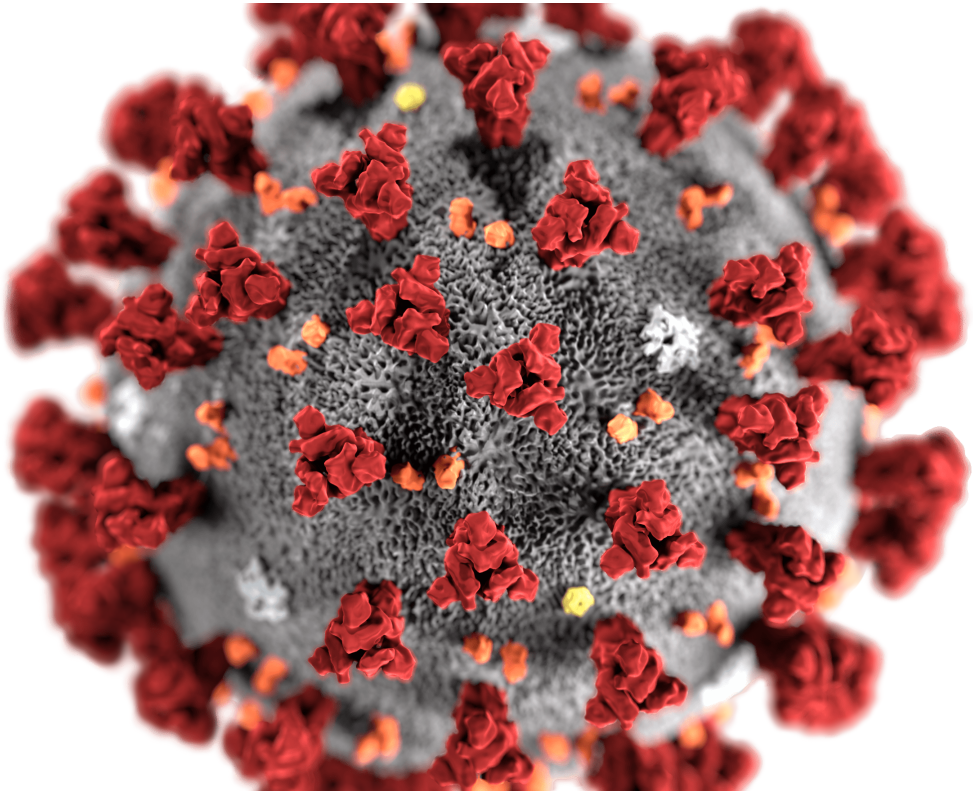
Update on COVID-19 Therapeutics and Vaccines



Barry S. Zingman, MD

Division of Infectious Diseases/AIDS Center

Montefiore/Einstein

Disclosures

Principal Investigator, Montefiore/Einstein; grants to Einstein

- NIH ACTT-1
  - Remdesivir vs placebo
- NIH ACTT-2
  - Remdesivir + baricitinib or placebo
- COVID-19 vaccine trials
  - AstraZeneca/Oxford
  - Janssen/Johnson & Johnson

Investigator, Montefiore/Einstein; grant to Einstein

- NIH ACTT-3
  - Remdesivir + interferon beta or placebo

Disclosures

Discussion of experimental treatments and vaccines vs COVID-19

Discussion of off-label use and non-FDA-approved drugs vs COVID-19

Please excuse if your favorite study or product not listed

I've no doubt missed some trial results or updates

2020 Words of the Year in COVID Therapeutics and Vaccines

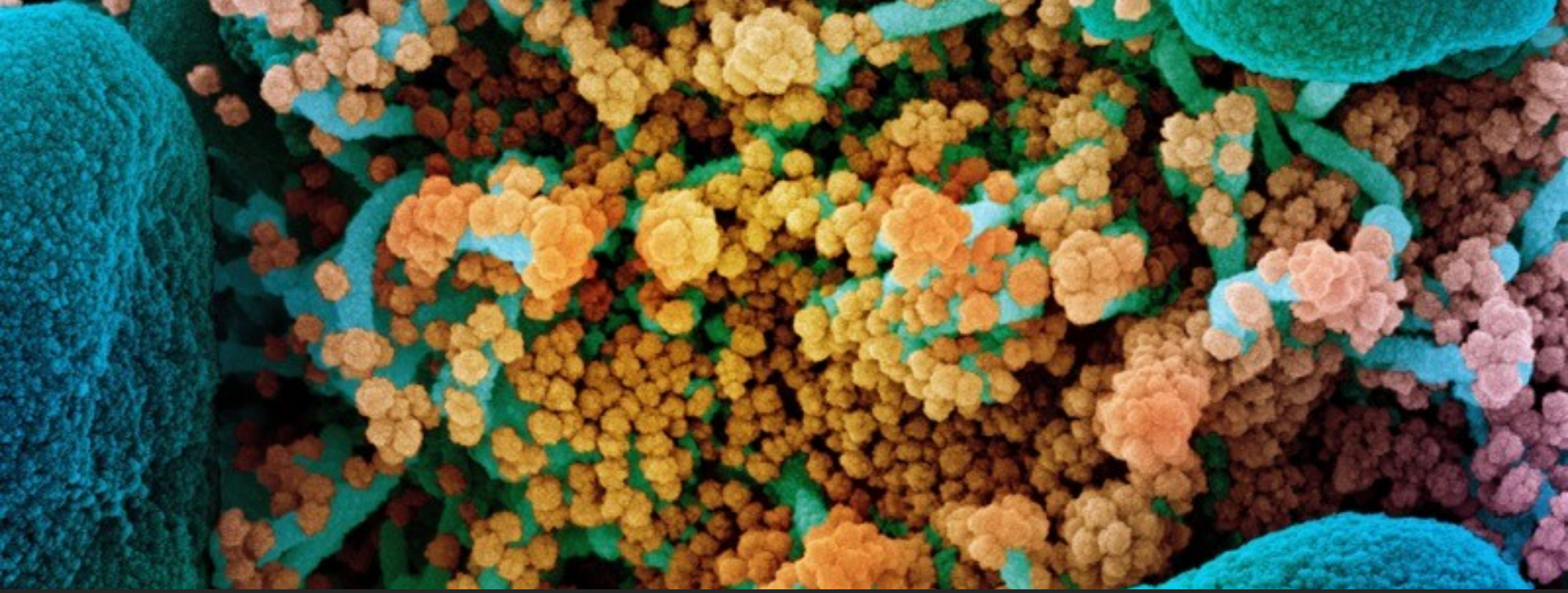
Repurposing

Pre-Prints

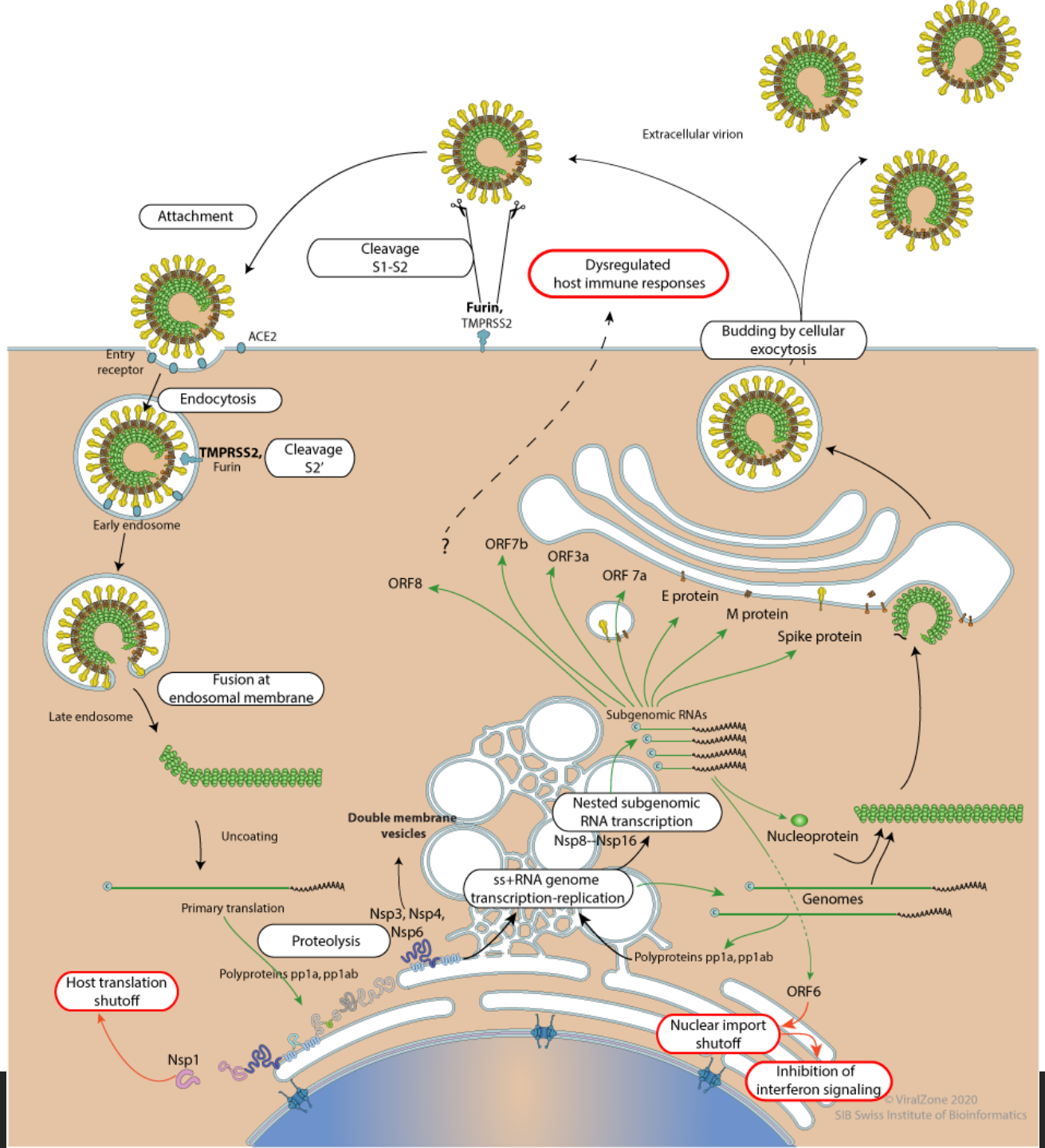
Warp Speed

Overview

1. Antivirals
2. Host Targeted/Immune Modulators
3. Mixed Mechanism
4. Symptomatic/Supportive
5. Vaccines



Antivirals


Extracellular virion
Attachment
Cleavage S1-S2
Furin, TMPRSS2
Dysregulated host immune responses
Budding by cellular exocytosis
ACE2
Entry receptor
Endocytosis
TMPRSS2, Furin
Cleavage S2'
Early endosome
?
ORF7b
ORF3a
ORF 7a
E protein
M protein
Spike protein
ORF8
Fusion at endosomal membrane
Late endosome
Subgenomic RNAs
Nested subgenomic RNA transcription
Nsp8--Nsp16
Nucleoprotein
Double membrane vesicles
Uncoating
ss+RNA genome transcription-replication
Genomes
Primary translation
Nsp3, Nsp4, Nsp6
Proteolysis
Polyproteins pp1a, pp1ab
Polyproteins pp1a, pp1ab
Host translation shutoff
ORF6
Nuclear import shutoff
Nsp1
Inhibition of interferon signaling
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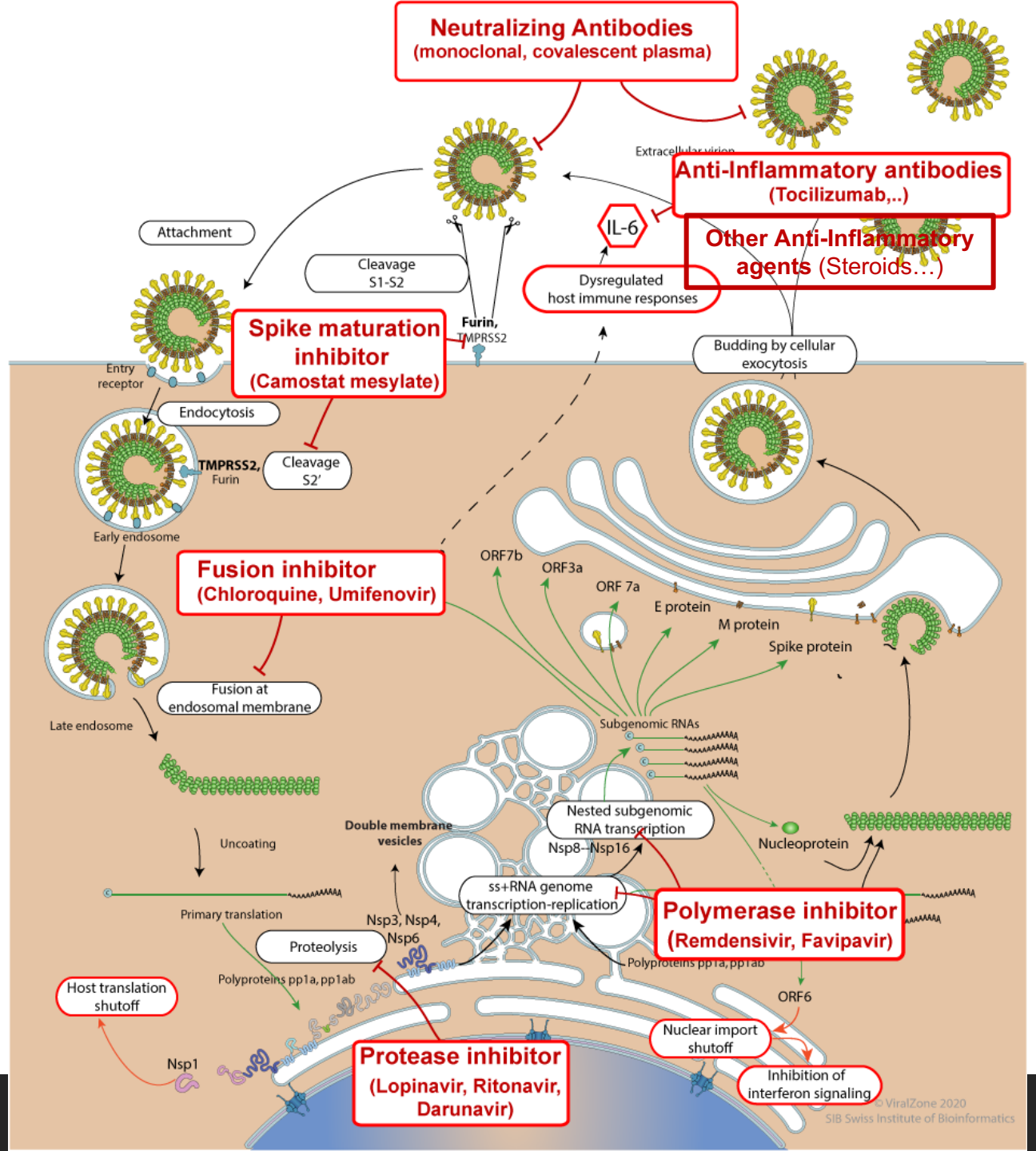
SIB Swiss Institute of Bioinformatics


