COVID-19/SARS-CoV-2 Science and Treatment

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Outline

- Timeline and Definitions
- Science
- Forecasting COVID-19
- Treatments
- COVID-19 - Impact on Human Resources

Timeline of COVID-19

[Nature March 17, 2020. https://www.nature.com/articles/d41586-020-00154-w]

21 January— First US case confirmed (30-year-old man in Washington state after a trip to China)

23 January— Chinese government closes off Wuhan

23 January— Chinese authorities lock down Huanggang

24 January— Second US infection (60's y-old woman returned home in Chicago after visiting Wuhan)

27 January— Scientists estimate how quickly virus spreads (how many people one person with the virus tends to infect — known as R0. An R0 > 1 means that countermeasures, such as quarantine, will be needed to contain the pathogen's spread - estimated R0 of 1.4 to 2.5)

28 January— Cases increase by more than 60%

28 January— First human-to-human transmission outside China (German man acquired the infection from a colleague who had returned from Wuhan)

30 January— Human-to-human transmission confirmed in the United States (woman living in Illinois who had visited Wuhan passed the virus to her spouse)

3 February — Study of live virus

14 February — Chinese authorities reveal number of infections in medical staff: 1,716 health workers had contracted the virus, 6 of whom died

Timeline of COVID-19

[Nature March 17, 2020. https://www.nature.com/articles/d41586-020-00154-w]

17 February— First case in Africa

25 February— U.S. emergency funding for coronavirus response

26 February— Brazil reports first case in South America

28 February— Coronavirus spreads to sub-Saharan Africa

4 March— Repurposed drugs in coronavirus

5 March— World Bank pledges US$12 billion for coronavirus response

5 March— China study suggests children are as likely to be infected as adults, but not getting sick

6 March—Congress approves US$8.3 billion for coronavirus response to CDC, NIH, FDA

11 March— Transgenic animals for coronavirus research in high demand

11 March— Coronavirus outbreak is a pandemic, says WHO.

13 March— US president declares ‘national emergency’

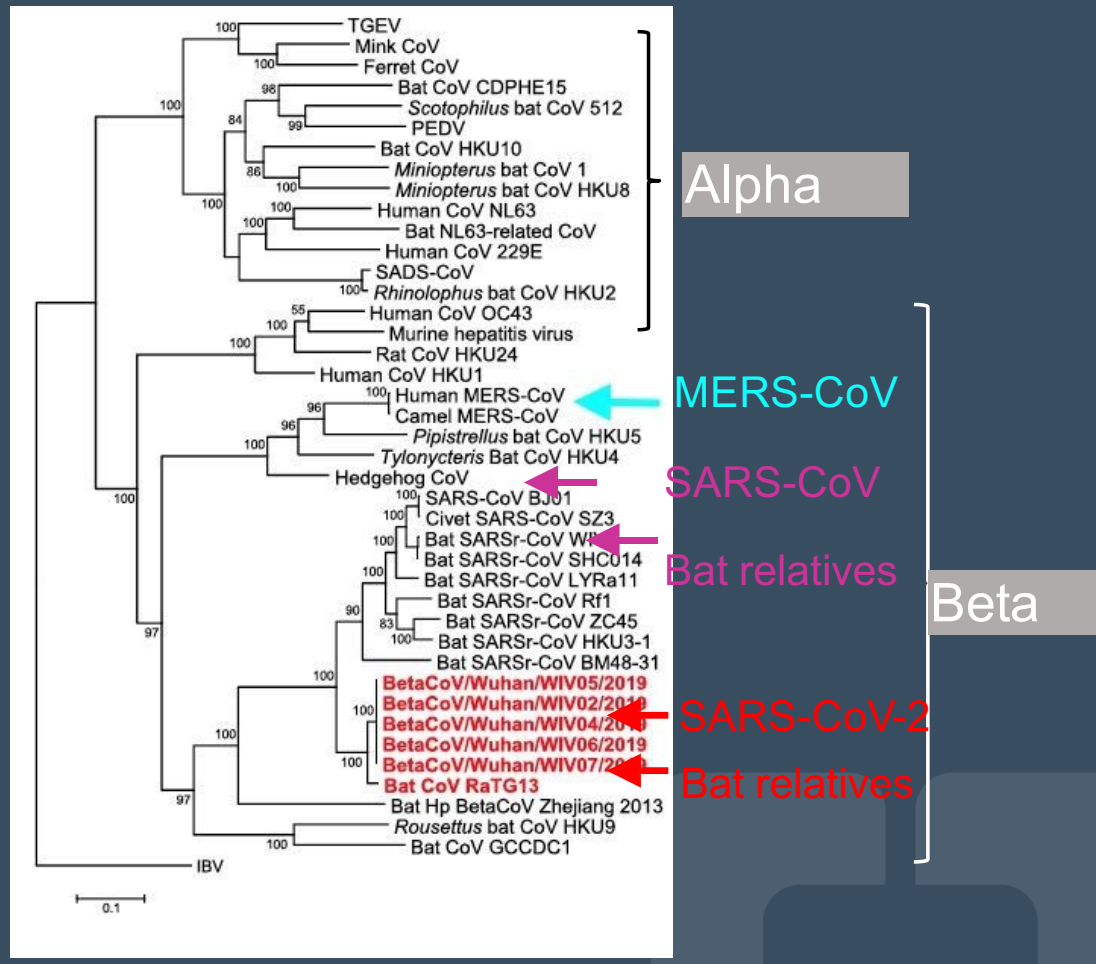
17 March— First vaccine clinical trials begin in U.S. (National Institute of Allergy and Infectious Diseases (NIAID) and Moderna - “launched in record speed,” 66 days from genetic sequencing of virus to the first human injection of the vaccine candidate

Definitions

- COVID-19 refers to the disease, (*i.e.,* having a positive 2019 coronavirus laboratory test regardless of disease signs or symptoms)
- 2019-nCOV was the initial name given by some infectious disease organizations for the virus, where nCOV stands for novel coronavirus. However, this name is hard to remember because it starts with a generic term (the year) and is also inconsistent with coronavirus naming conventions.
- SARS-CoV-2 is the Genbank name for the virus, because it is 96% identical in nucleotide sequence to SARS-CoV, the cause of SARS in 2003.

Coronaviruses (CoVs)

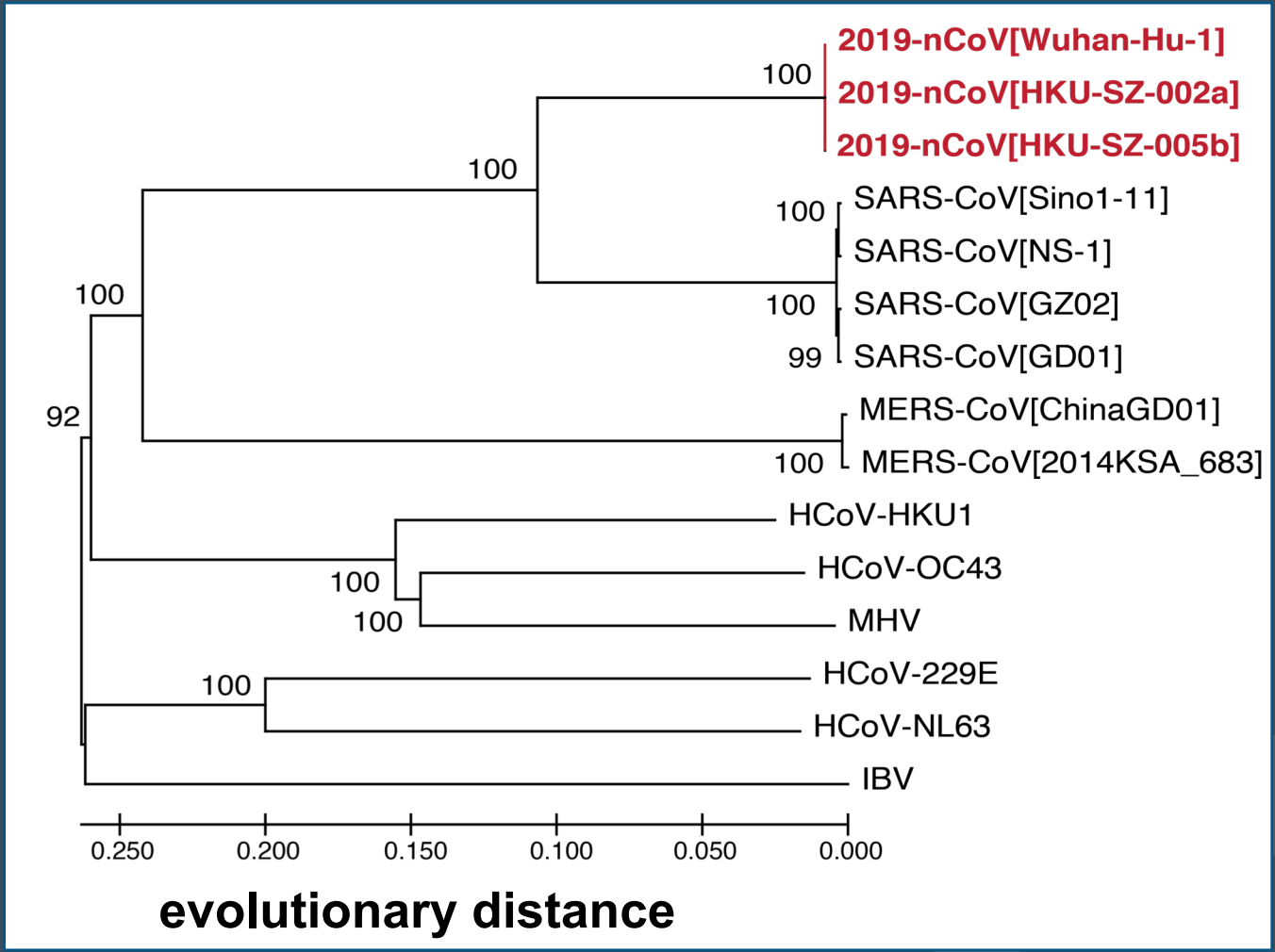
- Positive-strand RNA viruses with large genomes (≥27K bases)
- Alpha and beta types cause human disease
- Both types cause common cold (10-30% of cases) ([Pubmed 31971553])
- Easily hops between species
  - MERS-CoV from camels to humans
  - SARS-CoV from bats to humans and civets
  - SARS-CoV-2 from bats to humans [?]



https://www.sciencemag.org/news/2020/01/mining-coronavirus-genomes-clues-outbreak-s-origins

