


Fig. 1 SARS-CoV-2 neutralizing antibody isolation strategy.

Science. 2020 Jun 15;eabc7520. doi: 10.1126/science.abc7520



Science

RESEARCH ARTICLES

Cite as: T. F. Rogers *et al.*, *Science* 10.1126/science.abc7520 (2020).

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

Thomas F. Rogers[1,2*], Fangzhu Zhao[1,3,4*], Deli Huang[1*], Nathan Beutler[1*], Alison Burns[1,3,4], Wan-ting He[1,3,4], Oliver Limbo[3,5], Chloe Smith[1,3], Ge Song[1,3,4], Jordan Woehl[3,5], Linlin Yang[1], Robert K. Abbott[4,6], Sean Callaghan[1,3,4], Elijah Garcia[1], Jonathan Hurtado[1,4,7], Mara Parren[1], Linghang Peng[1], Sydney Ramirez[6], James Ricketts[1], Michael J. Ricciardi[8], Stephen A. Rawlings[2], Nicholas C. Wu[9], Meng Yuan[9], Davey M. Smith[2], David Nemazee[1], John R. Teijaro[1], James E. Voss[1], Ian A. Wilson[3,4,9], Raiees Andrabi[1,3,4], Bryan Briney[1,4,7], Elise Landais[1,3,4,5], Devin Sok[1,3,4,5†], Joseph G. Jardine[3,5†], Dennis R. Burton[1,3,4,10†]

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Science

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

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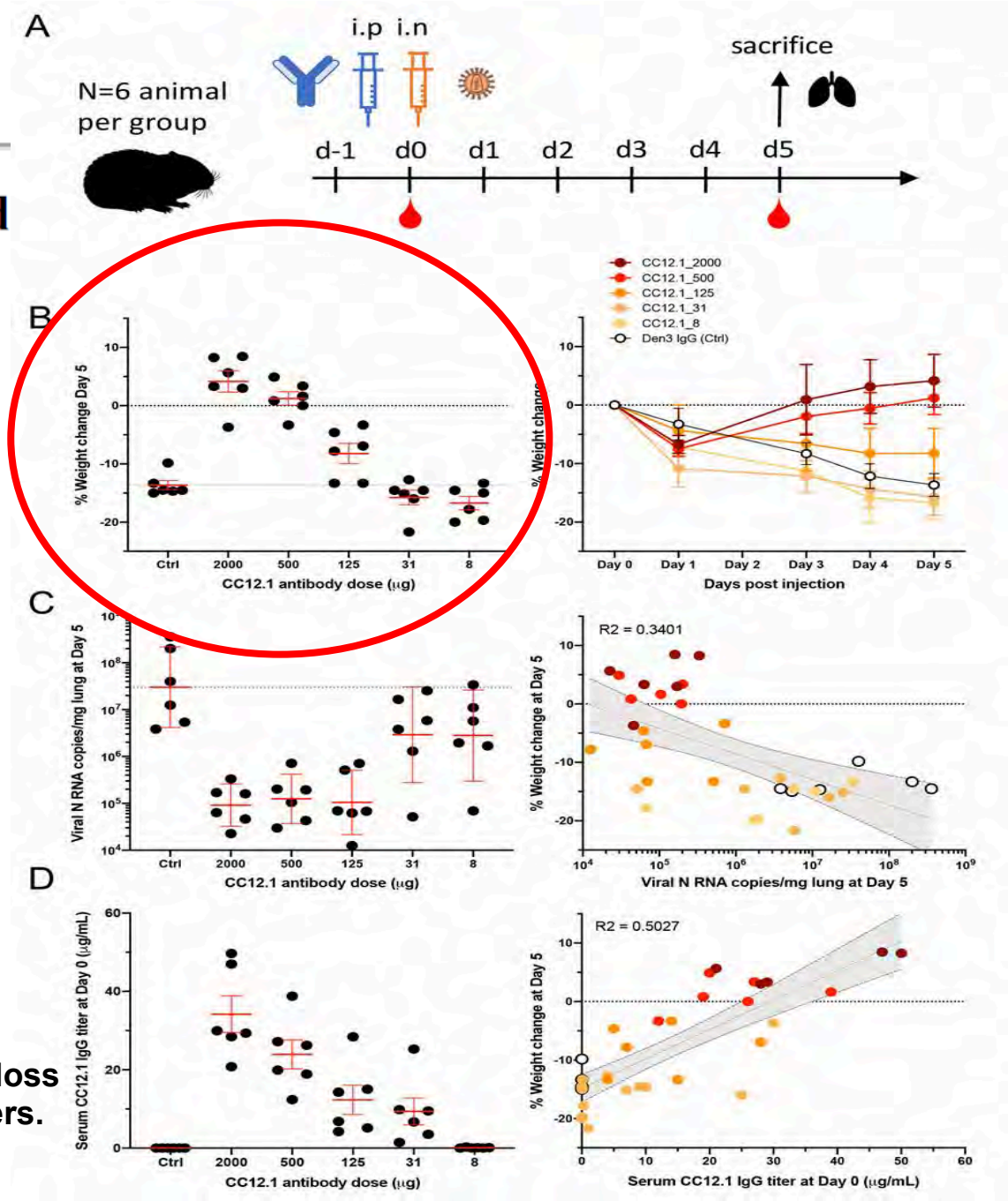