Neutralizing Antibodies
(monoclonal, covalescent plasma)
Extracellular virion
Anti-Inflammatory antibodies
(Tocilizumab,..)
IL-6
Other Anti-Inflammatory agents (Steroids…)
Dysregulated host immune responses
Attachment
Cleavage S1-S2
Furin, TMPRSS2
Spike maturation inhibitor
(Camostat mesylate)
Entry receptor
Endocytosis
TMPRSS2, Furin
Cleavage S2'
Early endosome
Budding by cellular exocytosis
Fusion inhibitor
(Chloroquine, Umifenovir)
ORF7b
ORF3a
ORF 7a
E protein
M protein
Spike protein
Fusion at endosomal membrane
Late endosome
Subgenomic RNAs
Nested subgenomic RNA transcription
Nsp8--Nsp16
Nucleoprotein
Double membrane vesicles
Uncoating
ss+RNA genome transcription-replication
Polymerase inhibitor
(Remdensivir, Favipavir)
Primary translation
Nsp3, Nsp4, Nsp6
Proteolysis
Polyproteins pp1a, pp1ab
Host translation shutoff
ORF6
Nuclear import shutoff
Nsp1
Protease inhibitor
(Lopinavir, Ritonavir, Darunavir)
Inhibition of interferon signaling
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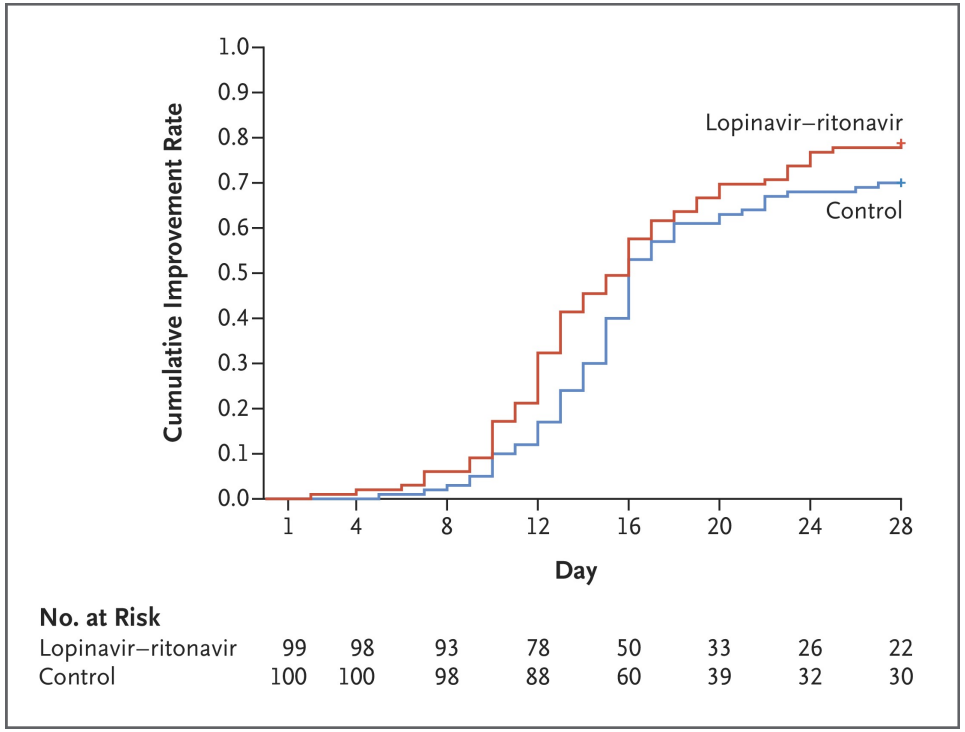
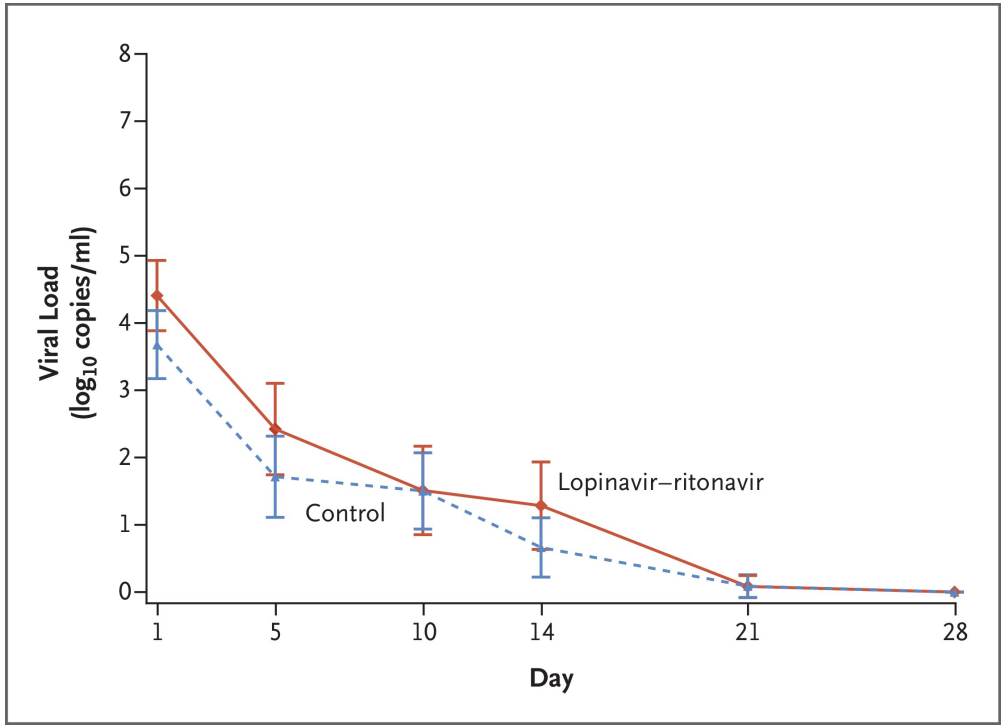
Lopinavir/ritonavir





No benefit: time to improvement or PCR- in hospitalized adults with severe COVID-19

Cao et al, NEJM 2020 DOI: 10.1056/NEJMoa2001282

Chloroquine/Hydroxychloroquine

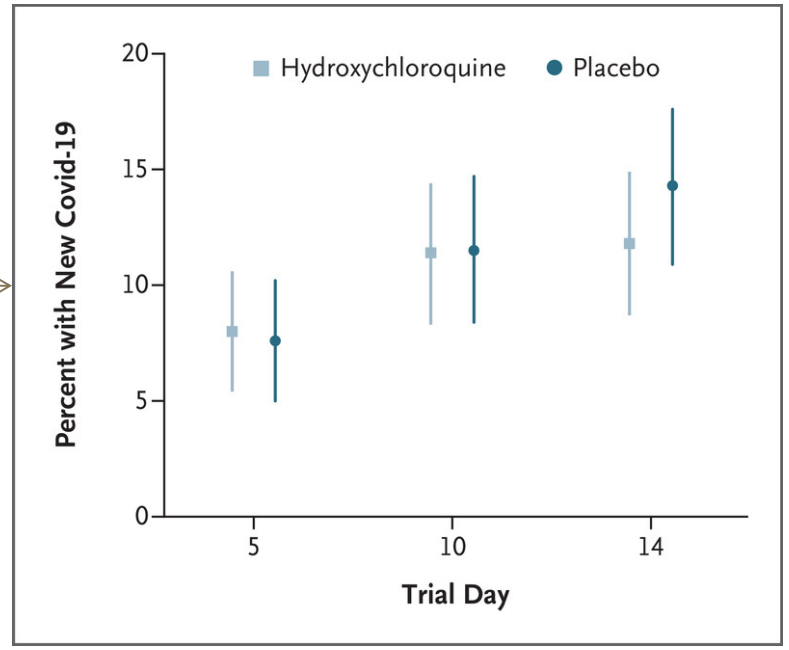
Uncontrolled, observational studies showed no benefit, possible harm in hospitalized patients *(Borba; Huang, Magagnoli; Tang; Mahevas; Geleris)*

- QT prolongation, arrhythmias, mortality, mortality with higher dosing and especially with azithromycin

RCTs showed no benefit

- **HCQ Post Exposure:** No benefit *(Boulware et al NEJM)*
- **HCQ, SOLIDARITY, WHO, inpatients:** stopped 6/2020
- **HCQ, RECOVERY, Europe, inpatients:** stopped 6/2020
- **HCQ, PETAL ORCHID trial, inpatients:** stopped 6/2020

FDA revoked emergency use authorization 6/15/2020



Borba et al, *JAMA Netw Open*. 2020;3(4):e208857; Huang et al, *J Mol Cell Biol*. 2020; Magagnoli et al, *medRxiv*. 2020. [Preprint]; Tang et al, *medRxiv*. 2020. [Preprint]; Mahevas et al, *medRxiv*. 2020. [Preprint]; Geleris et al, NEJM 2020, DOI: 10.1056/NEJMoa2012410; Boulware et al, NEJM 2020 June 3, DOI: 10.1056/NEJMoa2016638;

Hydroxychloroquine +/- Azithromycin

In progress

- **RCT, HERO-HCQ, HCW Pre-Exposure Prophylaxis:** HCQ, n=15,000
  - Poorly enrolled
  - Primarily a longitudinal study of COVID-19 in HCWs
- **RCT, outpatients; ACTG A5395;** 4-arms
  - HCQ/placebo x 7 days and Azithro/placebo x 5 days
  - Opened May, stopped June: 20 enrollees

Famotidine

Retrospective Chinese data

Molecular modeling suggesting drug may block papain-like protease in SARS-CoV-2

Northwell RCT opened 4/7; n=1170

- Hydroxychloroquine vs Hydroxychloroquine plus famotidine IV
- Study on indefinite hold: low enrollment
- Controversy: US review/funding, scientific merits

Ivermectin

In vitro and/or *in vivo* activity vs dengue, West Nile, flu, Zika

Potent inhibitor of SARS-CoV-2 *in vitro* (*Caly et al Antiviral Res 2020*)

Activity believed due to interruption of integrase and importin α/β1 heterodimer for nuclear import

PK/PD poor in relation to EC50 levels needed

Positive observational studies

33 trials listed incl RCTs internationally, U Kentucky

Most US studies have stopped; unreported data to date

Ivermectin + Doxycycline

Used in lower resourced areas; little evidence; inexpensive

Ivermectin + Doxycycline + Zinc: the “Australian Triple Therapy”

Favipiravir

Inhibits RNA-dependent RNA polymerase

- *Approved for influenza in Asia; small benefits*
- *Mutagen, potential teratogen*