Phylogenetic Analysis of SARS-CoV-2

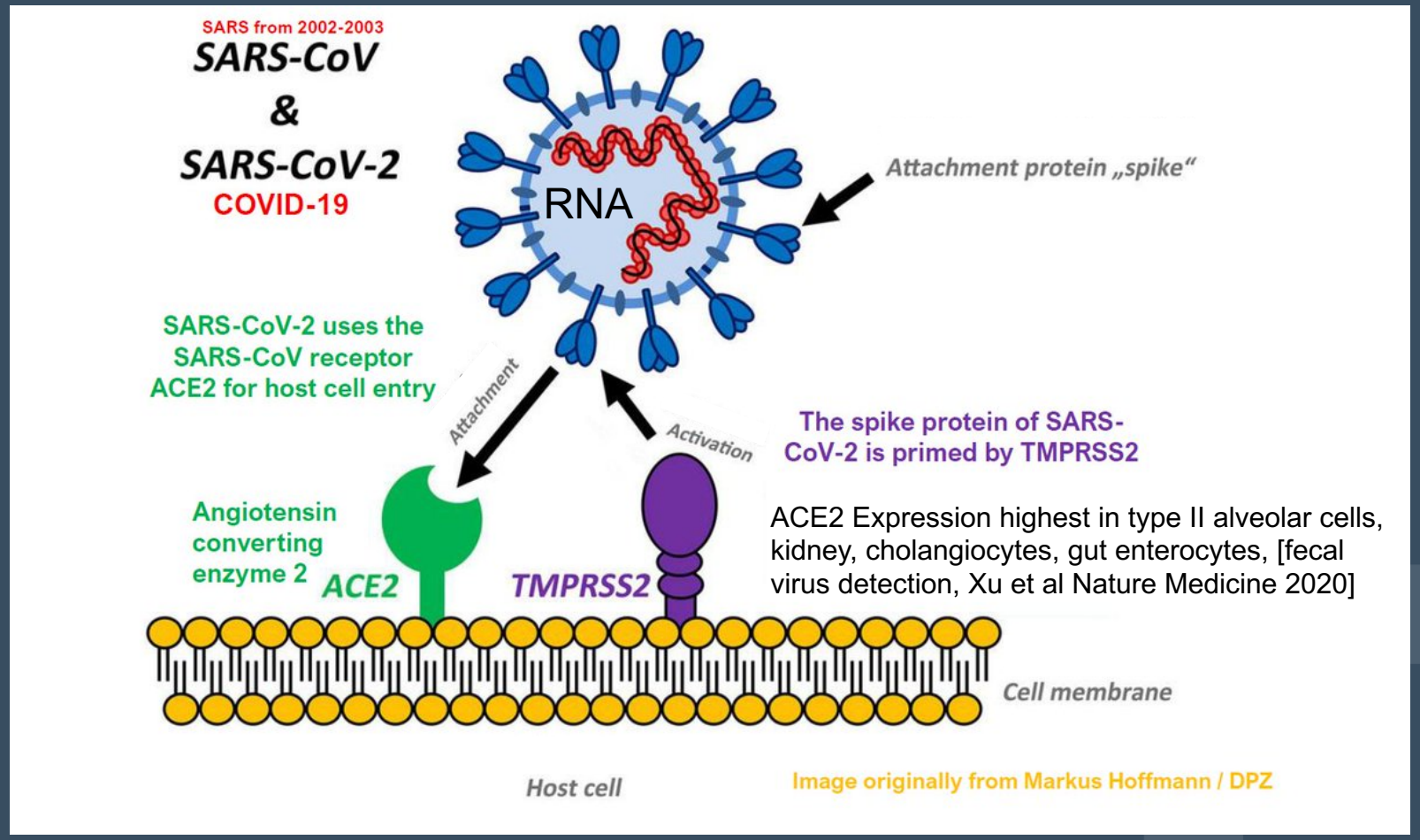
- Nearly all RNA viruses change sequence during replication
- Minor changes can be considered simple sequence variation (but not for different types of viruses)
- Sequence changes affect viral pathogenesis
- More studies needed



Zhou et al., *Cell Discovery* 2020

Virus Attachment to ACE2 Receptor Results in Invasion of Epithelial Cells

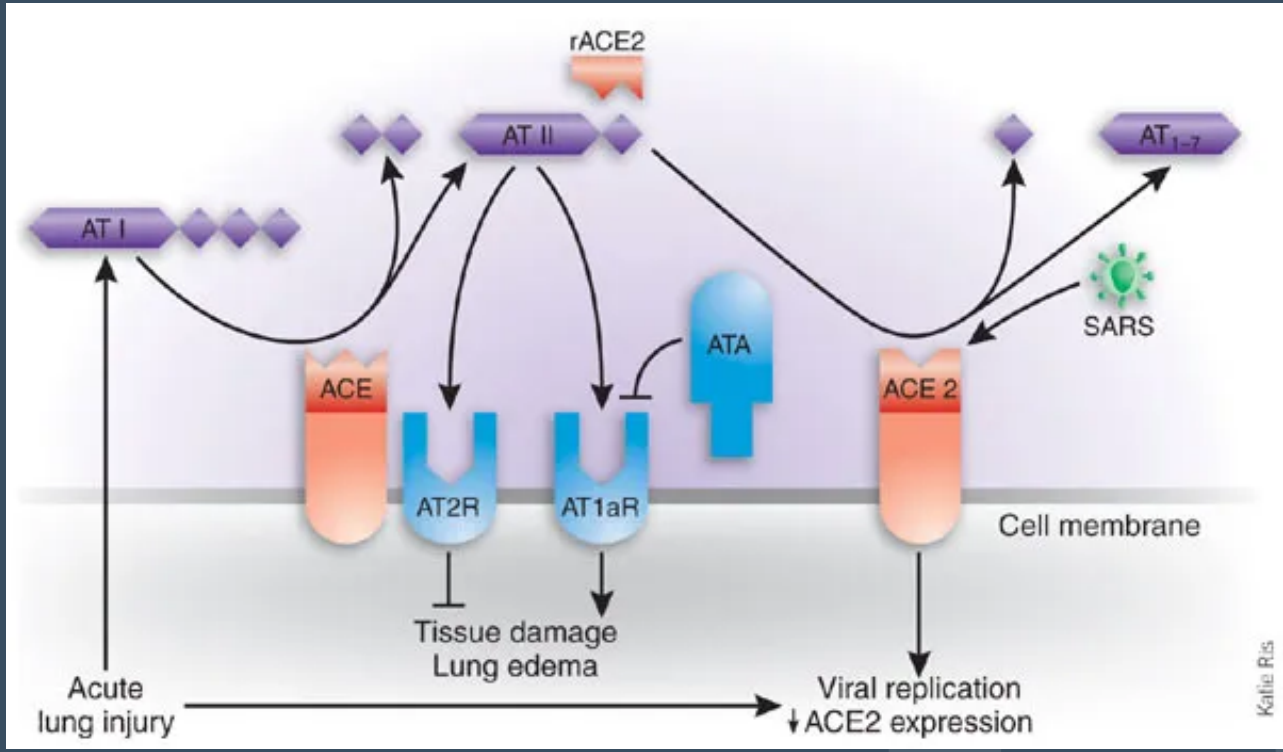
SARS-Cov2 spike protein has 10X higher affinity for ACE2 receptor than SARS-Cov



Liu et al., ACS Central Science 2020

ACE2 and Angiotensin II Receptors

- Angiotensin II (Ang II) directly or indirectly regulate blood pressure and of fluid and electrolyte homeostasis
- Modulate movement of Na^{++} and water across epithelia
- 32 coding variants in ACE2 identified in the ChinaMAP. (Cao et al., *Cell Discovery* 2020)
- Binding of excess ATII to AT1R can cause tissue damage (enhanced by loss of ACE2 due to viral binding and down-modulation)
- ACE2 decreases with aging, regulated by melatonin (Simko Molecules 2018)



Two types of Ang II receptors: Type 1 (AT_1) and Type 2 (AT_2)

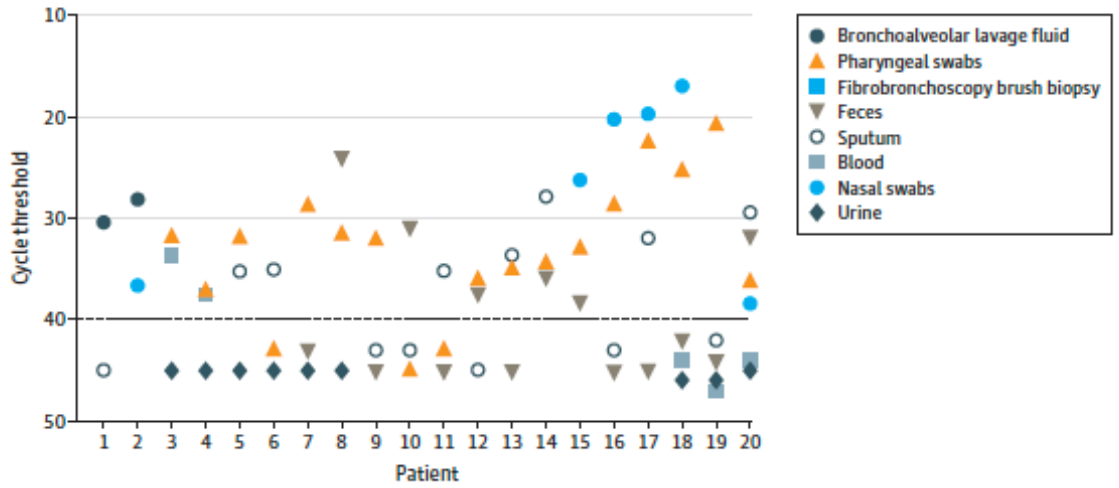
Detection of SARS-CoV-2 in Different Clinical Specimens

Table. Detection Results of Clinical Specimens by Real-Time Reverse Transcriptase–Polymerase Chain Reaction

Specimens and values	Bronchoalveolar lavage fluid (n = 15)	Fibrobronchoscope brush biopsy (n = 13)	Sputum (n = 104)	Nasal swabs (n = 8)	Pharyngeal swabs (n = 398)	Feces (n = 153)	Blood (n = 307)	Urine (n = 72)
Positive test result, No. (%)	14 (93)	6 (46)	75 (72)	5 (63)	126 (32)	44 (29)	3 (1)	0
Cycle threshold, mean (SD)	31.1 (3.0)	33.8 (3.9)	31.1 (5.2)	24.3 (8.6)	32.1 (4.2)	31.4 (5.1)	34.6 (0.7)	ND
Range	26.4-36.2	26.9-36.8	18.4-38.8	16.9-38.4	20.8-38.6	22.3-38.4	34.1-35.4	
95% CI	28.9-33.2	29.8-37.9	29.3-33.0	13.7-35.0	31.2-33.1	29.4-33.5	0.0-36.4	

Abbreviation: ND, no data.

Figure. Severe Acute Respiratory Syndrome Coronavirus 2 Distribution and Shedding Patterns Among 20 Hospitalized Patients



Wang et al., JAMA 2020

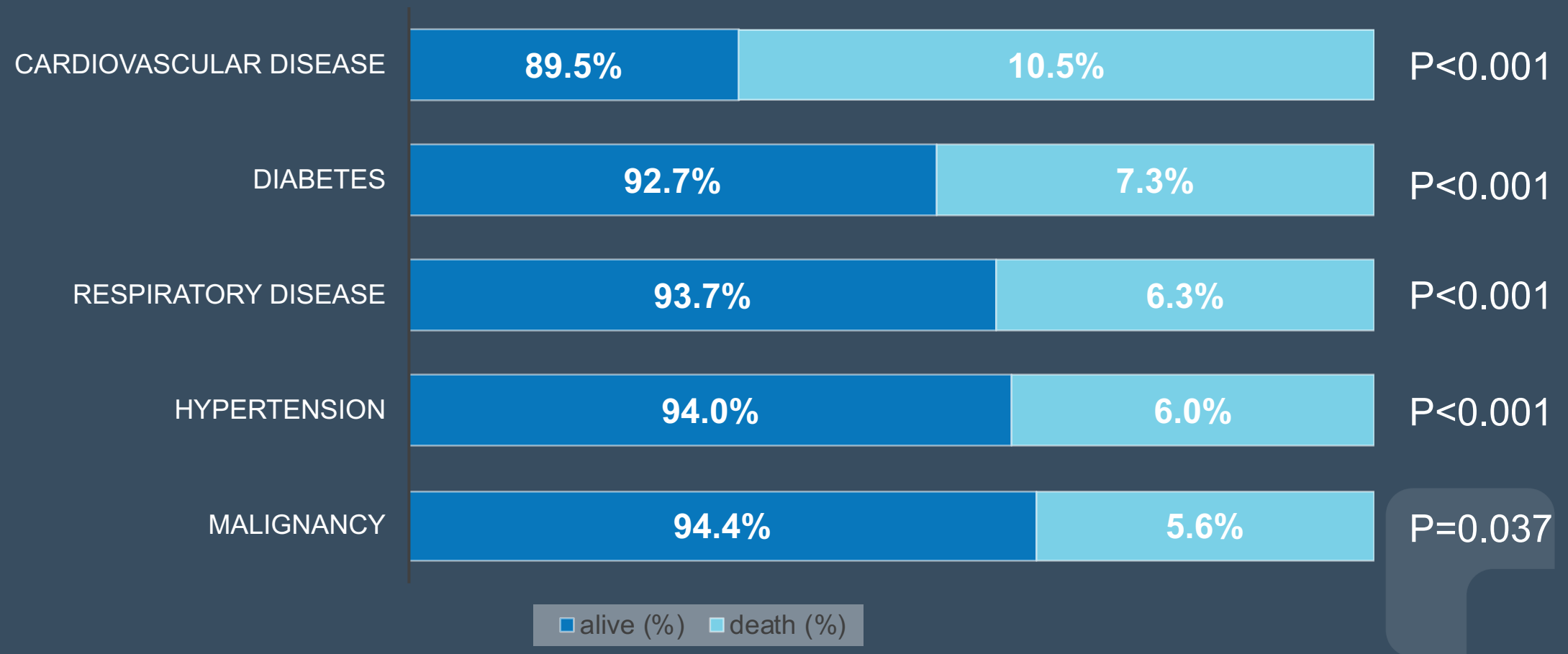
Table 1. Baseline Characteristics of Patients Infected With 2019-nCoV