Fig. 5 A potent SARS-CoV-2 RBD-specific neutralizing mAb protects against weight loss and lung viral replication in Syrian hamsters.

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?

COVID-19
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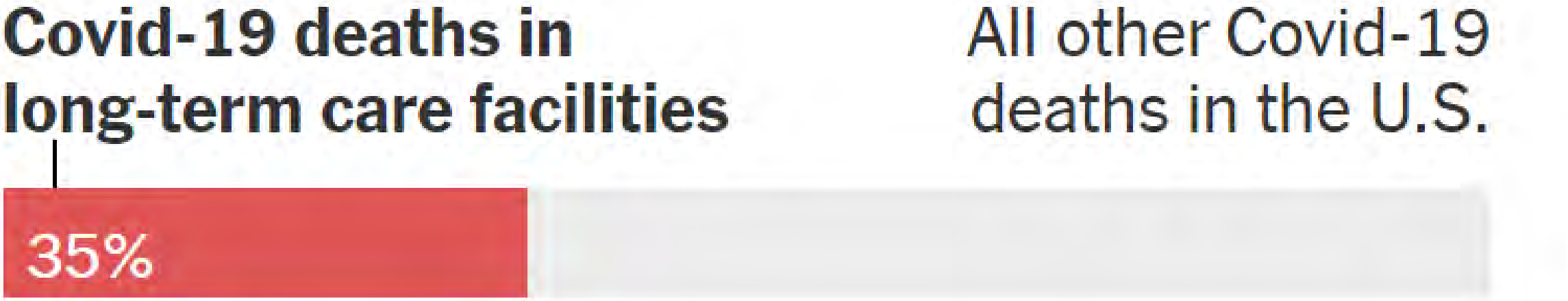
SARS-CoV-2 Spike Protein mAbs