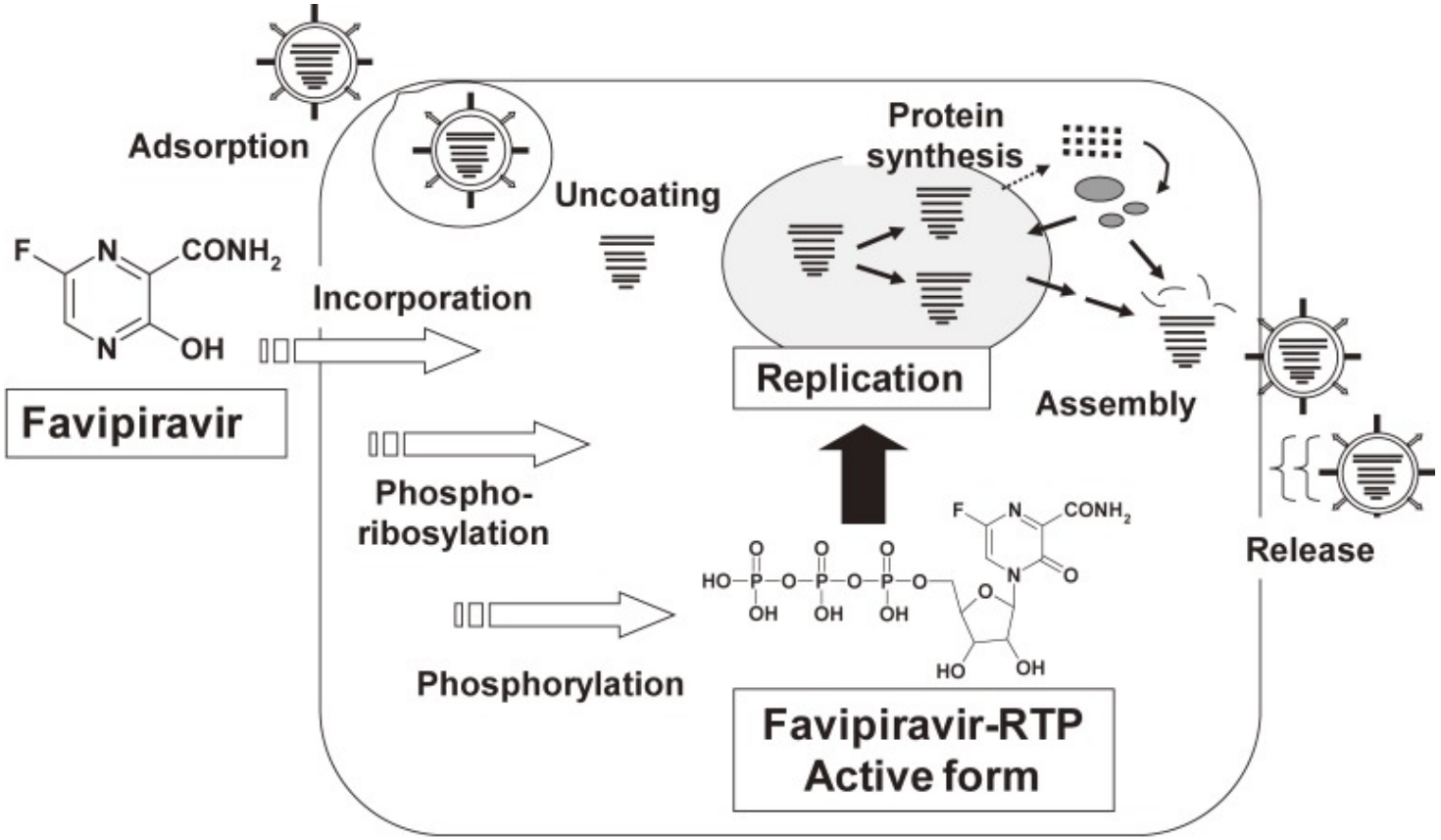
Small favorable observational studies in COVID-19

anorexia, diarrhea, increased uric acid, leukopenia

Approved for COVID-19 in Russia, China and India

Open-label, randomized, FVP+SOC vs SOC

- Mild disease: Stanford
- Moderate-severe, hospitalized pts: 8 US sites incl. B & W, MGH, UMass, Houston Methodist



Wang 2020 Cell Research https://doi.org/10.1038/s41422-020-0282-0

Favipiravir

Russian multicenter, open-label, randomized study of favipiravir vs standard of care

- 2 dosing groups of favipiravir vs SOC

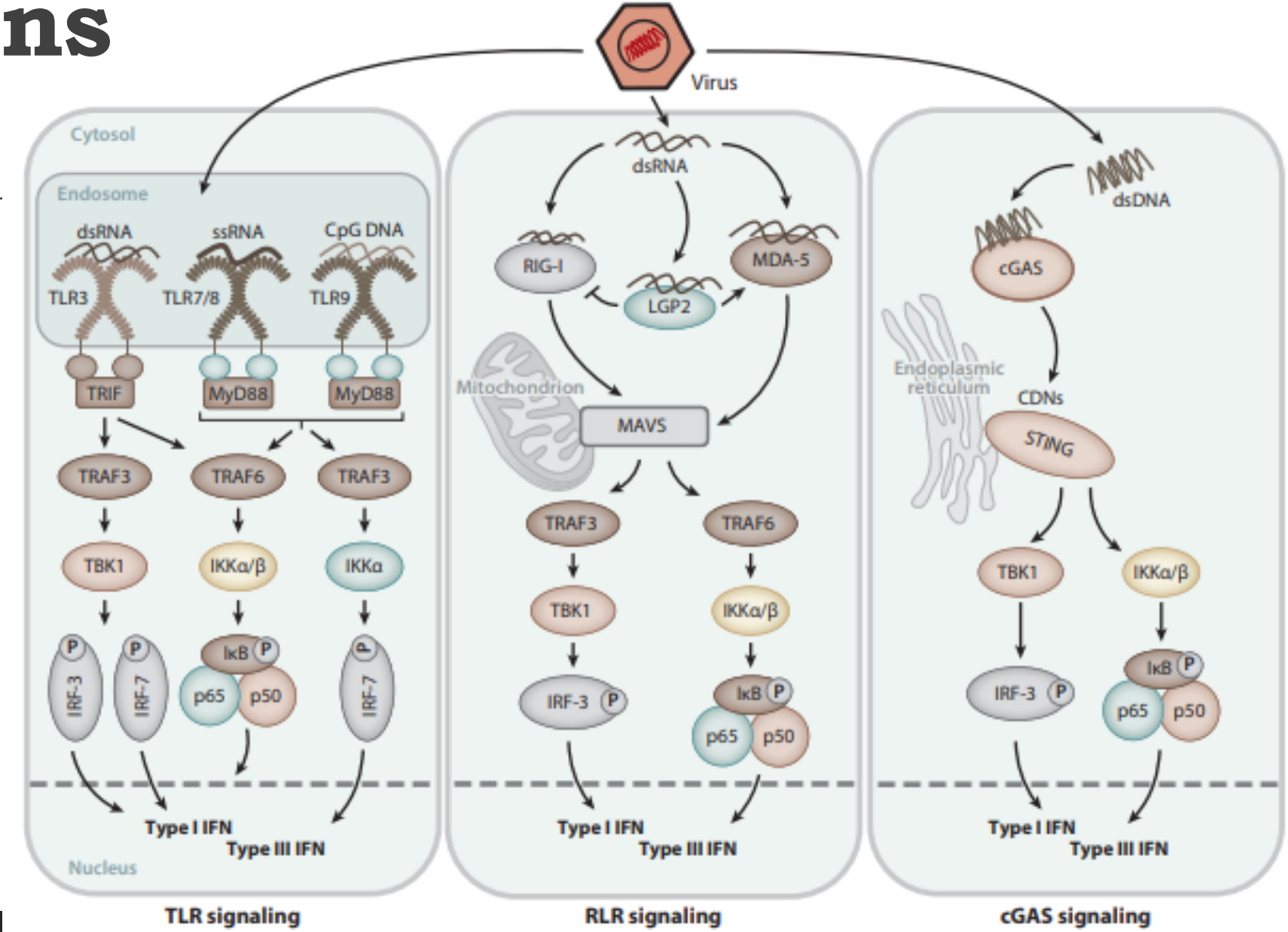
Pre-print 7/2020 Ivashchenko et al

- Early pilot data
- Significantly improved time to viral clearance, fever resolution
- Study ongoing

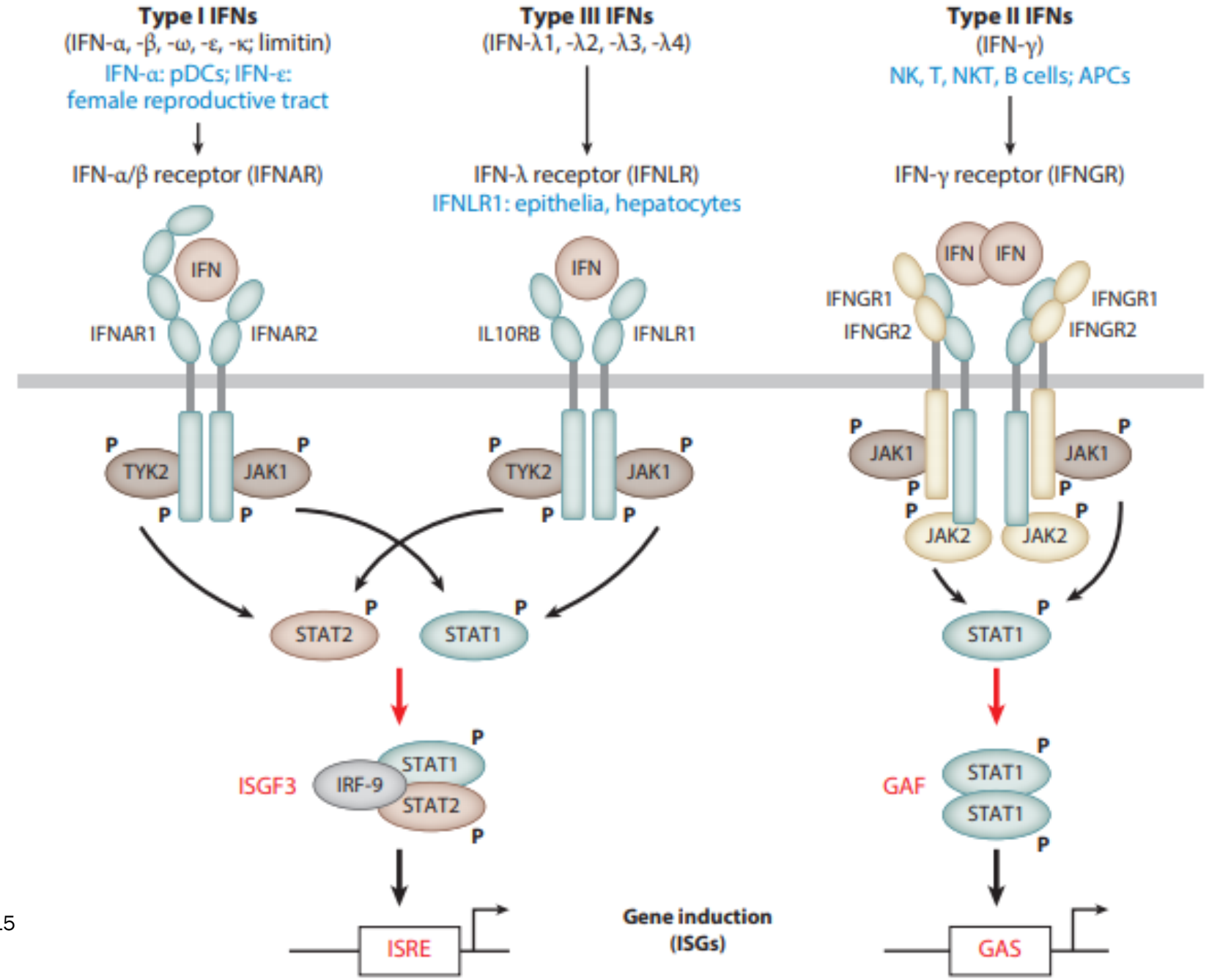
Interferons

A primary defense against a wide range of viruses

Viral infection triggers induction of IFN-β and IFN Stimulated Genes (ISGs)