	No. (%)			
	Total (N = 138)	ICU (n = 36)	Non-ICU (n = 102)	*P* Value[a]
Age, median (IQR), y	56 (42-68)	66 (57-78)	51 (37-62)	<.001
Sex				
Female	63 (45.7)	14 (38.9)	49 (48.0)	.34
Male	75 (54.3)	22 (61.1)	53 (52.0)	
Huanan Seafood Wholesale Market exposure	12 (8.7)	5 (13.9)	7 (6.9)	.30
Infected				
Hospitalized patients	17 (12.3)	9 (25.0)	8 (7.8)	.02
Medical staff	40 (29)	1 (2.8)	39 (38.2)	<.001
Comorbidities	64 (46.4)	26 (72.2)	38 (37.3)	<.001
Hypertension	43 (31.2)	21 (58.3)	22 (21.6)	<.001
Cardiovascular disease	20 (14.5)	9 (25.0)	11 (10.8)	.04
Diabetes	14 (10.1)	8 (22.2)	6 (5.9)	.009
Malignancy	10 (7.2)	4 (11.1)	6 (5.9)	.29
Cerebrovascular disease	7 (5.1)	6 (16.7)	1 (1.0)	.001
COPD	4 (2.9)	3 (8.3)	1 (1.0)	.054
Chronic kidney disease	4 (2.9)	2 (5.6)	2 (2.0)	.28
Chronic liver disease	4 (2.9)	0	4 (3.9)	.57
HIV infection	2 (1.4)	0	2 (2.0)	>.99

Wang,et. al.,
JAMA. 2020

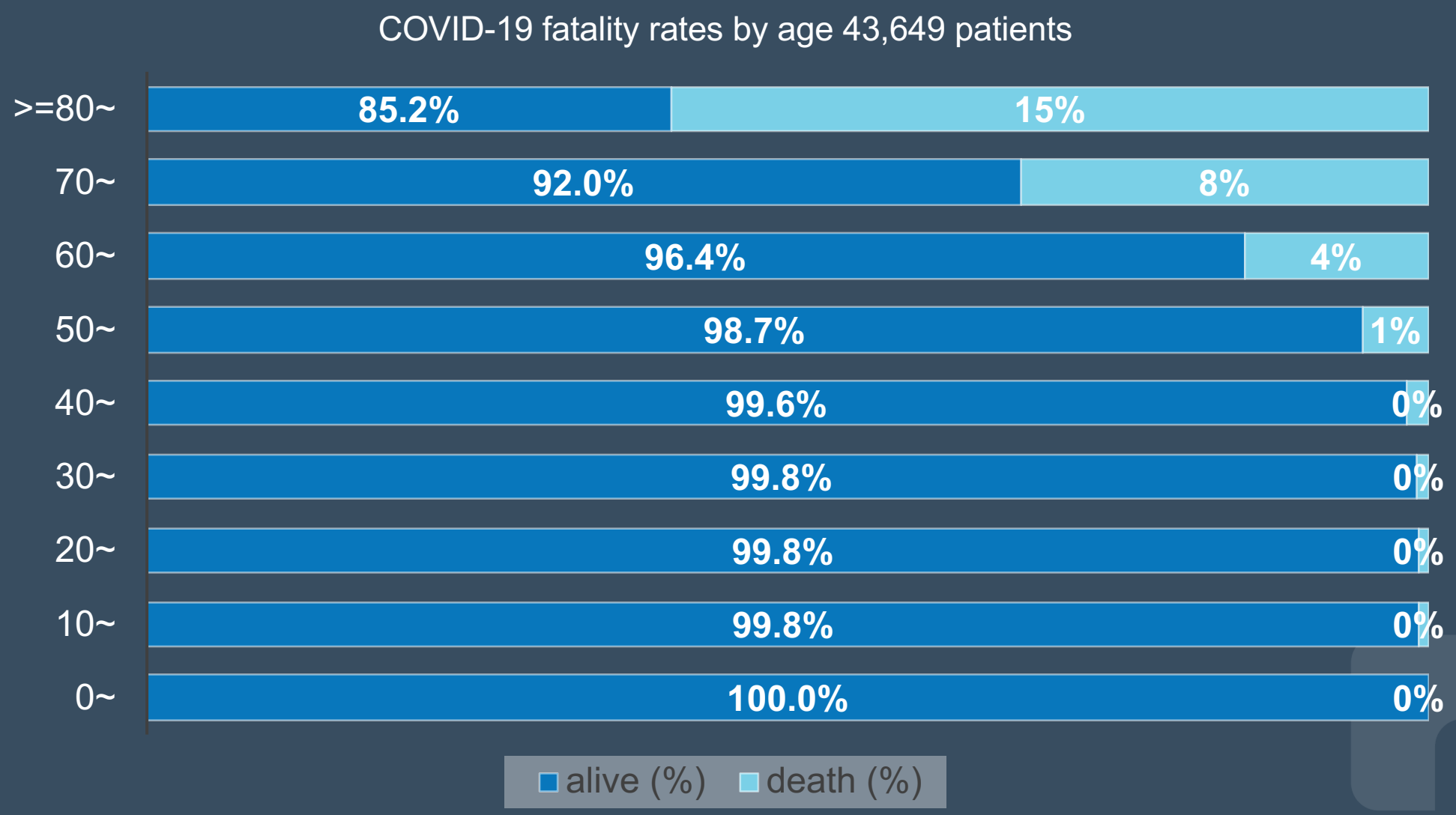
COVID-19 Fatality Rate by Health Conditions