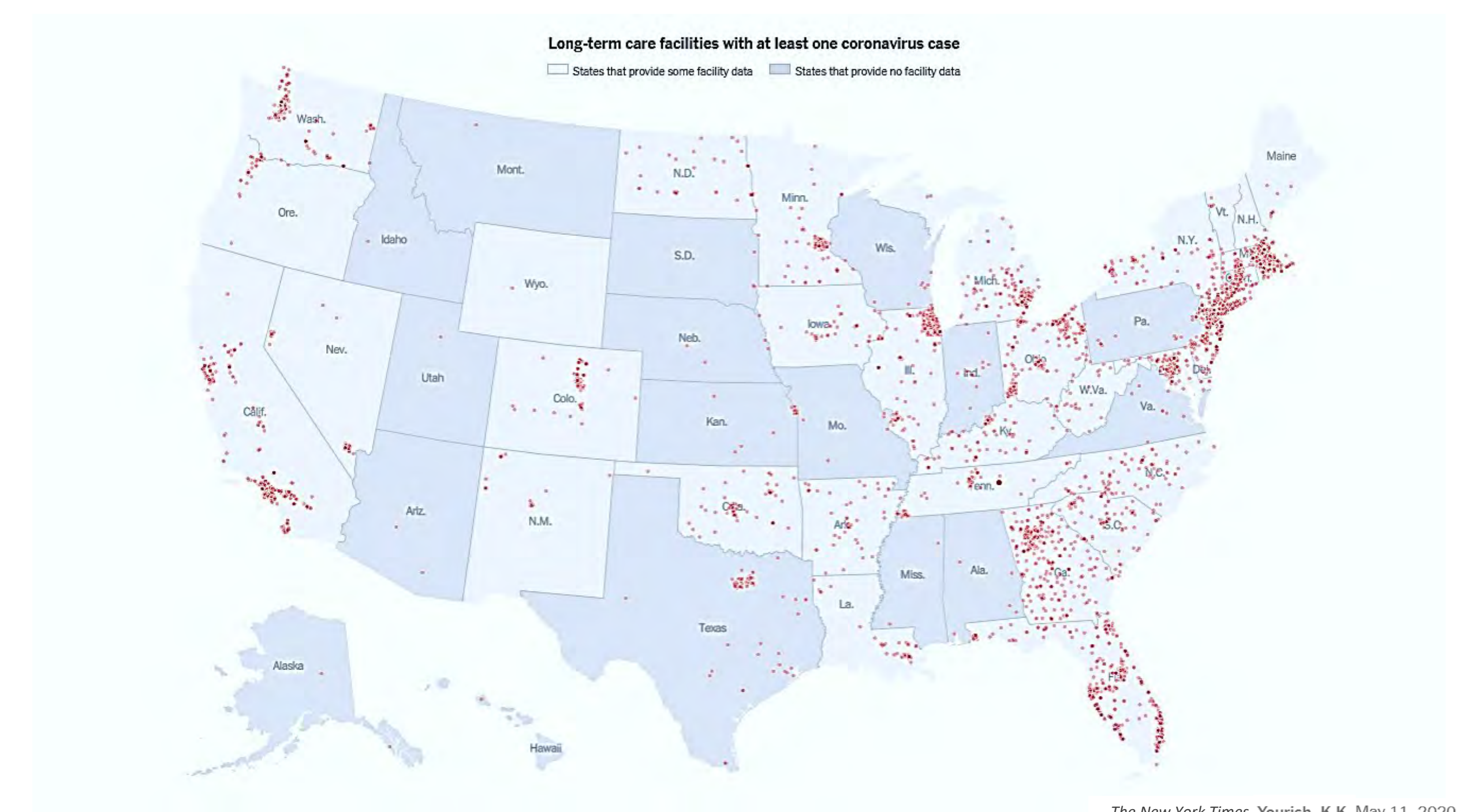
Lilly First in Human May 2020	LY-CoV-555, high affinity neutralizing antibody against RBD, isolated from a recovered SARS-CoV-2 patient Lilly in collaboration with AbCellera. First in human in hospitalized patients, May 2020. LY-JS-016 (CB6) with prophylactic efficacy demonstrated in NHP (Shi et al., Nature 2020), Lilly in collaboration with JunShi First in human in healthy volunteers, June 2020.
REGENERON science to medicine® First in Human June 2020	Two SARS-CoV-2 spike directed mAbs from their humanized Ab mouse platform and isolated from human convalescent serum First in human hospitalized patients, June 2020.
VIR First in Human July 2020	Vir mAb, S309, isolated from a SARS-CoV patient that is cross-reactive with SARS-CoV-2,
AstraZeneca First in Human July 2020	AZ has selected a 2 mAb combination against the SARS-CoV-2 spike protein (AZD7442) Plan Phase I single dose escalation study in normal volunteers, August 2020 (DARPA)
The Rockefeller University 1901 SCIENCE FOR THE BENEFIT OF HUMANITY	Michel Nussenzweig developed cocktail of two mAbs isolated from convalescent plasma, target two non-overlapping epitopes of the receptor binding domain Bristol Myers Squibb will manufacture antibodies

The New York Times

One-Third of All U.S. Coronavirus Deaths Are Nursing Home Residents or Workers



The New York Times. Karen Yourish, K.K. Rebecca Lai, Danielle Ivory and Mitch Smith Updated May 11, 2020