Fensterl et al, Annu. Rev. Virol. 2015



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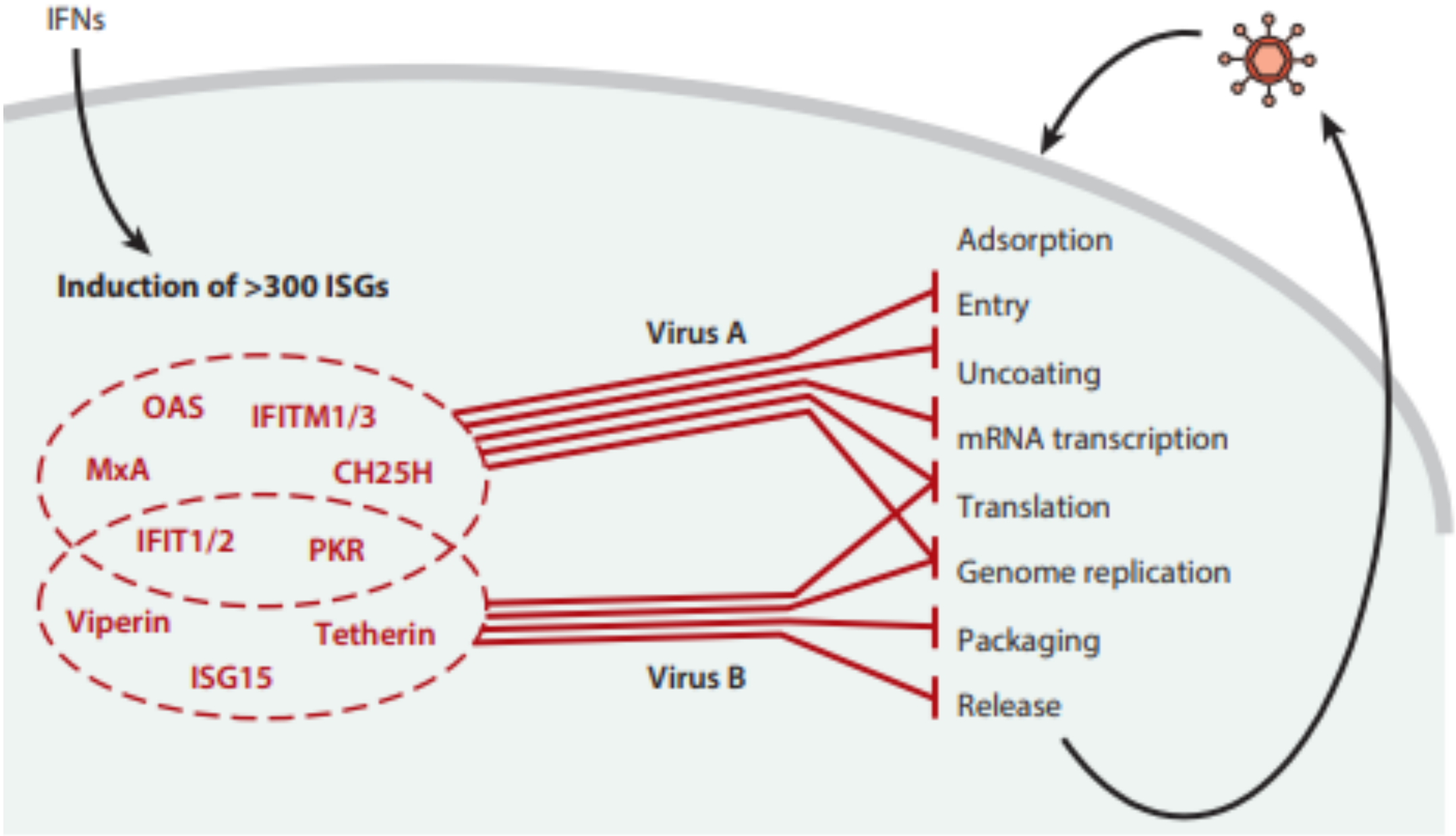
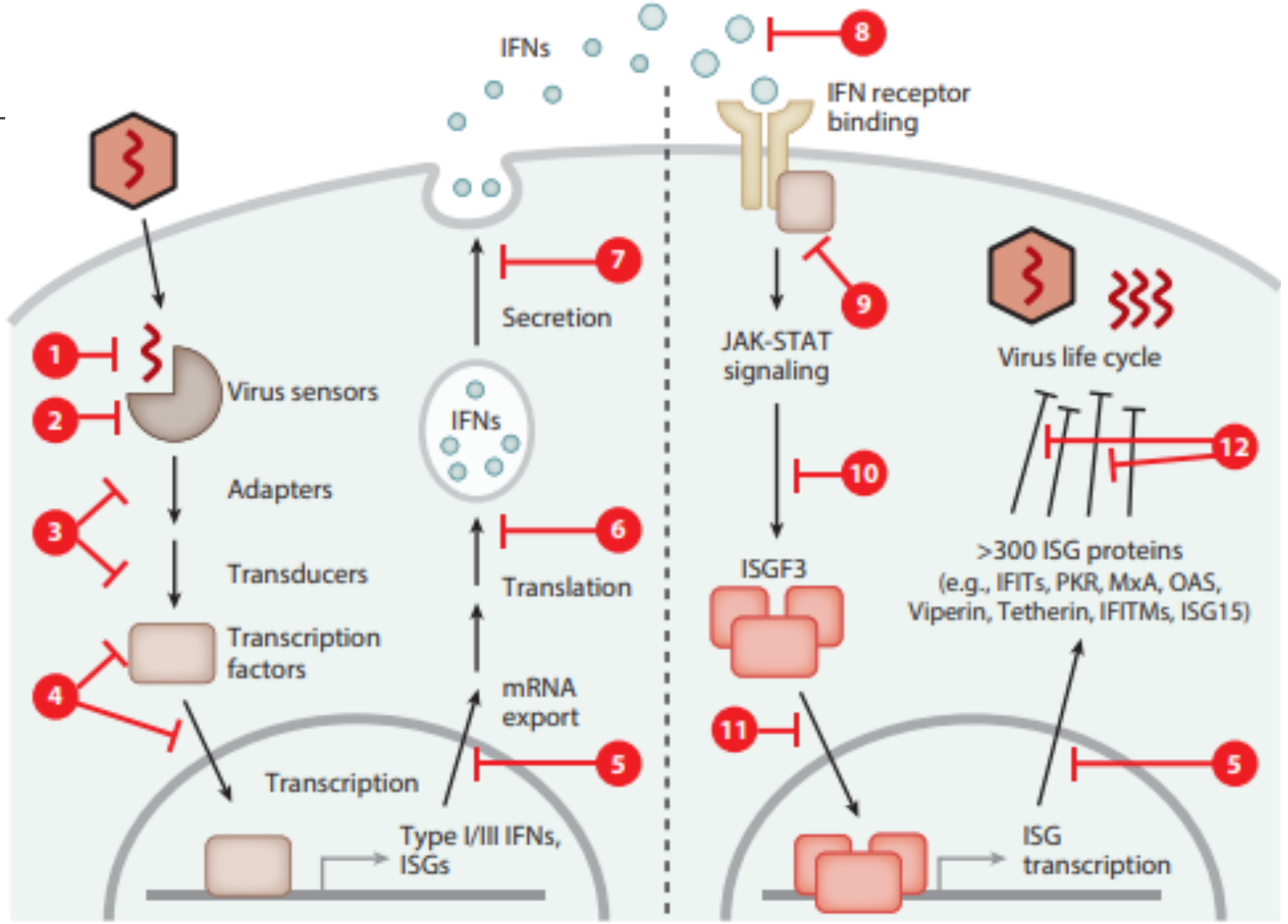


Fensterl et al, Annu. Rev. Virol. 2015

Viral Antagonism of Interferon System

Many viruses evade interferon defenses

Interferon production in response to SARS-CoV-2 infection appears to be low



Fensterl et al, Annu. Rev. Virol. 2015

Therapeutic use of Interferons

SARS: interferon beta>alpha in clinical activity

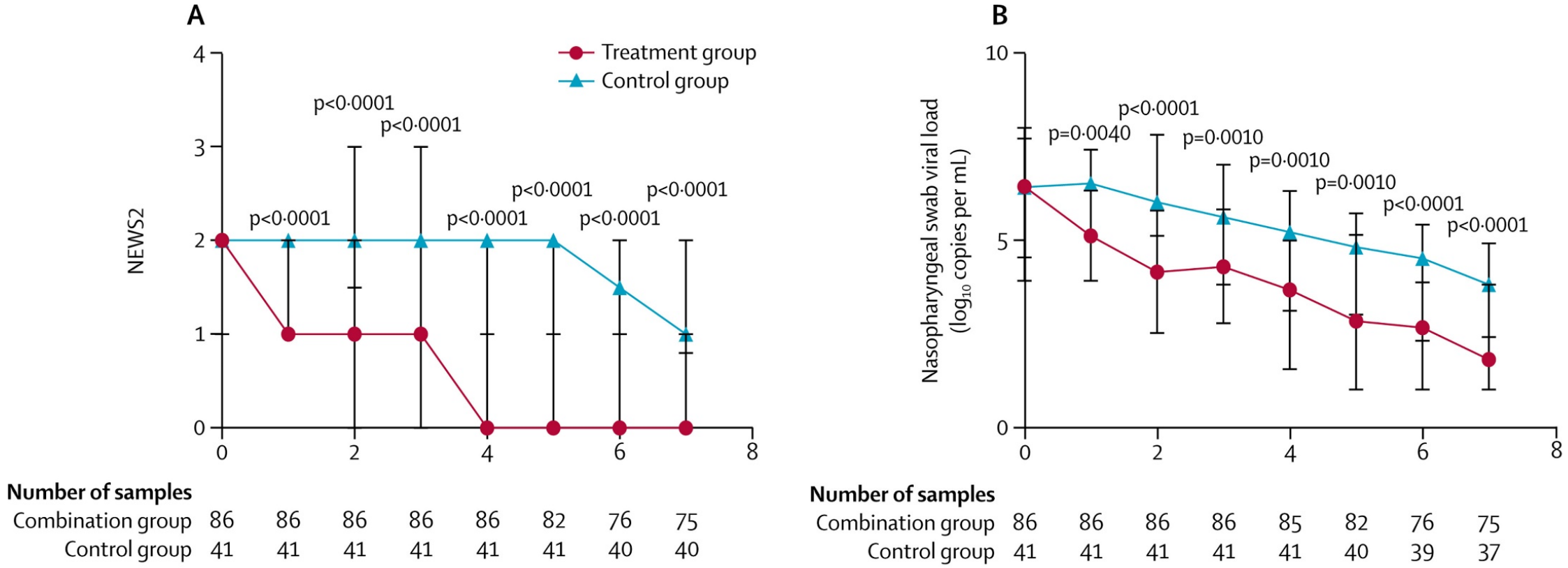
MERS: no benefit of interferon alpha

SARS-CoV-2: interferon beta more potent than alpha

COVID-19: ongoing use of/studies of alpha, beta 1-a, beta 1-b

Interferon beta-1b, lopinavir–ritonavir, and ribavirin in admitted patients: open-label, randomized, phase 2 trial

Hung, The Lancet DOI: 10.1016/S0140-6736(20)31042-4



**Limitations: Open label, small n, not ill or treated elsewhere, poorly controlled

Inhaled Interferon SNG001

UK double-blind, placebo-controlled RCT

COVID respiratory illness, not mechanically ventilated

Hospitalized (n=100) or at home (n=120)

Press Release 7/2020, hospitalized cohort

- Progression to ventilation or death reduced 79% (OR 0.21 [95% CI 0.04-0.97; p=0.046)
- Improved time to recovery at diff oxygen levels, improved time to d/c

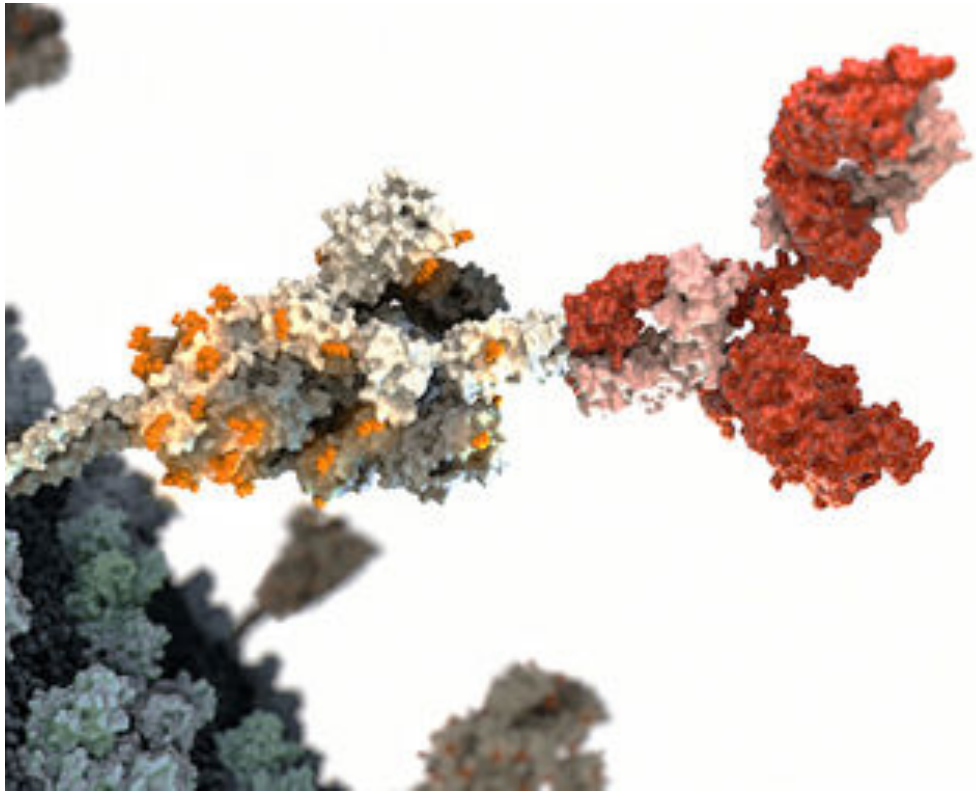
https://www.globenewswire.com/news-release/2020/07/20/2064154/0/en/Synairgen-announces-positive-results-from-trial-of-SNG001-in-hospitalised-COVID-19-patients.html

Antivirals
Antibody Therapies

Hyperimmune globulin

Monoclonal antibodies to SARS-CoV-2 spike protein *(single or combo) (Lilly, Regeneron, AstraZeneca, others)*

- ACTIV-2: outpatients; ACTG
- ACTIV-3: inpatients; PETAL network



ALTOUNIAN/*SCIENCE*; (IMAGES) W. SURYA, *BIOCHIM. BIOPHYS. ACTA* (2018); D. WRAPP, *SCIENCE*, (2020); E.O. SAPHIRE, *SCIENCE*, (2001); ORIENTATIONS OF PROTEINS IN MEMBRANES DATABASE

Clinical Trials of Coronavirus Drugs Are Taking Longer Than Expected

Antibody trials sponsored by Regeneron and Eli Lilly are off to a slow start because of a dearth of tests, overwhelmed hospitals and reluctant patients.