COVID-19 fatality rates by underlying health condition in 43,649 patients



Data downloaded from Wang,et. al., JAMA. 2020

COVID-19 Fatality Fate Across Patient Ages

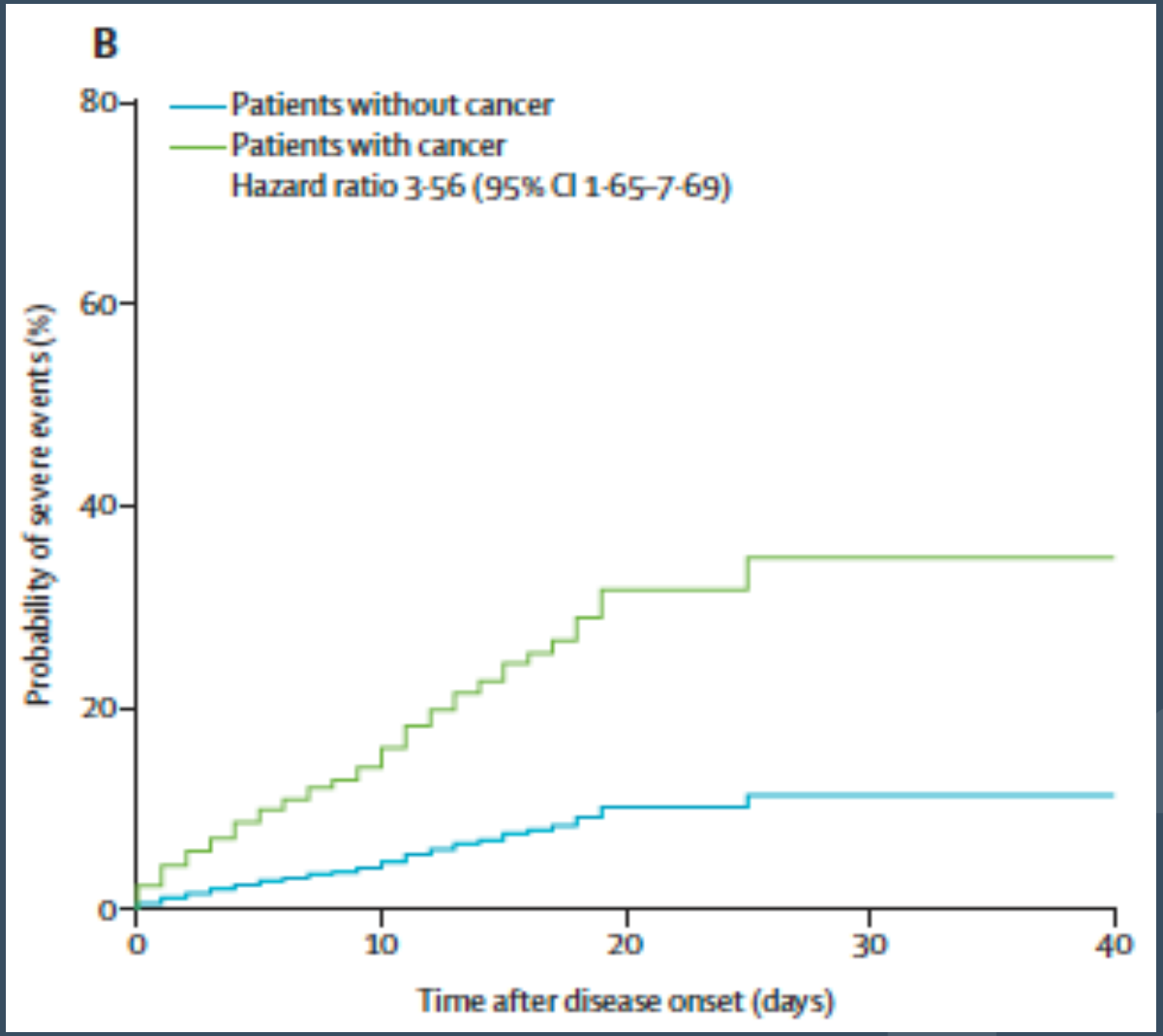


Data downloaded from Wang,et. al., JAMA. 2020

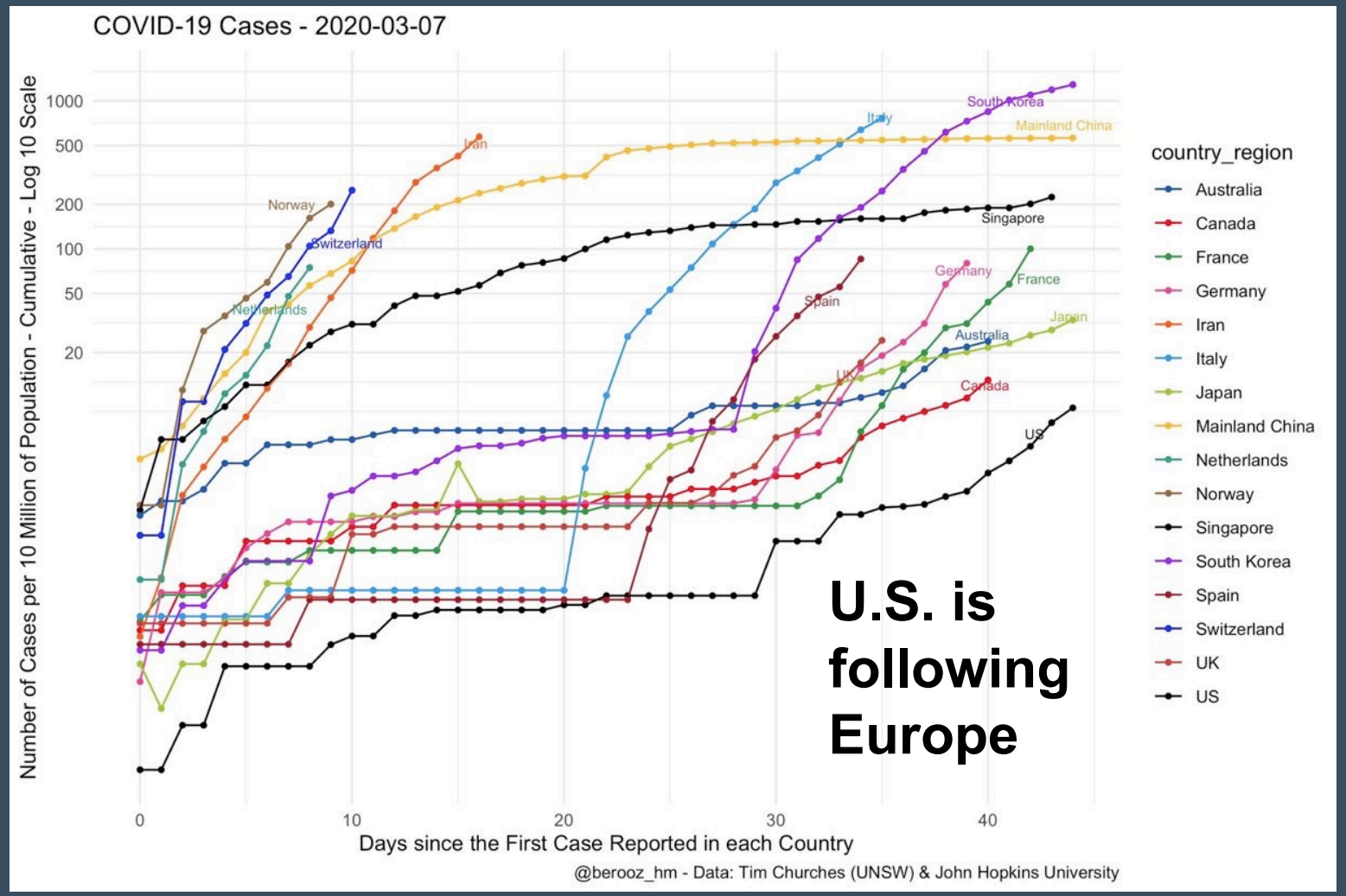
Cancer Patients in SARS-CoV-2 Infection

A nationwide analysis in China

Liang et al., *Lancet Oncology* 2020



Number of Infected Cases
(per 10M Population)

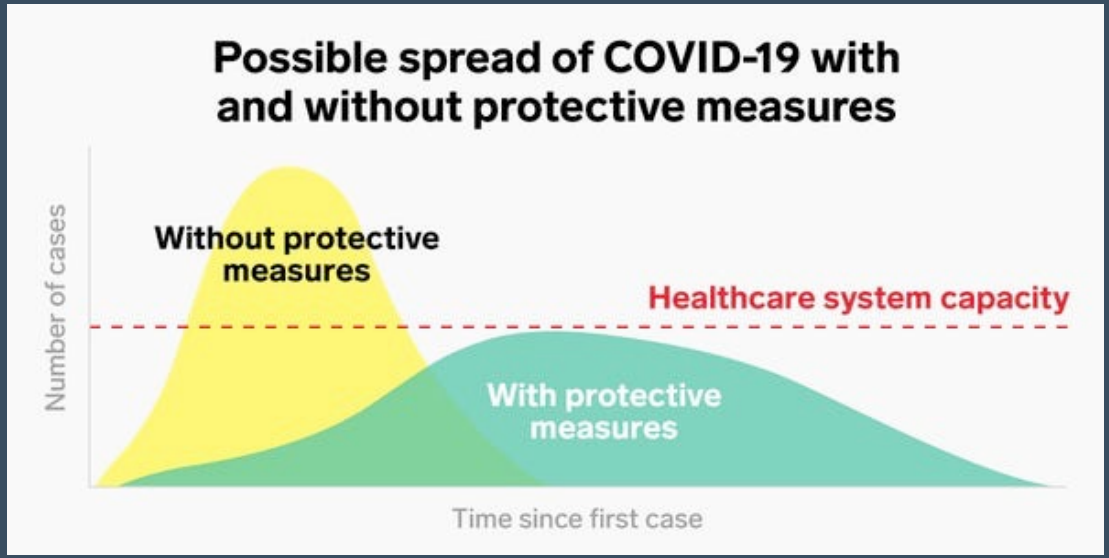


CDC and FDA Testing

- CDC initially inflexible on testing guidelines (*e.g.,* need travel or exposure history)
  - Their test required slow, overnight RT-PCR reaction on specific model, designed poor primers, and did not realize this for a month.
  - Strategic and tactical errors
- FDA had stringent rules on testing
  - Approved only CDC test; refused working tests from WHO and other countries
  - Required CDC to retest results of other labs
  - Allowed academic labs to develop own tests on 2/29
  - Approved rapid Roche test on 3/13

Goals of Mitigation in Pandemic

- ~5% of total infected (not *diagnosed* cases) require hospitalization and 2.5% require ICU
- Average hospital stay 3 weeks, starts 2 weeks after infection (1 wk after diagnosis) New York Times, Vox.com



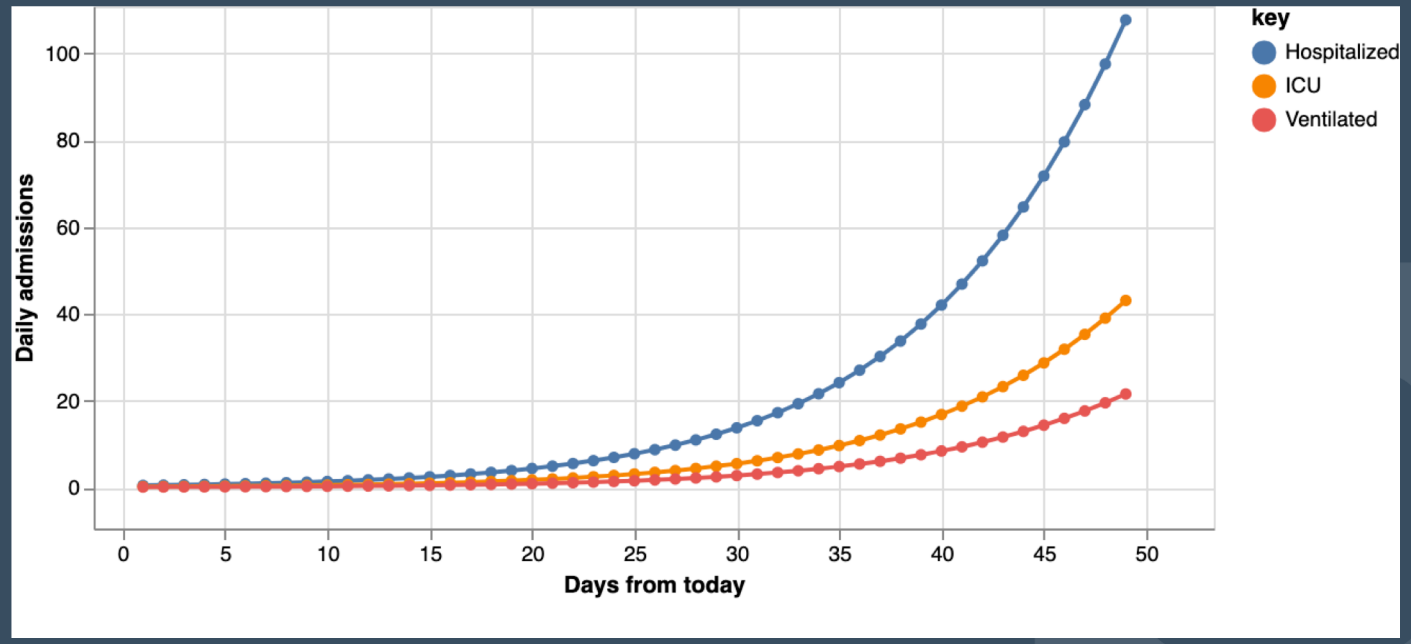
- Wuhan numbers are 15%/5%, but infection rate likely underdetected by 50%
- Calculations suggest biggest infection surge will occur weeks of 5/29 and 6/5, when 25% of population = 80M gets infected each week, resulting in up to 4M needing hospitalization starting 6/12 and another 4M starting 6/19.
  - Slow down doubling time from 1 week to >8 weeks, so at peak it is <500,000 hospitalizations in a week

UPenn Modeling of COVID-19 Hospital Impact Model for Epidemics

Estimate number of currently infected individuals is 533.

63 confirmed cases in the region imply a 12% rate of detection

Based on current inputs for hospitalization rate (5%), region size (4119405), and hospital market share (15%), an initial doubling time of 6 days and a recovery time of 14.0 days imply an R0 of 2.71.



Projected number of **daily** COVID-19 admissions at UPenn hospitals

COVID-19 Research Registry

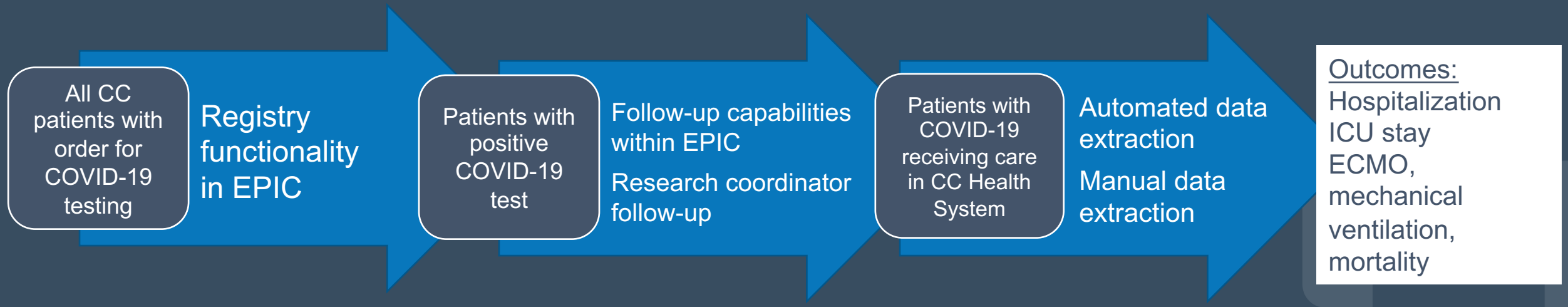
Team: L.Jehi, S.Gordon, R.Dweik, K.Dell, M.Kattan, J.Dalton, E.Boose, L.Posk, and growing
IRB submitted and approved 3/17/20

Use predictive analytics to address:

Aim 1: Who tests positive?
Value: better target assessing

Aim 2: Why are some patients sicker? How does COVID compare to flu?
Value: better target to follow-up

Aim 3: What works?
Value: identify ***available*** treatment options



Data collection to include demographics, risk factors, current medications (specifically those with therapeutic potential identified in drug re-purposing studies) , Social determinants of Health, treatment course

COVID-19 Prediction Models

(Running Real Time, in EPIC, like Readmission Prediction)

Predicted Probabilities of Clinical State Progression (probabilities for each →):

AT HIGH RISK → TESTING POSTIVE FOR COVID-19 → SEVERE DISEASE → DEATH FROM COVID-19

Predictor variables (inputs):

Labs (e.g., CRP)
Demographics and smoking history
Symptoms
Travel history
Comorbidities: Diabetes, Hypertension, Immunosuppression, Medications, Social determinants of health