The New York Times. **Yourish, K.K.** May 11, 2020

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)***

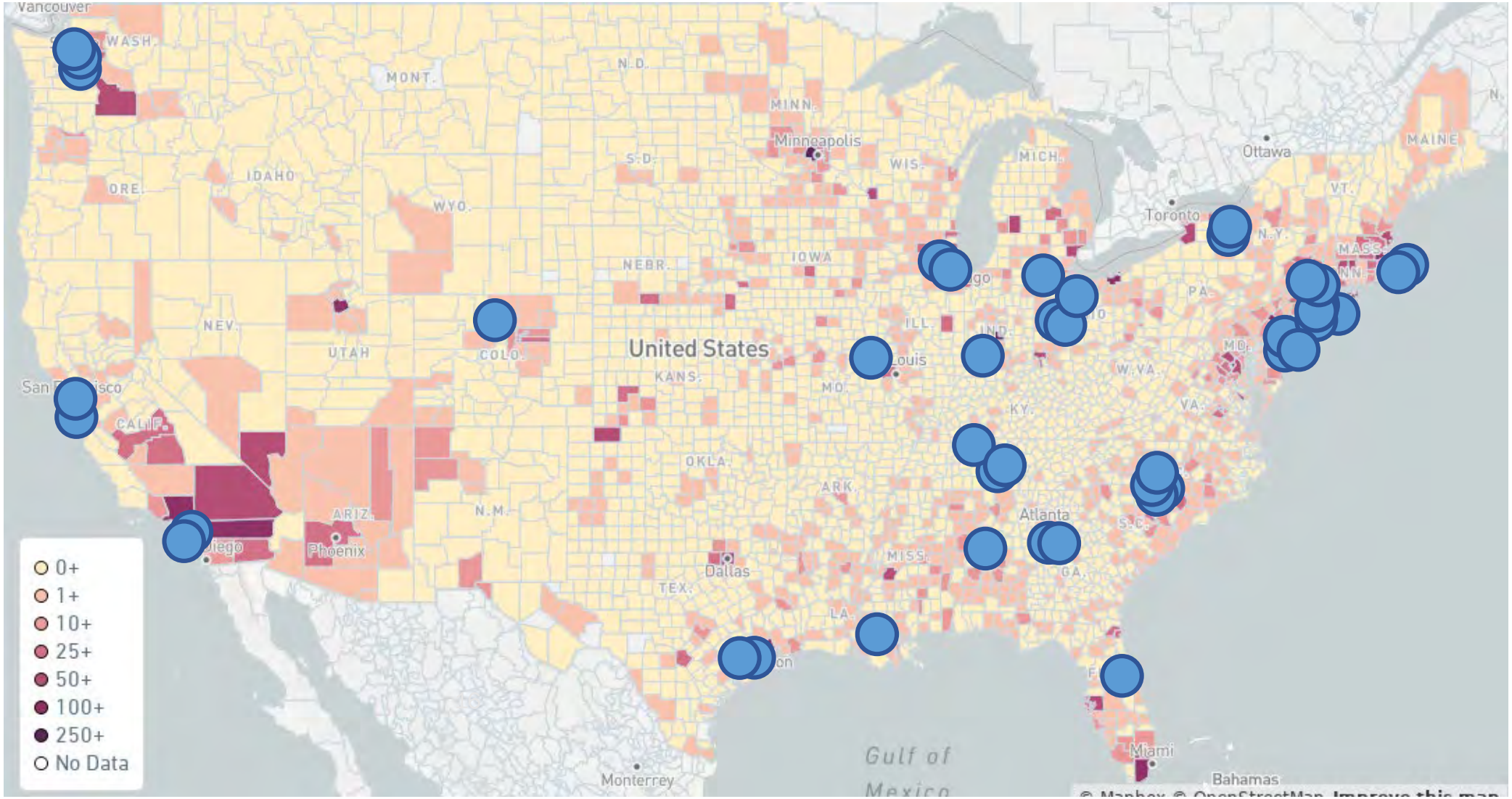
Further Evaluation of mAbs to alter COVID-19

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

COVID-19
Prevention Network

Mapping COVID-19 Incidence and NIAID Sites



EDITORIAL

Myron S. Cohen & Lawrence Corey

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 road to reducing 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 bathhouses) 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 very early in infection prior to development of symptoms—the same lesson learned from HIV. Given this rule

> **"HIV has taught us that multiple concomitant prevention strategies are essential."**

tiviral agents reduce the HIV viral load to a point where infected people no longer transmit. This approach, which uses combinations of powerful antiretroviral agents, is now the mainstay of HIV prevention worldwide.

For SARS-CoV-2, we have leapt into a cacophony of clinical trials of drug candidates with differing degrees of plausibility. Preliminary results from a large randomized controlled trial show that the antiviral drug remdesivir substantially reduced the duration of hospitalization for COVID-19. To date, COVID-19 testing results have been used primarily for patient isolation, contact tracing, and quarantine. But effective therapies will lend great urgency for the universal availability of rapid and reliable testing for SARS-CoV-2 infection, so that treatment can be provided when indicated.

Long-acting antiviral agents and monoclonal antibodies that neutralize SARS-CoV-2 may become important nonvaccine pharmacologic tools for prevention. Antiviral agents that prevent replication of SARS-CoV-2 could be used as pre-, peri-, or postexposure prophylaxis. Several different potent monoclonal antibody combinations designed to treat and prevent SARS-CoV-2 will enter clinical trials in June 2020.

Ultimately, a safe and effective vaccine is crucial for preventing COVID-19. Vaccine efforts started immediately after the discovery of SARS-CoV-2. Numerous vaccine candidates have been identified, and early-phase vaccine studies of several are underway. Proof of vaccine efficacy will require large trials with 6000 to [illegible]000 participants [illegible] is moving

. Science. 2020 May 8;368(6491):551.

THANK YOU!

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