NY Times
August 14, 2020

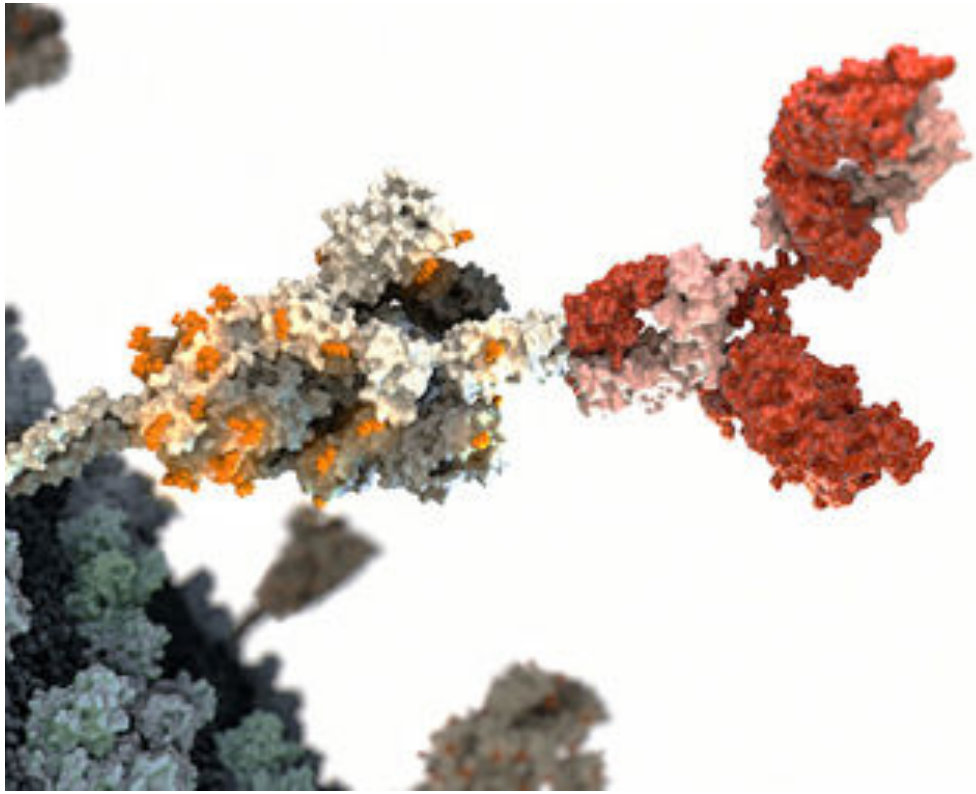
"… testing delays, staffing shortages, space constraints and reluctant patients …"

https://www.nytimes.com/2020/08/14/health/covid-19-antibody-treatments.html?action=click&module=Top%20Stories&pgtype=Homepage

Other Experimental Antivirals

EIDD-2801 (*Sheahan, Sci Trans Med 2020*)

- Oral, broad spectrum, potent, cytidine nucleoside analog prodrug
- Excellent *in vitro* and/or *in vivo* activity vs SARS-CoV-2, SARS-CoV-1, MERS; also active vs flu, chikungunya, Ebola, EEE
- Outpatient and inpatient studies 2020



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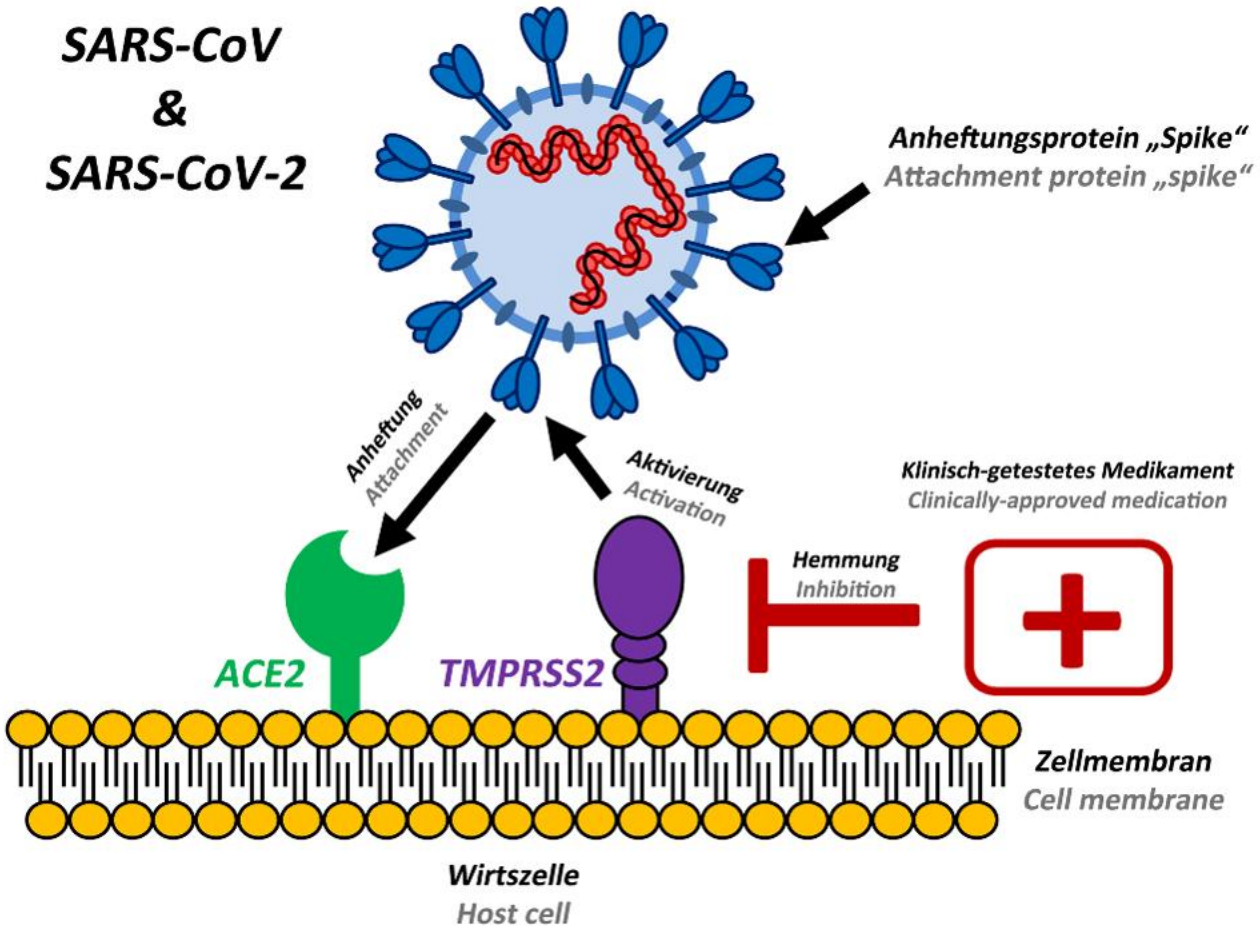
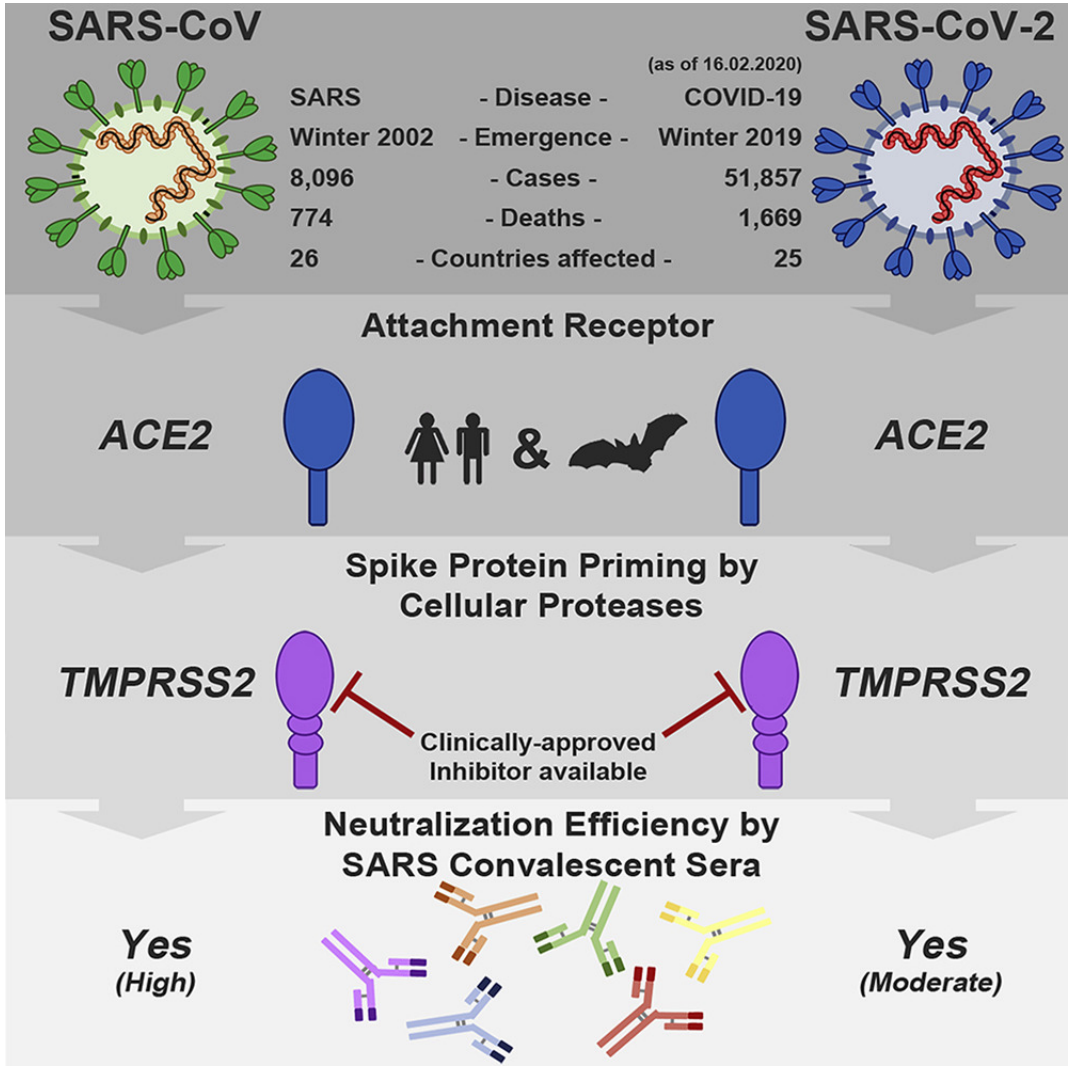




The spike protein of SARS-CoV and SARS-CoV-2 is activated by the protease TMPRSS2 before it binds to the ACE2 receptor.
MARKUS HOFFMANN / GERMAN PRIMATE CENTRE

Cell 2020 181271-280.e8DOI: (10.1016/j.cell.2020.02.052)

TMPRSS2 Protease Inhibitors

Prevent fusion of SARS-CoV-2 envelope with TMPRSS2

Camostat

Low EC50 vs pathogenic coronaviruses

Potential antiviral and anticoagulant activity

Approved in Japan: chronic pancreatitis and postop reflux esophagitis; well-tolerated

Oral, TID-QID, short $T_{1/2}$

5 ongoing trials (incl Kentucky, Yale): hospitalized or outpatients, usually combination

Nafamostat

Generally 1-2 log lower EC50 than Camostat vs SARS

Potential antiviral and anticoagulant activity

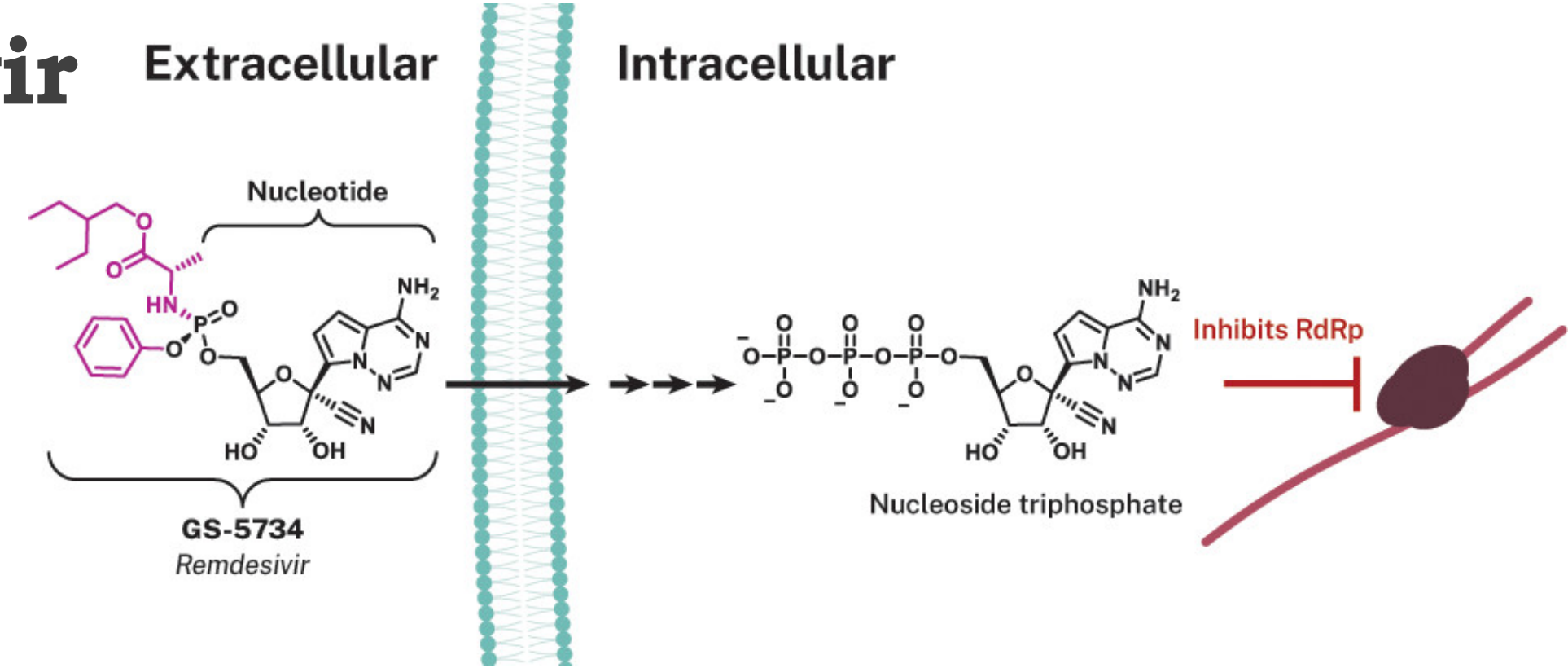
Approved for chronic pancreatitis; well-tolerated

IV only by continuous infusion, very short $T_{1/2}$

Ongoing RCT vs SOC: hospitalized, severe, Italy, Japan, Zurich

Zhou 2015 Antiviral Res 116:76; https://www.ncbi.nlm.nih.gov/pmc/articles/pmid/31412955/; TMPRSS-2 and coronaviruses: Totura, Allison L., and Sina Bavari. “Broad-Spectrum Coronavirus Antiviral Drug Discovery.” Expert Opinion on Drug Discovery 14, no. 4 (April 3, 2019): 397–412. https://doi.org/10.1080/17460441.2019.1581171. Hoffman 2020 Cell DOI:https://doi.org/10.1016/j.cell.2020.02.052

Remdesivir (GS-5734)



Prodrug of broad-spectrum adenosine nucleoside analog

Inhibits RNA-dependent RNA polymerase activity among RNA viruses including pathogenic coronaviruses (1-5).