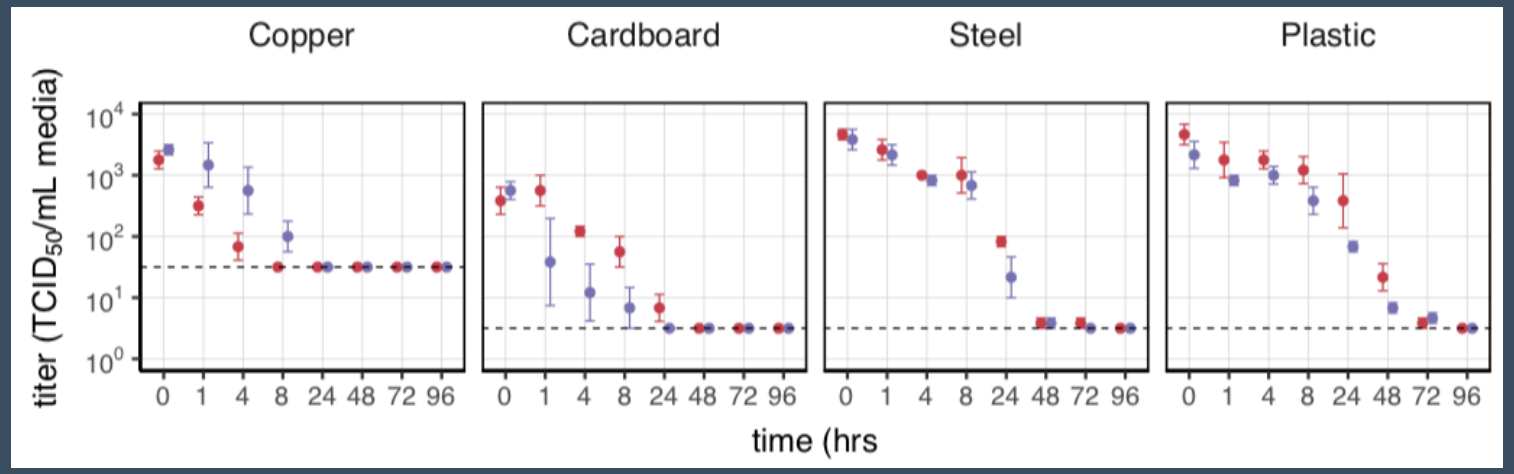
Oxygen (including high flow)
Ventilation (including mechanical)
ECMO (including type)
Other procedures performed in hospital
Sequential Organ Failure Assessment score
d-dimer
(plus variables predicting positive test, left)

What Can Flatten the Curve?

- Cough etiquette/hand hygiene
- Clinical suspicion to identify potentially infected/test as appropriate/respiratory isolation
- Social distancing: Current R0 rate ~ 3 (one person infects 3 other people. If they do this in ~10 days, it would account for doubling time 1 week)
  - Drop R0 to 1.5: Doubling time would increase ~4-fold.
  - Drop R0 to 1.25: Doubling time would increase ~8-fold.
  - Drop R0 to 1.0: Doubling time would become infinite (constant rate of new cases).
- Facility/hospital quarantine: in Wuhan study, changed R0 from 3.4 to 0.32 (www.medrxiv.org/content/10.1101/2020.03.03.20030593v1).
- Weather: 10ºF increases doubling time 2x (Pubmed 22312351, by decreasing virus survival time, and reducing time × concentration of people indoors).
- Because of the SARS experience, Ontario first followed a precautionary principle using N95 in line with CDC recommendations, which were changed March 2020 to use droplet/contact other than for aerosolized generating procedures
  - Canadian federal guidelines are pretty much in keeping with WHO: https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/health-professionals/interim-guidance-acute-healthcare-settings.html

How Do You Kill SARS-CoV-2?

- Enveloped virus (with a plasma membrane)
- Soap/detergents, ethanol, Windex (contains detergents), bleach
- Survival depends on surface
- On steel and plastic, 10-fold drop in ~12 hours; on cardboard, 1 hour
- Likely to be sensitive to temperature (SARS-Cov-1 was)
- On a napkin, survival should be similar to cardboard or lower, and virus will be trapped by the fibers



SARS-CoV-1 and SARS-CoV-2 applied to surfaces
(how exactly not described)

Cleveland Clinic Testing

As of 3/16/20, 20% of patients tested had Flu/RSV; 3% positive for COVID19

COVID-19 Total Resulted Tests

2,001

COVID-19 Total Positive Results

37

COVID-19 Positive Results (CUMUL.)

Hosp Code	Original Event Type (gro..	March
Avon	ER	3
	Inpatient	0
	Outpatient	0
Euclid	ER	0
	Inpatient	0
Fairview	ER	9

COVID-19 Tests Resulted Today (Starting 00:00, may include modifications on results from prior days)

293

COVID-19 Today's Positive Results (Starting 00:00)

6

COVID-19 Total Positive Results All Hospital(s)

	Collect Date March								
	8	9	10	11	12	13	14	15	16
COVNP Completed Tests	0	0	3	18	70	267	641	822	126
COVID-19 Positive Results	0	0	0	2	1	11	18	5	0

Pending Covid-19 Tests

1,157

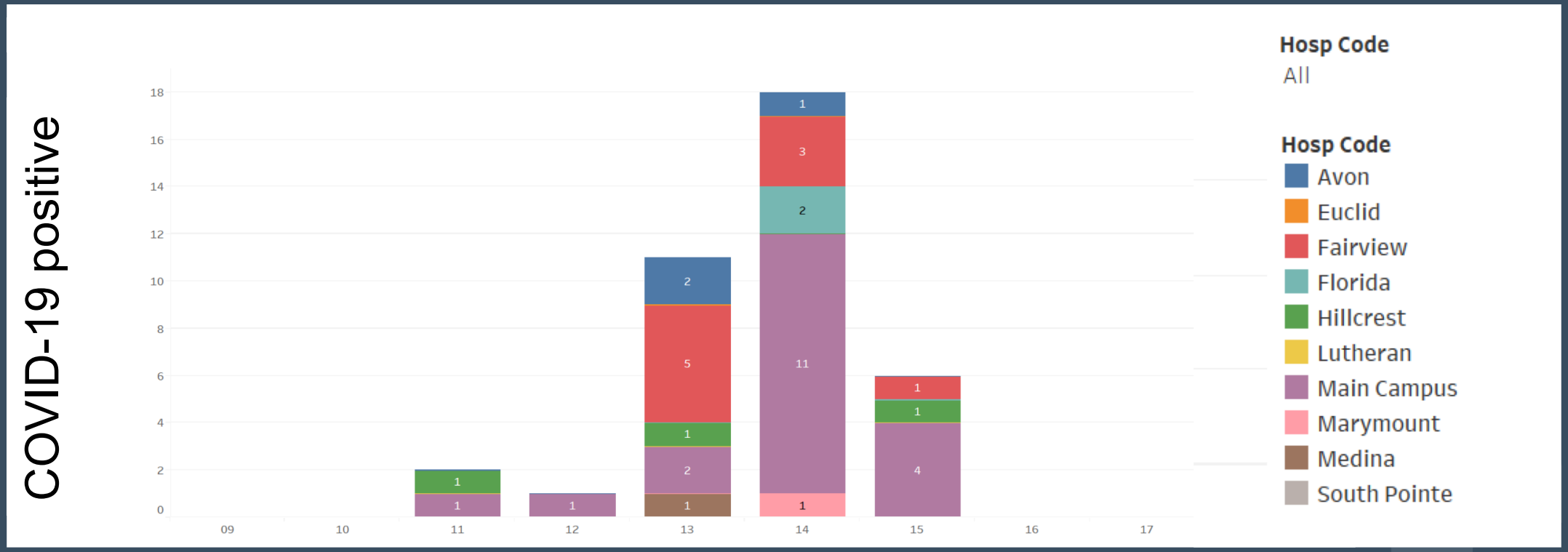
Dashboard Info.

Hospital
All

As of this 3/18/20 43 positive with 8 inpatients in our system;
12 positives from drive through testing to date

http://analytics.ccf.org/#/site/EBI/workbooks/19148/views

Positive Tests by Day by Hospital



Collection Date

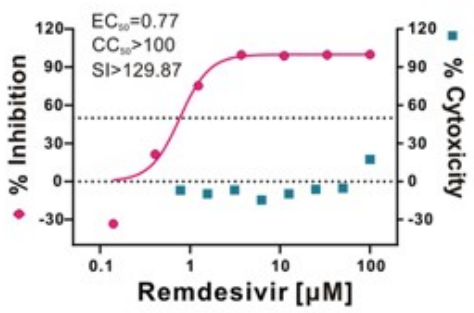
COVID-19 Clinical Trials Registration List

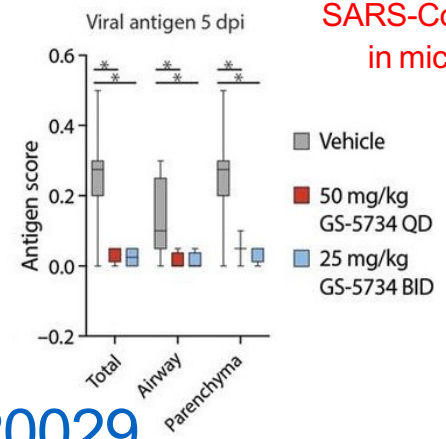
Registration number	Intervention	Type	Registration date
ChiCTR2000029308	Lopinavir/ritonavir; interferon α 2b	Antiviral	1/23/2020
ChiCTR2000029386	Lopinavir/ritonavir; methylprednisolone; interferon α	Antiviral; Corticosteroid	1/28/2020
ChiCTR2000029387	Lopinavir/ritonavir; ribavirin; interferon α-1b	Antiviral	1/28/2020
NCT04244591	Methylprednisolone	Corticosteroid	1/28/2020
ChiCTR2000029468	Lopinavir/ritonavir; emtricitabine/tenofovir alafenamide fumarate	Antiviral	2/2/2020
ChiCTR2000029496	Lopinavir/ritonavir; Novaferon	Antiviral	2/3/2020
ChiCTR2000029539	Lopinavir/ritonavir	Antiviral	2/3/2020
ChiCTR2000029541	Darunavir/cobicistat; Lopinavir/ritonavir; thymosin	Antiviral	2/3/2020
ChiCTR2000029542	Chloroquine	Antiviral	2/3/2020
ChiCTR2000029548	Baloxavir Marboxil; Favipiravir; Lopinavir/ritonavir	Antiviral	2/4/2020
NCT04252885	Umifenovir (Arbidol)	Antiviral	2/5/2020
NCT04255017	Umifenovir (Arbidol); Oseltamivir; Lopinavir/ritonavir	Antiviral	2/5/2020
NCT04257656	Remdesivir	Antiviral	2/6/2020
ChiCTR200029600	Favipiravir, Lopinavir/Ritonavir + alpha-Interferon	Antiviral	2/6/2020
ChiCTR2000029853	Azvudine	Antiviral	2/16/2020
NCT04273529	Thalidomide	Immunomodulatory agent	2/18/2020
ChiCTR2000030000	Ganovo (Danoprevir)/ritonavir; Peginterferon alfa-2a	Antiviral	2/19/2020
NCT04280588	Fingolimod	Receptor modulator	2/21/2020
ChiCTR2000030055	Dipyridamole	Inhibitor	2/22/2020

Antivirals – Remdesivir

- Works against SARS-CoV-2 in cells, EC50 = 770nM (left image)
- Dosed to >11 US patients on compassionate basis, with good anecdotal results
- In randomized controlled trials in China, data due mid-April
- Designed to inhibit Ebola RNA-dependent RNA polymerase (RdRp)
- Already known to inhibit replication of SARS-CoV-1 in mice (middle)
- SARS-CoV-1 RdRp (P0C6X7/R1AB_CVHSA) and SARS-CoV-2 RdRp (YP_009725307) are 96% identical (right image)

SARS-CoV-2 in human cells





SARS-CoV-1 in mice

PMID 32020029

SARS-CoV-1 query vs SARS-CoV-2

RNA-dependent RNA polymerase [Severe acute respiratory syndrome coronavirus 2]