A trial in rhesus macaques infected with SARS-CoV-2 found that remdesivir was effective in reducing clinical disease and damage to lungs (6).

1. Brown AJ, Antiviral Res. 2019; 2. Sheahan TP, Nat Commun. 2020.; 3. Agostini ML, mBio. 2018; 4. de Wit E, Proc Natl Acad Sci USA. 2013; 5. de Wit E, Proc Natl Acad Sci USA. 2020; 6. Williamson BN, bioRxIV. 2020. DOI: https://doi.org/10.1101/2020.04.15.043166

ORIGINAL ARTICLE

Remdesivir for the Treatment of Covid-19 — Preliminary Report

John H. Beigel, M.D., Kay M. Tomashek, M.D., M.P.H., Lori E. Dodd, Ph.D., Aneesh K. Mehta, M.D., Barry S. Zingman, M.D., Andre C. Kalil, M.D., M.P.H., Elizabeth Hohmann, M.D., Helen Y. Chu, M.D., M.P.H., Annie Luetkemeyer, M.D., Susan Kline, M.D., M.P.H., Diego Lopez de Castilla, M.D., M.P.H., Robert W. Finberg, M.D., et al., for the ACTT-1 Study Group Members*

May 22, 2020
DOI: 10.1056/NEJMoa2007764

Randomized, double-blind, placebo-controlled study of remdesivir; 1:1

200 mg IV load x 1, then 100 mg IV q24H x up to 10 days total while hospitalized; or a saline solution

Primary endpoint: time to recovery (score 1-3) on 8-pt ordinal score

68 sites: US, Asia, Europe, Mexico

- Montefiore/Einstein and NYU/Bellevue

1063 enrolled

NIH Adaptive COVID-19 Treatment Trial (ACTT-1): Primary Endpoint/Scoring

Day of recovery: the first day at one of the last three categories from ordinal scale, to Day 29

- Death (8)
- Hospitalized, on invasive mechanical ventilation or ECMO (7)
- Hospitalized, on non-invasive ventilation or high flow O_2 devices (6)
- Hospitalized, requiring supplemental O_2 (5)
- Hospitalized, not requiring O_2 - requiring ongoing medical care (4)
- Hospitalized, not requiring O_2 - no longer requires ongoing medical care (3)
- Not hospitalized, limitation on activities and/or requiring home O_2 (2)
- Not hospitalized, no limitations on activities (1)

Ordinal 4 includes: ¾ **mild/moderate** dz (SpO2 >94% on RA & RR <16) + ¼ **severe** dz (SpO2 ≤94% or RR>16)

ACTT-1 Baseline Demographic and Clinical Characteristics

Score on ordinal scale — no. (%)			
4. Hospitalized, not requiring supplemental oxygen, requiring ongoing medical care (Covid-19–related or otherwise)	127 (11.9)	67 (12.4)	60 (11.5)
5. Hospitalized, requiring supplemental oxygen	421 (39.6)	222 (41.0)	199 (38.1)
6. Hospitalized, receiving noninvasive ventilation or high-flow oxygen devices	197 (18.5)	98 (18.1)	99 (19.0)
7. Hospitalized, receiving invasive mechanical ventilation or ECMO	272 (25.6)	125 (23.1)	147 (28.2)
Baseline score missing	46 (4.3)	29 (5.4)	17 (3.3)

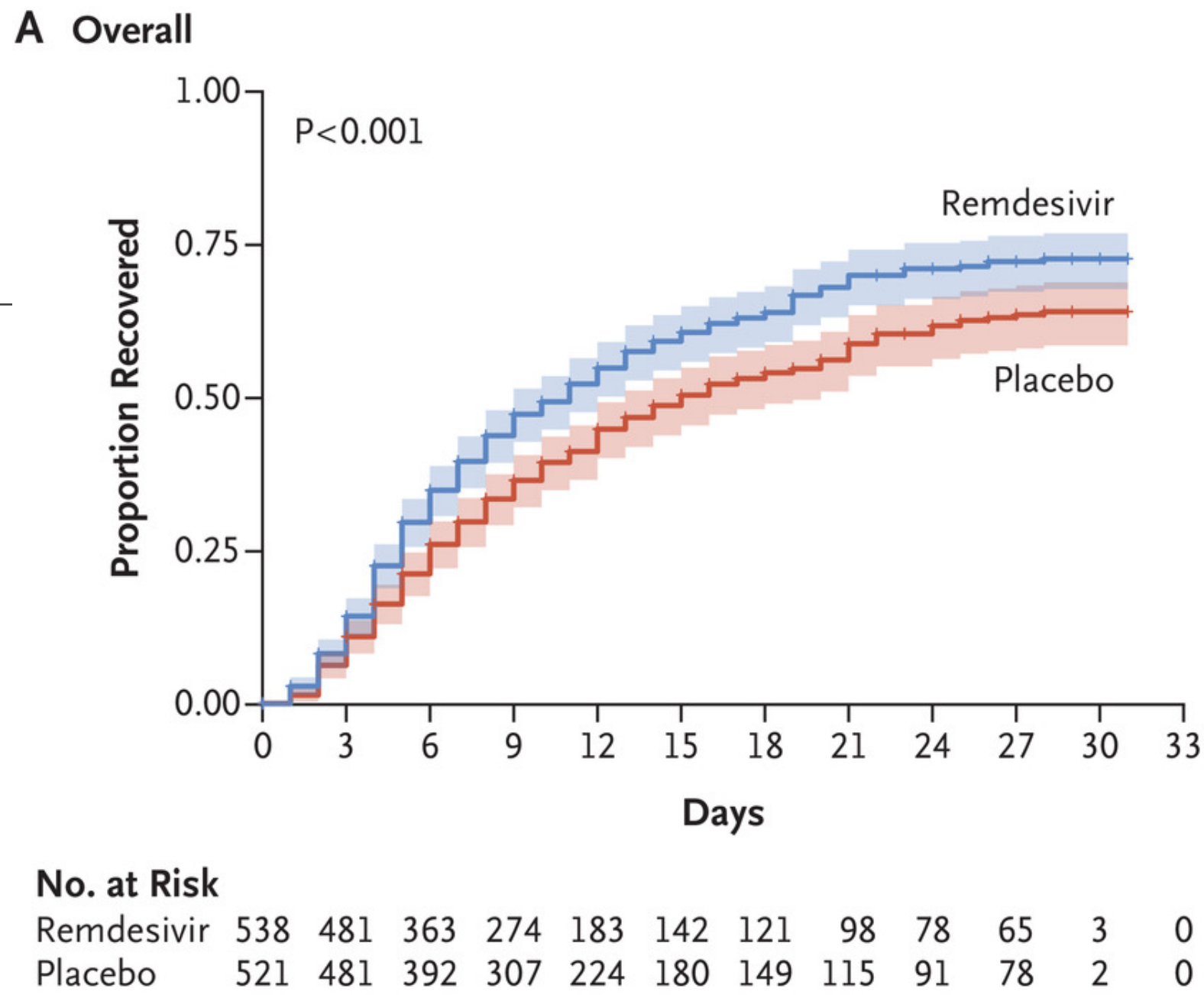
(Beigel et al, NEJM May 22, 2020, DOI: 10.1056/NEJMoa2007764)

Kaplan–Meier Estimates of Cumulative Recoveries

Overall population

Median recovery time

- 11 vs 15 days *(95% CI, 9 to 12) vs (95% CI, 13 to 19)*
- Recovery rate ratio 1.32 (95% CI, 1.12 to 1.55; P<0.001)



(Beigel et al, NEJM May 22, 2020, DOI: 10.1056/NEJMoa2007764)

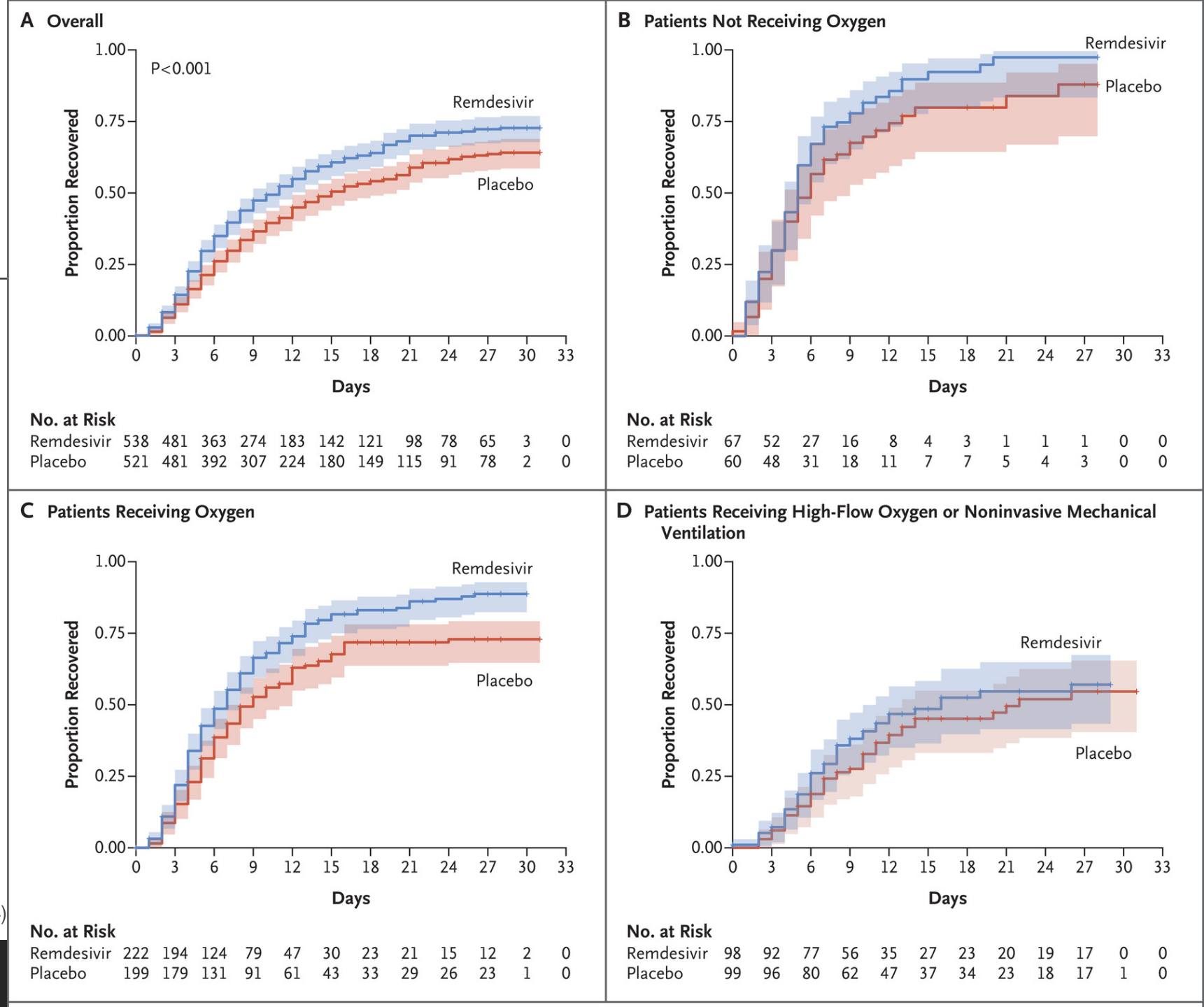
Kaplan–Meier Estimates of Cumulative Recoveries.

Panel A: Overall

Panel B: 4 *(not receiving oxygen) (Mild/Moderate & some Severe)*

Panel C: 5 *(oxygen by NC/NRB) (Severe)*

Panel D: 6 *(high-flow oxygen or NIV) (Severe)*



(Beigel et al, NEJM May 22, 2020, DOI: 10.1056/NEJMoa2007764)

Adaptive COVID-19 Treatment Trial (ACTT)-1 Results

Overall Mortality at 14 days

- 7.1% (remdesivir) vs 11.9% (hazard ratio for death, 0.70; 95% CI, 0.47 to 1.04)

Clearest benefit in ~40% requiring low flow Oxygen

- Median days to recovery (7 rem vs 9 days)
- Recovery rate ratio (1.47, 95% CI, 1.17-1.84) for remdesivir
- Risk of death (2.4% rem vs 10.9%; hazard ratio 0.22, 95% CI, 0.08-0.58)

Trends to benefit in those on no oxygen or high-flow/non-invasive; smaller sample sizes

Well tolerated

(Beigel et al, NEJM May 22, 2020, DOI: 10.1056/NEJMoa2007764)

ACTT-1 Results

Numerical trends to faster recovery if ordinal score 4 and 6

- Smaller n's (60-99)
- Ordinal score 4: small diff in time to recovery (5 vs 6 d); low mortality rate (1.5-2.5%)

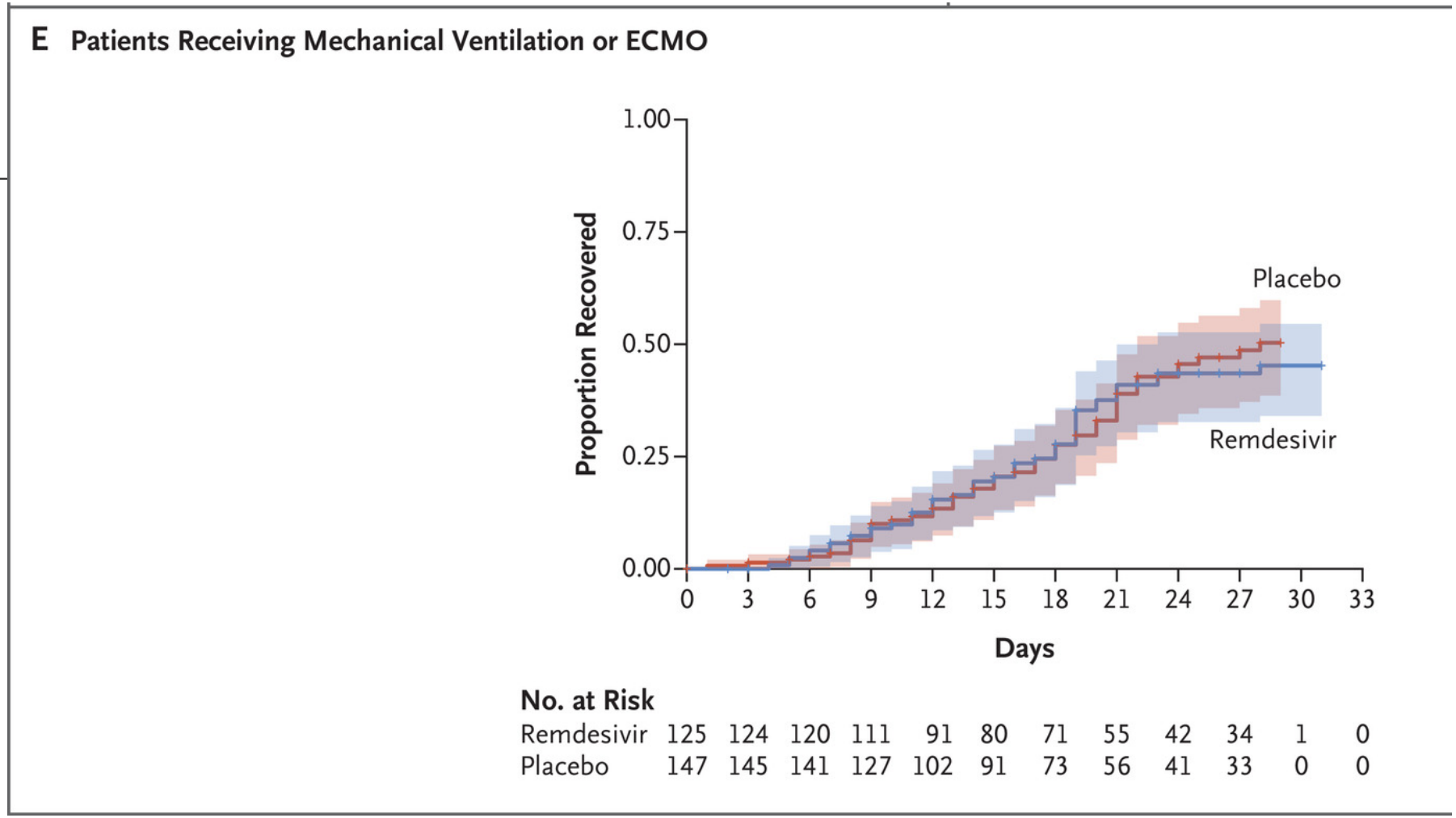
Appendix only:

	Mild/Mod (3/4 of OrdSc 4)	**Severe** (OrdSc 5,6,7, ¼ of 4)
Median recovery (days)	5 rem vs 5 placebo	12 rem vs 18 placebo
Recovery ratio	1.09 (0.73, 1.62)	1.37 (1.15, 1.63)
Death (hazard ratio)	0.48 (0.04, 5.27)	0.71 (0.48, 1.05)
	(deaths: rem 1, placebo 1)	(deaths: rem 31, placebo 53)

(Beigel et al, NEJM May 22, 2020, DOI: 10.1056/NEJMoa2007764)

Kaplan–Meier Estimates of Cumulative Recoveries.

7 (mechanical ventilation or ECMO) (Severe)



(Beigel et al, NEJM May 22, 2020, DOI: 10.1056/NEJMoa2007764)

ACTT-1 Conclusions/Opinions

Remdesivir: moderate activity; treatment of choice for hospitalized COVID-19 patients with severe lower respiratory tract infection

- No difference based on length of symptoms before treatment *(data not shown)*

Little benefit if not requiring oxygen, low mortality

No benefit shown if mechanically ventilated or on ECMO but benefit for some not ruled out due to low n

- Remdesivir may be used; data not strong enough to recommend against
- Urgent focus for new agents and approaches

Treatment before mechanical ventilation (and HFO2 or NIV) critical

Remdesivir

Final ACTT-1 analysis soon to be submitted

Full or conditional approval in many countries

US FDA approved Emergency Use Authorization (EUA) for Severe COVID-19 Disease

- Severe: SpO2 ≤94% on RA or requiring supplemental oxygen, mechanical ventilation, or ECMO

Many distribution and supply issues

What is a FDA Emergency Use Authorization (EUA)?

"In certain …. emergencies … FDA can issue an … EUA to provide more timely access to critical medical products … when there are no adequate, approved, and available alternative options. …. different than full FDA approval … significantly less data … within weeks … using the evidence that is available …. EUAs … in effect until the emergency declaration ends … revised or revoked as we evaluate the needs … or as products … become approved, cleared, or licensed by the FDA.

- On February 4, 2020, the HHS Secretary … issued declarations justifying the use of EUAs … to prevent, treat and diagnose COVID-19. … over 100 EUAs have been issued…."

Products under an EUA do not require an investigational protocol, can be more easily and widely distributed and prescribed, more likely covered by insurance

EUA authorization – *controversially* – may provide an impression of efficacy or accuracy and safety; concern about influence/process; may stymie optimal study

https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-frequently-asked-questions

Products Approved under EUA for COVID-19 by FDA

1) Diagnostics
   - Molecular tests for SARS-CoV-2
   - Antibody tests for SARS-CoV-2
     - "On April 28, 2020, FDA issued an umbrella EUA for SARS-CoV-2 Antibody Tests (Lateral flow or … ELISA tests)…."
     - "On July 21, 2020, FDA determined … that circumstances support revocation of this umbrella EUA so that FDA may issue individual EUAs."
2) PPE
3) Ventilators and Other Medical Devices
4) Drug Products
   - Chloroquine and Hydroxychloroquine EUA revoked 6/15/2020

Remdesivir

Gilead submitted New Drug Application to FDA

- Montefiore/Einstein FDA inspection; 2 other sites, NIH, data managers

Need studies in those with GFR <30; excluded from trials to date

- Kidney disease patients have high COVID mortality
- EUA does not specifically exclude GFR <30
- Often being used if “benefits outweight risks”

Remdesivir and Kidney Disease

>50% of GFRs <30 in COVID due to AKI; minority from CKD or ESRD

Remdesivir and its active metabolite (remdesivir triphosphate) 74% renally eliminated

Plasma $t_{1/2}$ of remdesivir 1–2 hours, $t_{1/2}$ of metabolite ~20–25 hours

Limited water solubility, IV prep in *cyclodextrin* carrier, low amounts

Potential toxicity: remdesivir directly & accumulation of cyclodextrin

Remdesivir and Kidney Disease

Remdesivir

- Low mitochondrial toxicity; small risk with 5-10-day course

Cyclodextrin

- IV voriconazole; minimal toxicity with short courses
- Dialyzed off by CRRT or HD

No toxicity in Chinese COVID RCT w/ kidney disease pts or Ebola

Consider remdesivir via EUA if stable AKI/CKD (GFR ≥15) or HD/CRRT

Watch LFTs

Gilead RCT in development

JASN July 2020, 31 (7) 1384-1386; DOI: 10.1681/ASN.2020050589; Sci Transl Med 9: eaal3653, 2017pmid:28659436; Nature 531: 381–385, 2016pmid:269342

ORIGINAL ARTICLE

Remdesivir for 5 or 10 Days in Patients with Severe Covid-19

Jason D. Goldman, M.D., M.P.H., David C.B. Lye, M.B., B.S., David S. Hui, M.D., Kristen M. Marks, M.D., Raffaele Bruno, M.D., Rocio Montejano, M.D., Christoph D. Spinner, M.D., Massimo Galli, M.D., Mi-Young Ahn, M.D., Ronald G. Nahass, M.D., Yao-Shen Chen, M.D., Devi SenGupta, M.D., et al., for the GS-US-540-5773 Investigators*

"SIMPLE – Severe" Study

Metrics

May 27, 2020
DOI: 10.1056/NEJMoa2015301

Coexisting conditions of interest — no. (%)		
Diabetes	47 (24)	43 (22)
Hyperlipidemia	40 (20)	49 (25)
Hypertension	100 (50)	98 (50)
Asthma	27 (14)	22 (11)
Clinical status on the 7-point ordinal scale — no. (%)§		
2: Receiving invasive mechanical ventilation or ECMO	4 (2)	9 (5)
3: Receiving noninvasive ventilation or high-flow oxygen	49 (24)	60 (30)
4: Receiving low-flow supplemental oxygen	113 (56)	107 (54)
5: Not receiving supplemental oxygen but requiring medical care	34 (17)	21 (11)
Median duration of hospitalization before first dose of remdesivir (IQR) — days	2 (1–3)	2 (1–3)
Median duration of symptoms before first dose of remdesivir (IQR) — days	8 (5–11)	9 (6–12)

Note: primarily enrolled those that ended up benefiting in ACTT

Results: no differences between 5- or 10-days treatment

SIMPLE-Severe, initial phase

5 days' treatment is adequate for subgroups shown so far to respond to remdesivir

- Practice is that if improved/ready for discharge prior to day 5, stop treatment

Pending further trial results in critical illness, most still use 10 days if mechanical ventilation, ECMO, or septic shock

Gilead Press Release 7/10/2020 & 23rd International AIDS Conference

- SIMPLE-severe (n=312) vs historical matched controls (n=818)
- 62% reduction in mortality (day 14: 7.6% vs 12.5% SOC, aOR 0.38, p=0.001)
- improved recovery time (day 14: 74.4% vs 59% SOC)

Goldman et al. NEJM 2020 May 27; DOI: 10.1056/NEJMoa2015301

Other Key Remdesivir Studies

Pediatrics RCT

Outpatient IV short course

Inpatient nebulized remdesivir

Ongoing pregnancy compassionate use protocol

Next Steps and Challenges in Studies of New Antivirals

Remdesivir is standard of care in patients with severe disease

- Steroids +/- remdesivir if mechanically ventilated

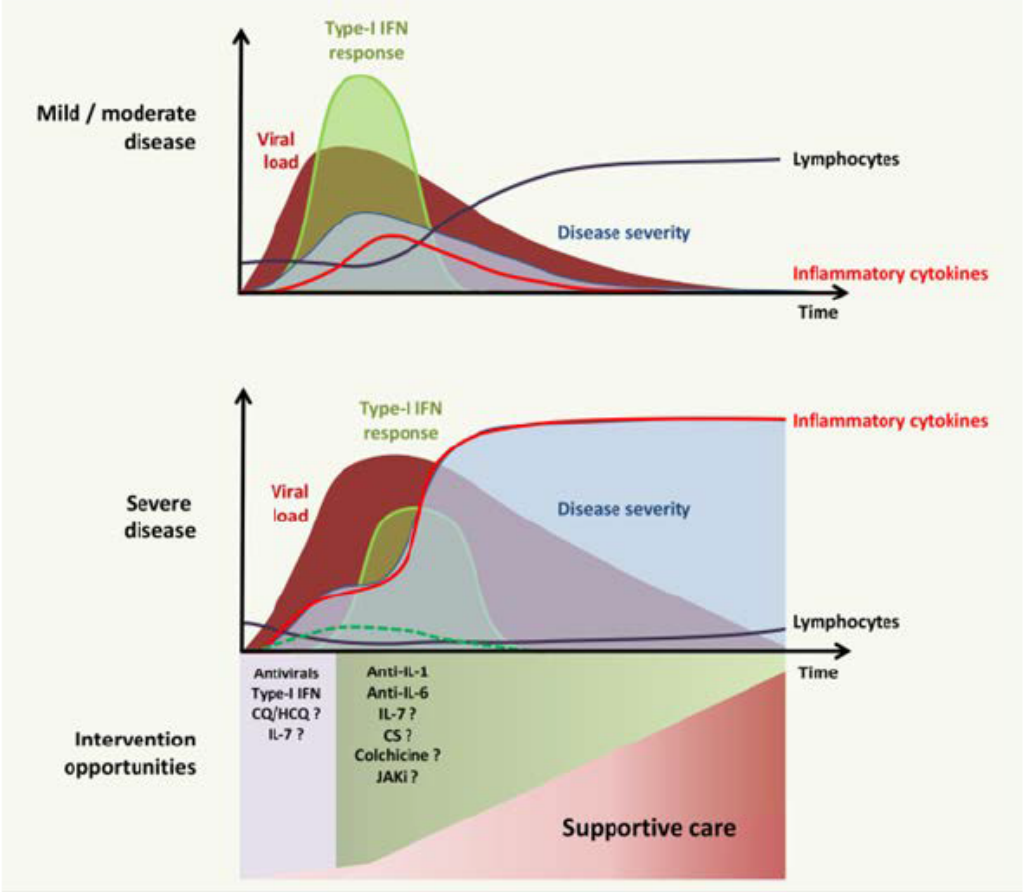
Many combination studies ongoing with remdesivir, 2nd agent with varying mechanisms across COVID-19 pathogenesis

Need clarity on approach to pre-exposure/post-exposure prophylaxis, moderate disease, critical illness, non-respiratory manifestations

Adaptive COVID-19 Treatment Trial (ACTT-3)

Data from hospital cohorts indicate that there may be a subset of patients who despite high viral titers lack a prominent type-1 interferon response and this phenotype may be associated with poor clinical outcomes (5-7).