Sequence ID: YP_009725307.1 Length: 932 Number of Matches: 7

Range 1: 1 to 932 GenPept Graphics ▼ Next Match ▲ Previous Match

Score	Expect	Method	Identities	Positives	Gaps
1914 bits(4957)	0.0	Compositional matrix adjust.	898/932(96%)	916/932(98%)	0/932(0%)

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             SADA +FLNRVCGVSAARLTPCGTGTSTDVVYRAFDIYN+KVAGFAKFLKTNCCRFQEKD
Sbjct  1     SADAQSFLNRVCGVSAARLTPCGTGTSTDVVYRAFDIYNDKVAGFAKFLKTNCCRFQEKD  60

Query  4430  EEGNLLDSYFVVKRHTMSNYQHEETIYNLVKDCPAVAVHDFFKFRVDGDMVPHISRQRLT  4489
             E+ NL+DSYFVVKRHT SNYQHEETIYNL+KDCPAVA HDFFKFR+DGDMVPHISRQRLT
Sbjct  61    EDDNLIDSYFVVKRHTFSNYQHEETIYNLLKDCPAVAKHDFFKFRIDGDMVPHISRQRLT  120

Query  4490  KYTMADLVYALRHFDEGNCDTLKEILVTYNCCDDDYFNKKDWYDFVENPDILRVYANLGE  4549
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Sbjct  121   KYTMADLVYALRHFDEGNCDTLKEILVTYNCCDDDYFNKKDWYDFVENPDILRVYANLGE  180

Query  4550  RVRQSLLKTVQFCDAMRDAGIVGVLTLDNQDLNGNWYDFGDFVQVAPGCGVPIVDSYYSL  4609
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Sbjct  241   LMPILTLTRALTAESHVDTDLTKPYIKWDLLKYDFTEERLKLFDRYFKYWDQTYHPNCVN  300

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Sbjct  301   CLDDRCILHCANFNVLFSTVFPPTSFGPLVRKIFVDGVPFVVSTGYHFRELGVVHNQDVN  360

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Sbjct  361   LHSSRLSFKELLVYAADPAMHAASGNLLLDKRTTCFSVAALTNNVAFQTVKPGNFNKDFY  420

Query  4790  DFAVSKGFFKEGSSVELKHFFFAQDGNAAISDYDYYRYNLPTMCDIRQLLFVVEVVDKYF  4849
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Sbjct  421   DFAVSKGFFKEGSSVELKHFFFAQDGNAAISDYDYYRYNLPTMCDIRQLLFVVEVVDKYF  480

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Sbjct  481   DCYDGGCINANQVIVNNLDKSAGFPFNKWGKARLYYDSMSYEDQDALFAYTKRNVIPTIT  540

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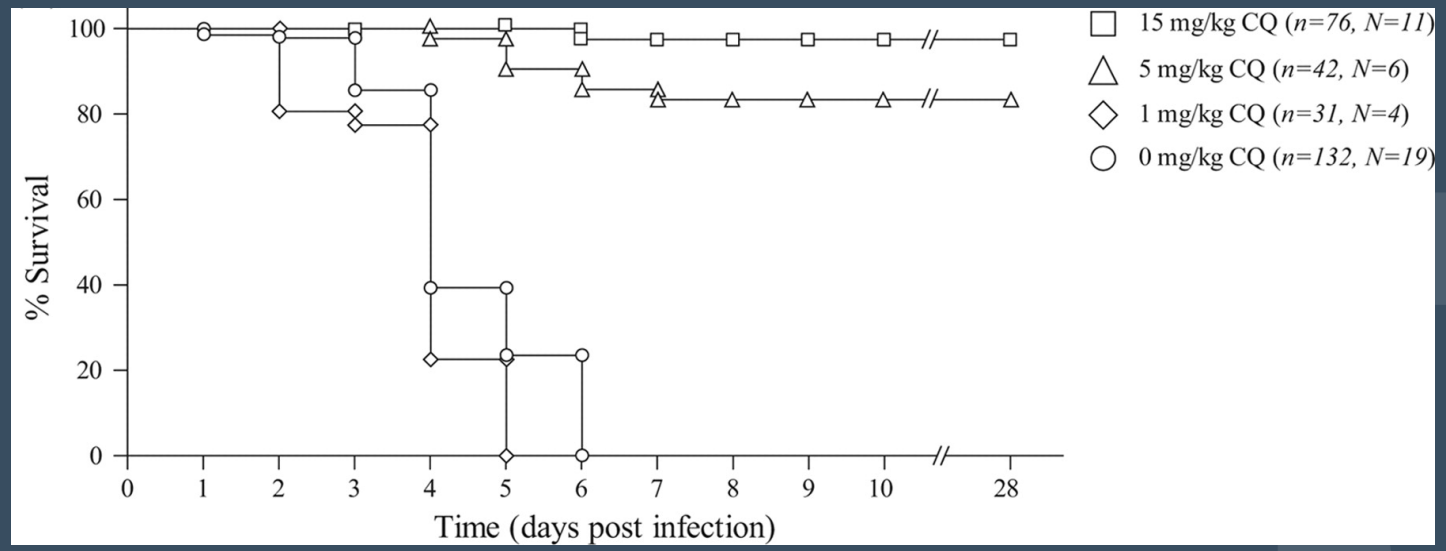
Antivirals - Chloroquine

- Works against SARS-CoV-2 in human cells, EC50 = 1130nM (Pubmed 32020029).
- Works against CoV OC43 in mice (Pubmed 19506054). Raises pH in lysosomes, prevents autophagy needed by virus.
- Chinese health ministry new briefing early February: “results from more than 100 patients have demonstrated that chloroquine phosphate is superior to the control treatment in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus-negative conversion, and shortening the disease course according to the news briefing” but no data shown (Pubmed 32074550).
- Side-effects serious, but has been used for malaria
- In prophylactic trials in China and U.S.

CoV OC43 in mice

3/15/20

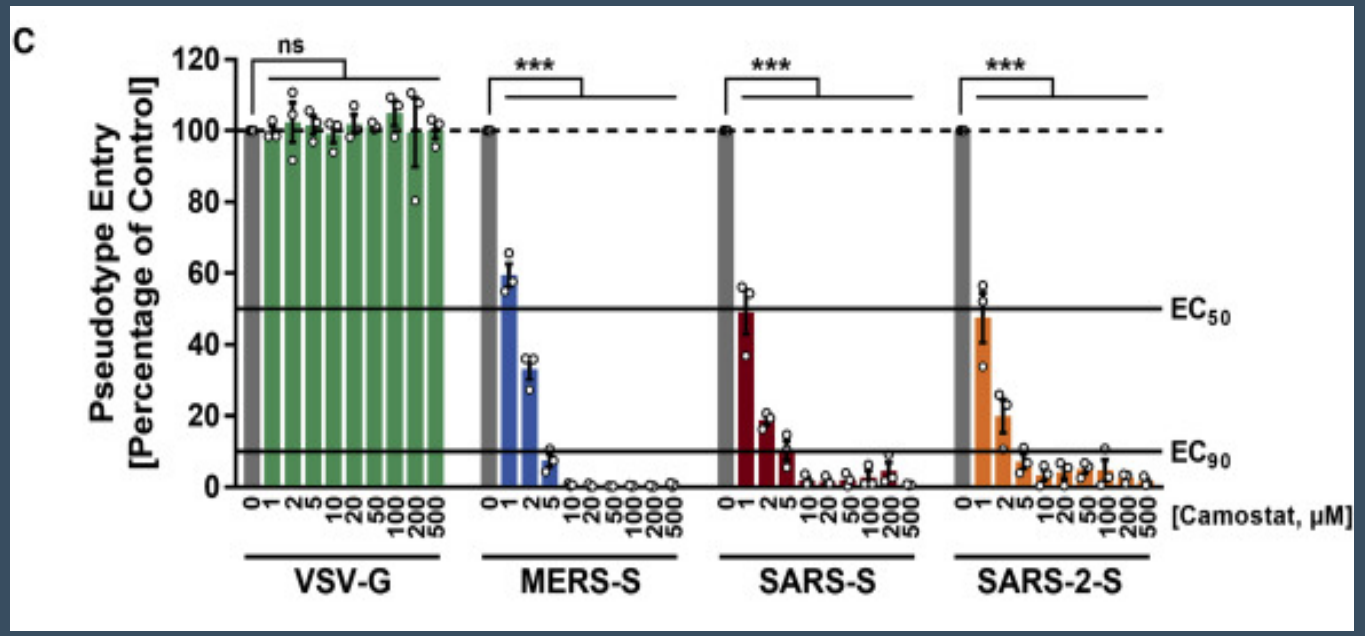


Antivirals - Camostat

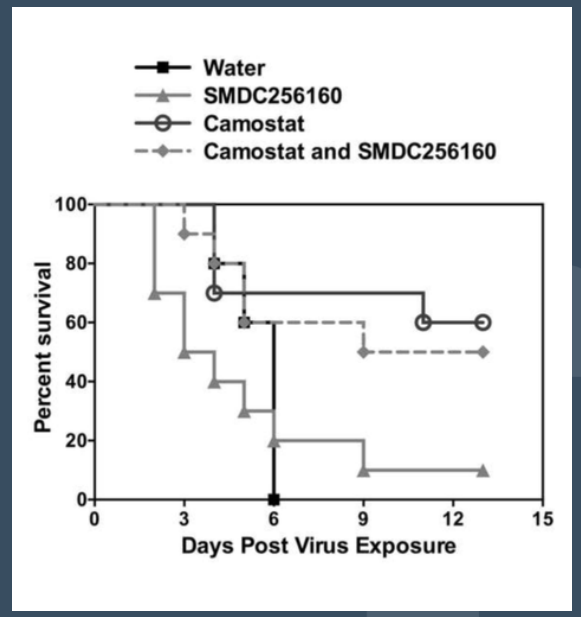
Camostat

- Coronavirus known to require activity of the cellular protease **TMPRSS2** for entry, camostat blocks it
- Inhibits SARS-CoV-2 cell entry with EC50 = 1000 nM (left, from doi.org/10.1016/j.cell.2020.02.052)
- Also helps prevent death in mice with SARS-CoV-1 (right, Pubmed 25666761)
- Camostat approved in Japan for pancreatitis, off-label use possible already

MERS-CoV SARS-CoV-1 SARS-CoV-2



SARS-CoV-1 in mice



Kaletra, Anti-IL6, Angiotensin Receptor Blockade

Combination of flu and HIV drugs (Kaletra, Lopinavir and Ritonavir) shows promise, but mechanism is unknown as there is nothing like HIV protease in the SARS-CoV-2 genome.

Death is often from cytokine release syndrome (cytokine storm) treatment: once virus replicates to high levels in the lungs, the large release of cytokines cause multi-organ failure

Anti-IL-6 mAb was approved for CRS in COVID-19 by China

AT1R blocker losartan is being tested based on a proposal that it will upregulate the SARS-CoV-2 receptor ACE2, preventing loss of ACE2 function which may be protective against the acute respiratory distress syndrome that is one cause of death by SARS and COVID-19 , This comes from an old hypothesis (2005) that SARS lethality was due to downregulation of ACE2

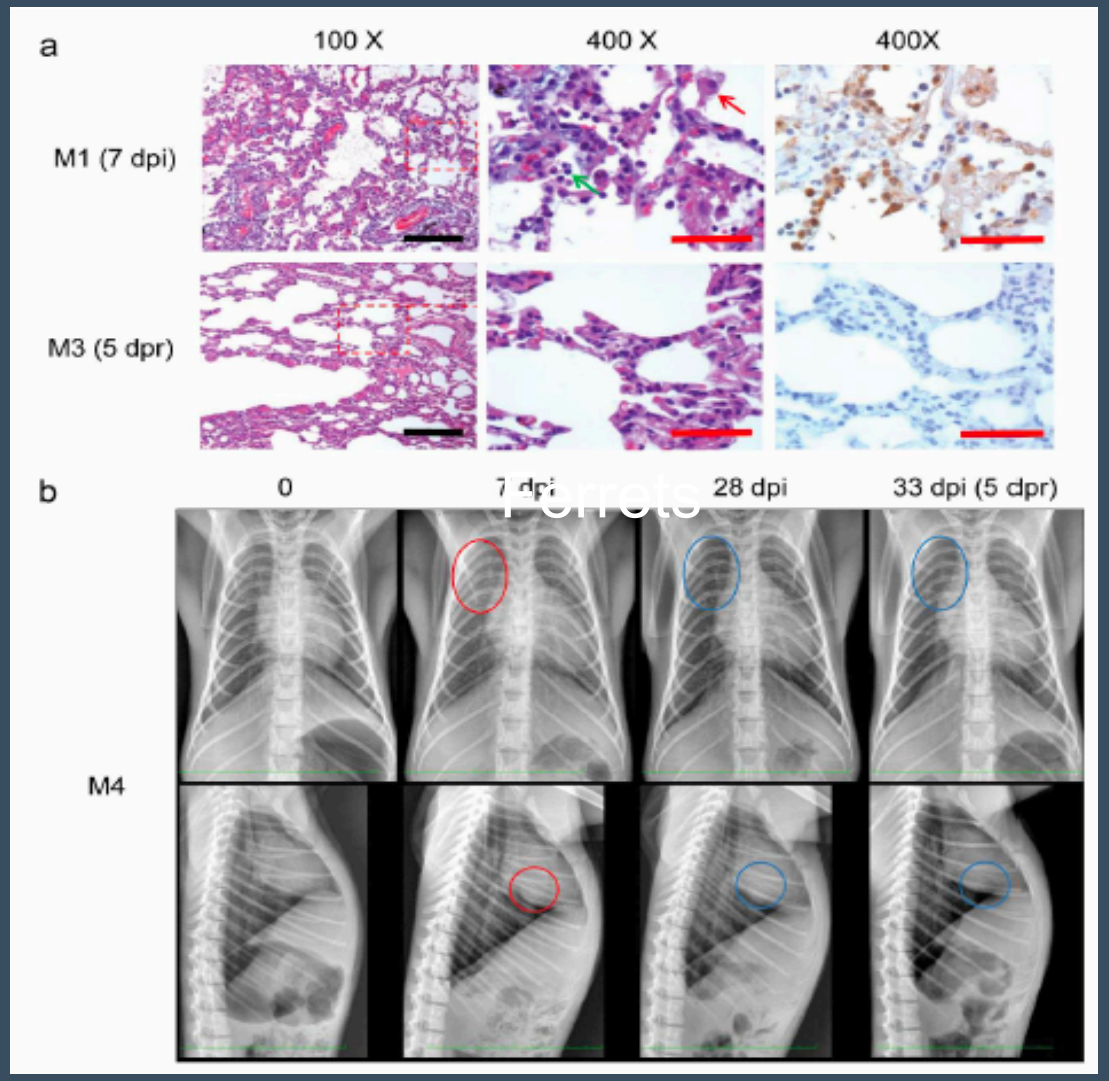
Others have suggested that upregulating the receptor for the virus with losartan might increase susceptibility to the initial infection; this probably is not significant

Using Science to Update Cleveland Clinic Treatment Guidelines

- Patients with cardiac diseases, hypertension, or diabetes, who are treated with Angiotension Converting Enzyme Inhibitors (ACEi), may be at higher risk for severe COVID-19 infection. This may be related to SARS-CoV-2 binding to ACE2 and attenuating residual activity. This skews the ACE/ACE2 balance to a state of predominant ACE/AngII/AT1 axis signaling, in which AngII causes pulmonary vasoconstriction, and inflammatory and oxidative organ damage, progressing towards acute lung injury. This theory is supported by higher serum AngII levels in patients with COVID-19 than in non-infected individuals, and levels linearly associated with viral load and lung injury [Henry et al, BMJ 2020; Lancet Respiratory Med 2020]. There are no guidelines for treatment of COVID-19 patients, but current observational data and pathway analyses in COVID-19 patients, should provide information on whether patients taking Angiotension Receptor Blockade may be associated with better outcomes than patients on ACEi.

- While there is no direct evidence, and only sporadic reports, it has also been suggested that NSAIDs may risk of worsening of disease.

Reinfection Could not Occur in SARS-CoV-2 Infected Rhesus Macaques (or Ferrets)



Vaccines should work!

Bao et al., https://doi.org/10.1101/2020.03.13.990226

New Vaccines: RNA Vaccines are Frontrunners

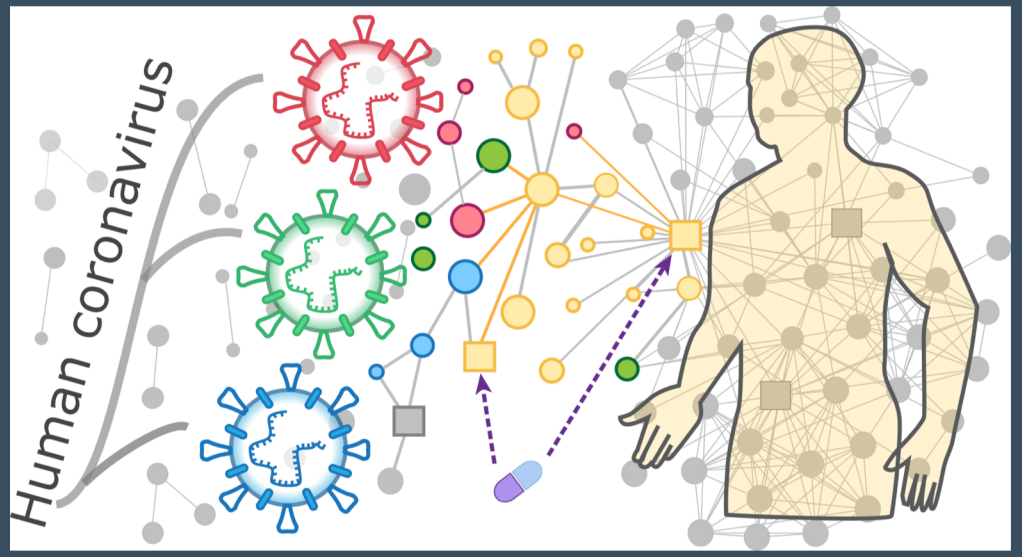
- Phase I clinical trial at Kaiser Permanente Washington Health Research Institute in Seattle
- Four adults (of 45 eventual participants) received first doses of vaccine developed through NIAID and Moderna, a biotech company based in Cambridge, Mass.
- Will test a range of doses; patients will receive first dose and second 28 days later
- Follow up by phone and in person over 14 months, with blood samples to test immune response
- Beginning of a long process to test the drug's safety and efficacy

2019-nCoV Vaccine (mRNA-1273) A Phase 1 clinical trial

ClinicalTrials.gov Identifier: NCT04283461

Big Data Analytics/Screen for Drugs to Treat COVID-19

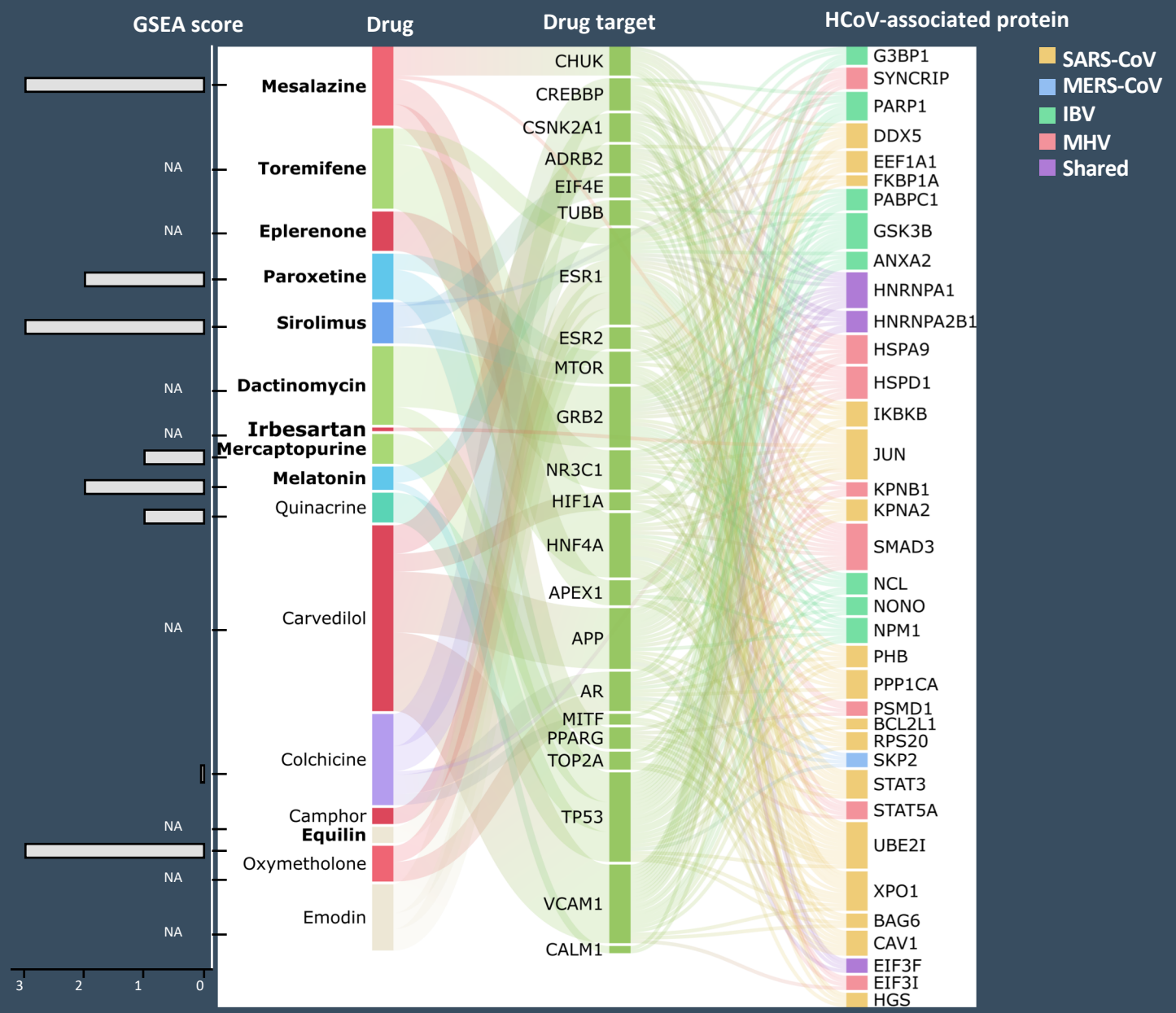
- Traditional antiviral discovery generally targets quickly evolving virus protein
- Computational approach targets interaction between human and virus proteins
- Drug repurposing already approved by the FDA, so we know pharmacokinetic properties and toxicity profiles



Cleveland Clinic has now expedited this work through partnership with Oak Ridge/ IBM supercomputer capabilities.

Targeting virus-host proteins

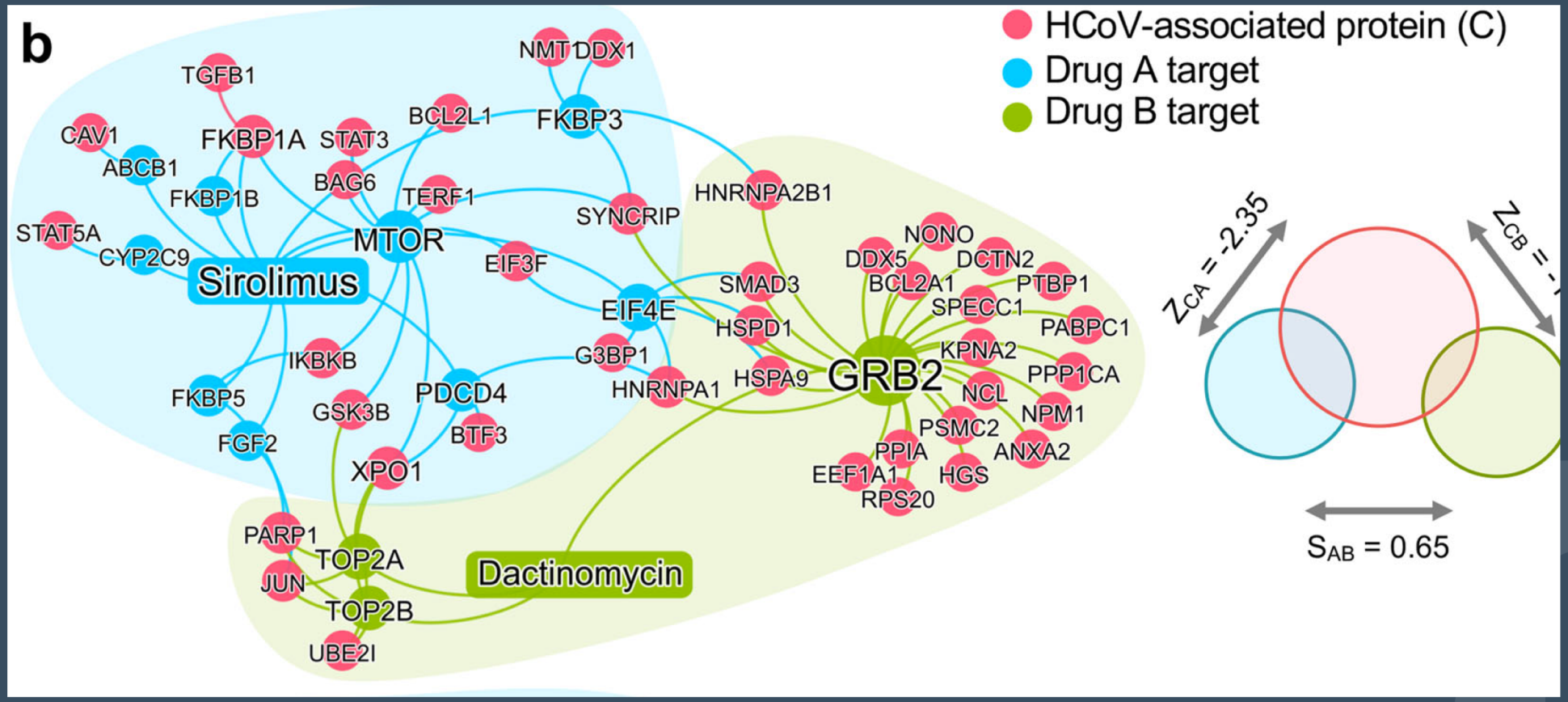
Drug Repurposing for COVID-19



Zhou et al., *Cell Discovery* 2020

Anti-Viral Therapies

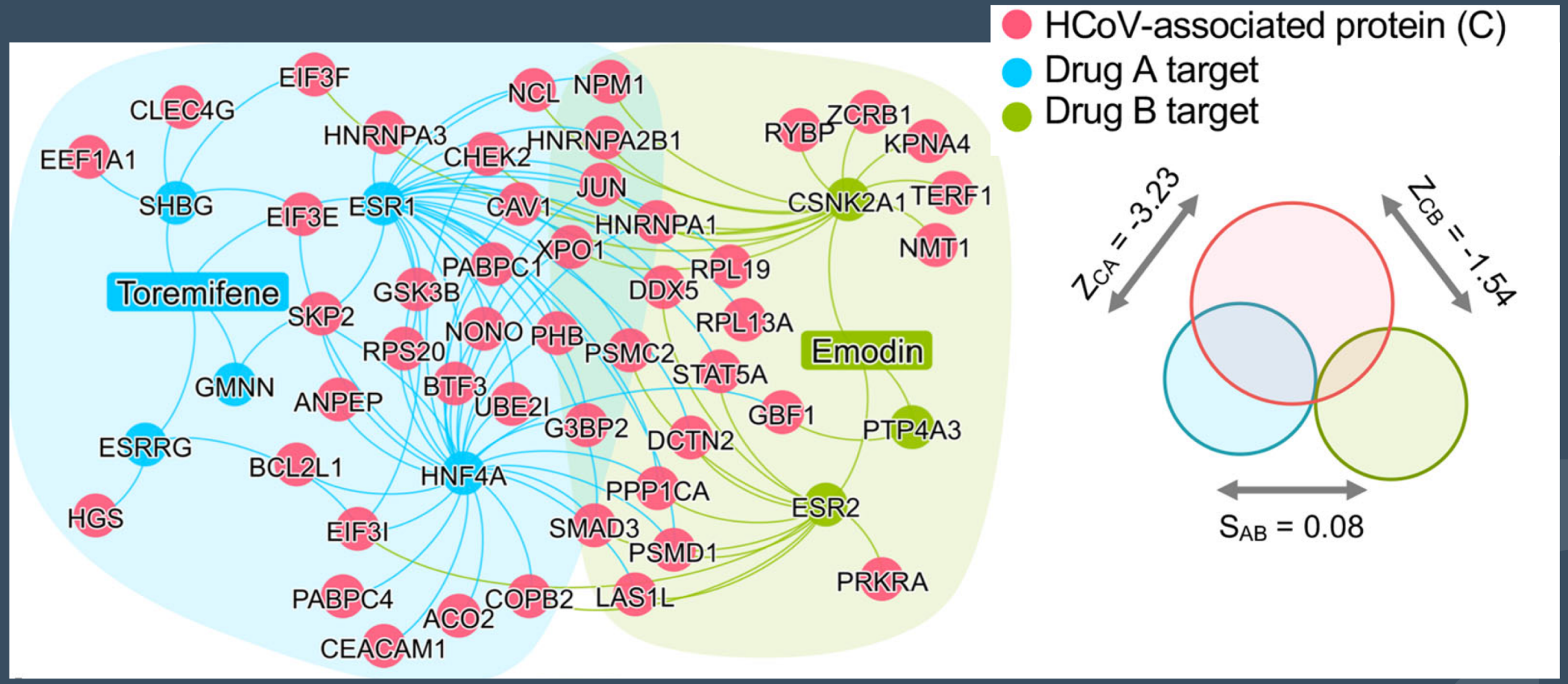
Sirolimus (mTOR inhibitor with both antifungal and antineoplastic properties) + dactinomycin (RNA synthesis inhibitor used in cancer treatments)



Zhou et al., *Cell Discovery* 2020

Anti-Viral Therapies

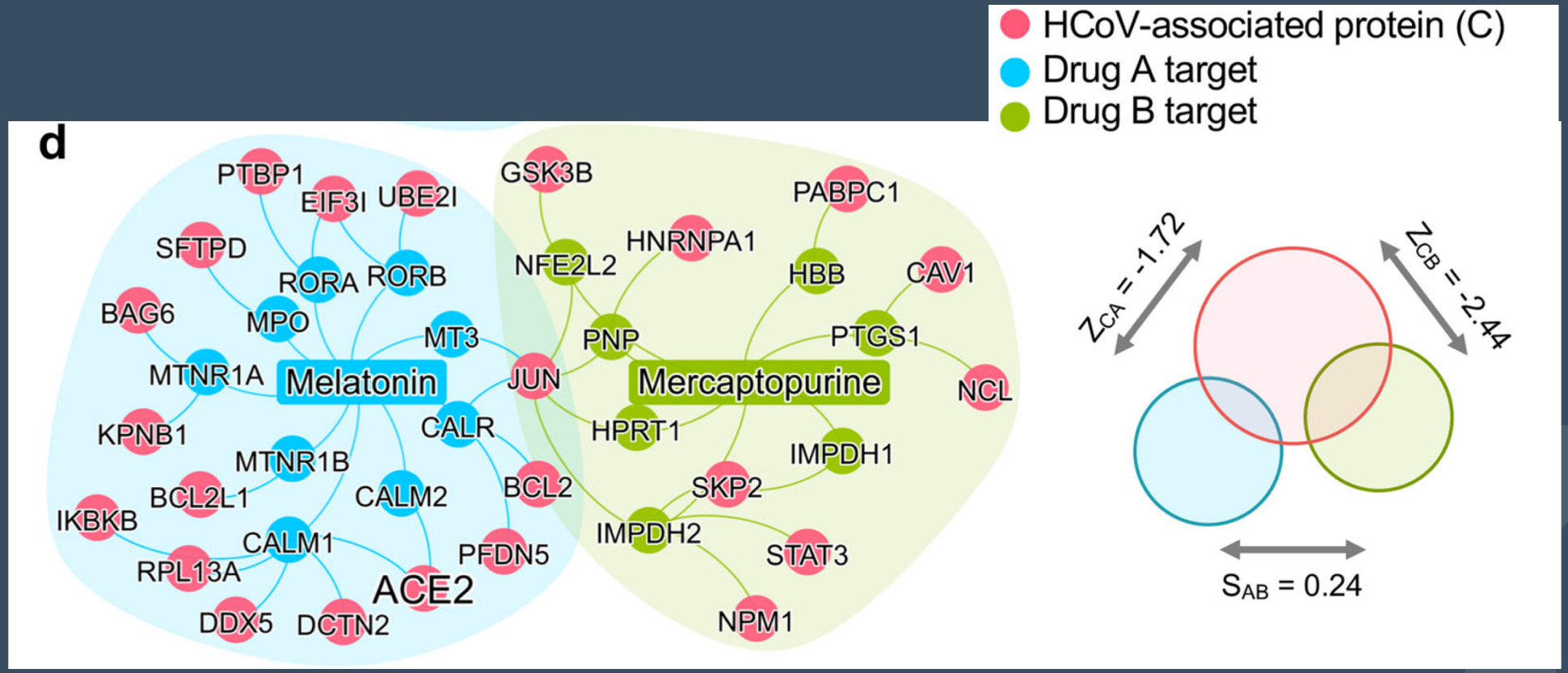
Toremifene (nonsteroidal selective estrogen receptor modulator used in the treatment of metastatic breast cancer) + emodin (anthraquinone reported to have antiviral effects)



Zhou et al., *Cell Discovery* 2020

Anti-Viral Therapies

Mercaptopurine (selective inhibitor of SARS-CoV and MERS-CoV targets papain-like protease) + melatonin (biogenic amine indirectly regulates ACE2 expression)



Zhou et al., *Cell Discovery* 2020

What Are We Doing in Lerner?

Feixiong Cheng: Using AI to identify repurposable drugs to treat COVID-19

Robert Silverman: Working with UPenn to investigate how coronaviruses interact with and antagonize the interferon antiviral response

Lara Jehi leading COVID-19 registry through CCBIO-R

Mike Kattan: developing individualized risk prediction models, which will be integrated in and available through EPIC, and also leading comparative effectiveness analyses

Thad Stappenbeck and Jae Jung: will evaluate SARS-mediated cell death vs host pathogenic pathways that can create tissue damage in COVID-19

Christine McDonald and Conni Bergmann will study how immune mediators help to control infection and the specific mechanisms that contribute to viral persistence in mouse CoV.

Nima Sharifi will study the *TMPRSS2,* which is required for coronavirus entry and also known to be regulated by androgen in the prostate (and perhaps in the lungs)

HR & Caregiver Support

- Physical protection
  - Well under control with existing initiatives
- Mental/Emotional support
  - Prevent panic
  - Overcome fear
  - Recalibrate perceptions of risk

Caregiver Support

- In the U.S., 18 deaths on March 16 (worst day on record)
- Also consider:
  - Secondhand smoke kills 112/day
  - automobile accidents, ~ 102/day
  - firearms, ~ 109/day
  - opioid overdoses, ~ 130/day
- Ensure access to psychological support (similar to NASA space program)
- Consider specialized mental health care with assigned support person potentially with daily access
- Ensure front-line people are heard and feel part of the team (not like soldiers sent into the battlefield)

Special Thanks

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Jae Jung
Asha Kallianpur
Mike Kattan
Thad Stappenbeck

Michael Lin (Stanford)

Cleveland Clinic

Every life deserves world class care.