Administering IFN beta-1a early in the clinical course may compensate for insufficient endogenous IFN levels in patients infected with SARS-CoV-2.



Jamilloux Y., Henry T., Belot A, et. al. , Autoimmunity Reviews, 2020

1. Blanco-Melo D, Cell, 2020; 2. Hadjadj J, medRxiv, 2020; 3. Trouillet-Assant S, J Allergy Clin Immunol, 2020; 4. unpublished data, NIAID's Immune Phenotyping in a COVID-19 Cohort study (IMPACC).

ACTT-3

Hospitalized patients with severe disease

ACTT-3 Study Intervention

- The study will accrue until we get 831 recoveries. Assuming 80% recovery by Day 29, the total sample size will be about 1038.
- Subjects will be randomized to one of two study arms

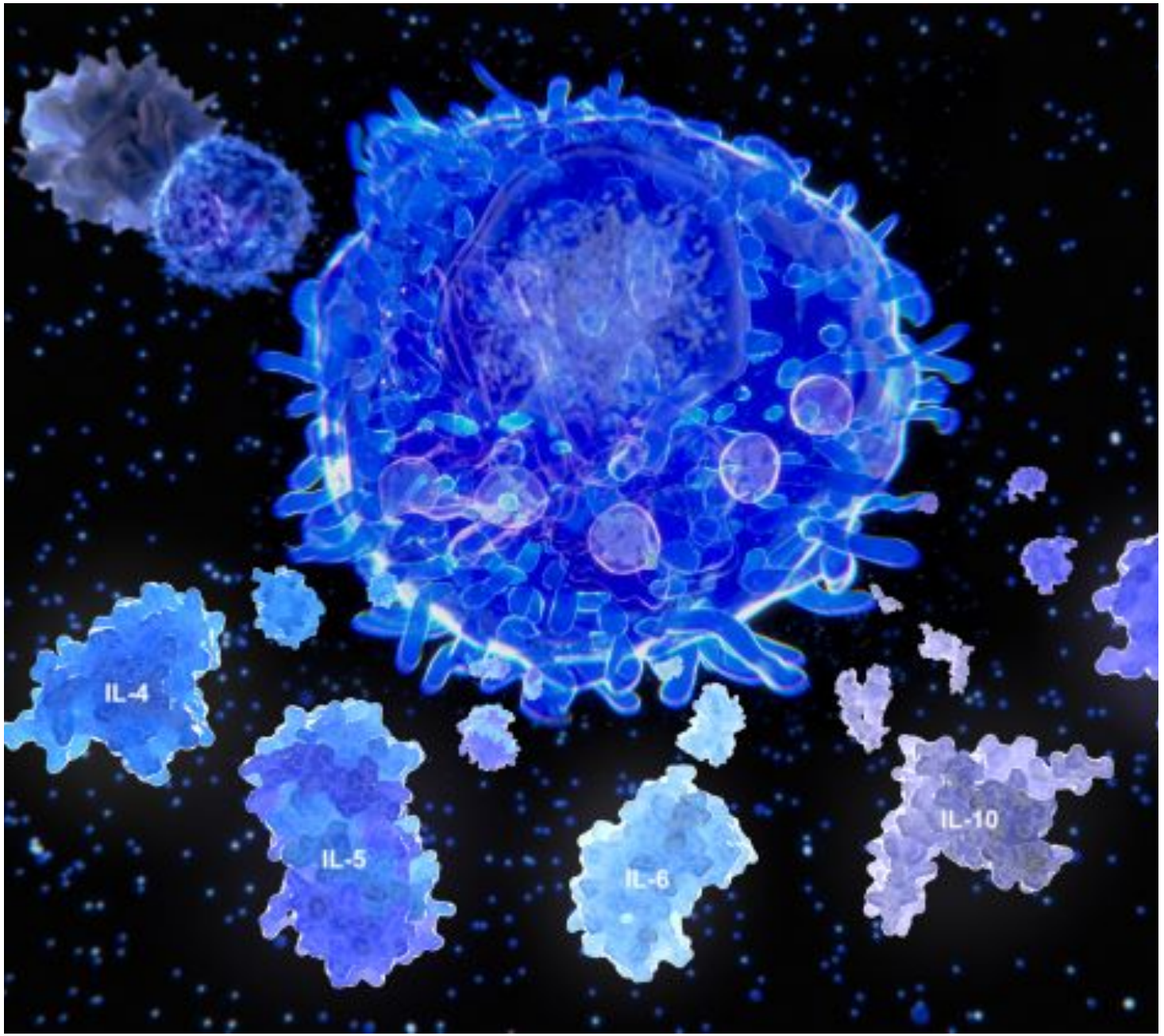
Arm 1	Arm 2
IFN beta-1a SQ injection + remdesivir IV	Placebo SQ injection + remdesivir IV

Montefiore/Einstein PI: Robert Grossberg

No steroid restrictions

Host Targeted

Immune Modulators



https://www.nursingcenter.com/getattachment/34c33c2b-bf80-493b-acdf-32dec77d5ea5/Is-COVID-19-Fueled-by-a-Cytokine-Storm.aspx

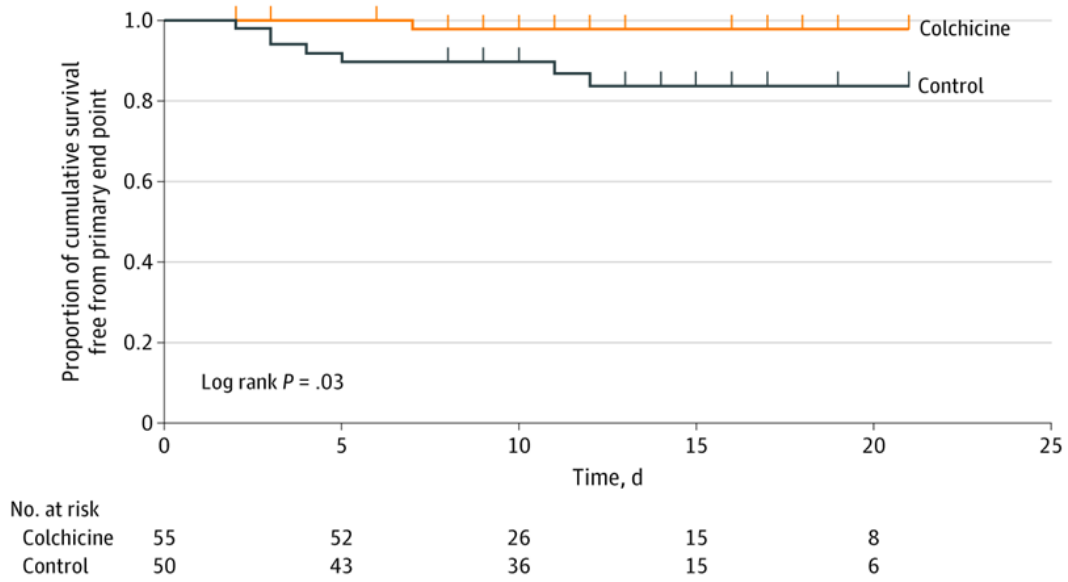
Host Targeted/Immune Modulators: Broad Spectrum

Azithromycin

- No convincing results, significant toxicity
- Not recommended outside of trials

Colchicine *(Deftereos et al, JAMA Netw Open 24 JUN 2020; doi:10.1001/jamanetworkopen.2020.13136)*

- Some benefit on combined endpoint of progression or death



Host Targeted/Immune Modulators: Broad Spectrum

UK RECOVERY trial *(Horby et al, pre-print 6-22-2020)*

- Randomized, open label
- 2104 dexamethasone 6 mg x 10d vs 4321 usual care
- Shorter hospitalization with dexa: 12 vs 13 days
- Progression to mechanical ventilation lower: 0.76 RR, 95% CI 0.61-0.96; p=0.21

	Mortality at 28 Days		
Group	Dexamethasone	Placebo	Relative Risk (95% CI, p value)
Overall	21.6%	24.6%	0.83 (0.74-0.92; p<0.001)
Mechanical ventilation	29.0%	40.7%	0.65 (0.51-0.82; p=0.0003)
Other oxygen	21.5%	25.0%	0.80 (p=0.002)
No oxygen			1.22 (0.93-1.61; p=0.14)

Effect of Systemic Glucocorticoids on Mortality or Mechanical Ventilation in Patients With COVID-19

J. Hosp. Med. 2020 August;15(8):489-493. Published Online First July 22, 2020 | DOI 10.12788/jhm.3497

By: Marla J Keller, MD ✉, Elizabeth A Kitsis, MD, MBE, Shitij Arora, MD, Jen-Ting Chen, MD, MS, Shivani Agarwal, MD, MPH, Michael J Ross, MD, Yaron Tomer, MD, William Southern, MD, MS

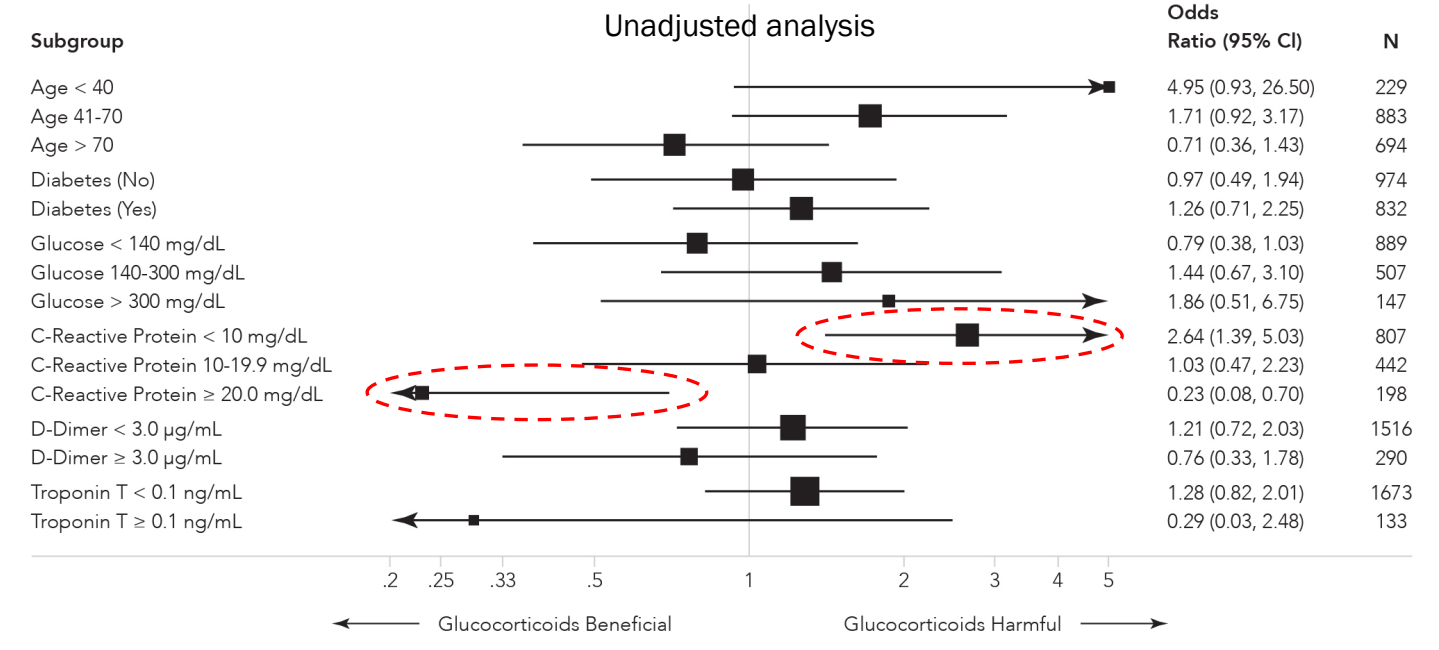
140 patients given steroids within 48 hrs of admission (treated) vs 1666 never given (controls)

Excluded those who died or placed on mechanical ventilation within 48 hrs of admission

Primary outcome: composite of in-hospital mortality or in-hospital mechanical ventilation

J Hosp Med 2020 July 22, DOI: 10.12788/jhm.3497

A



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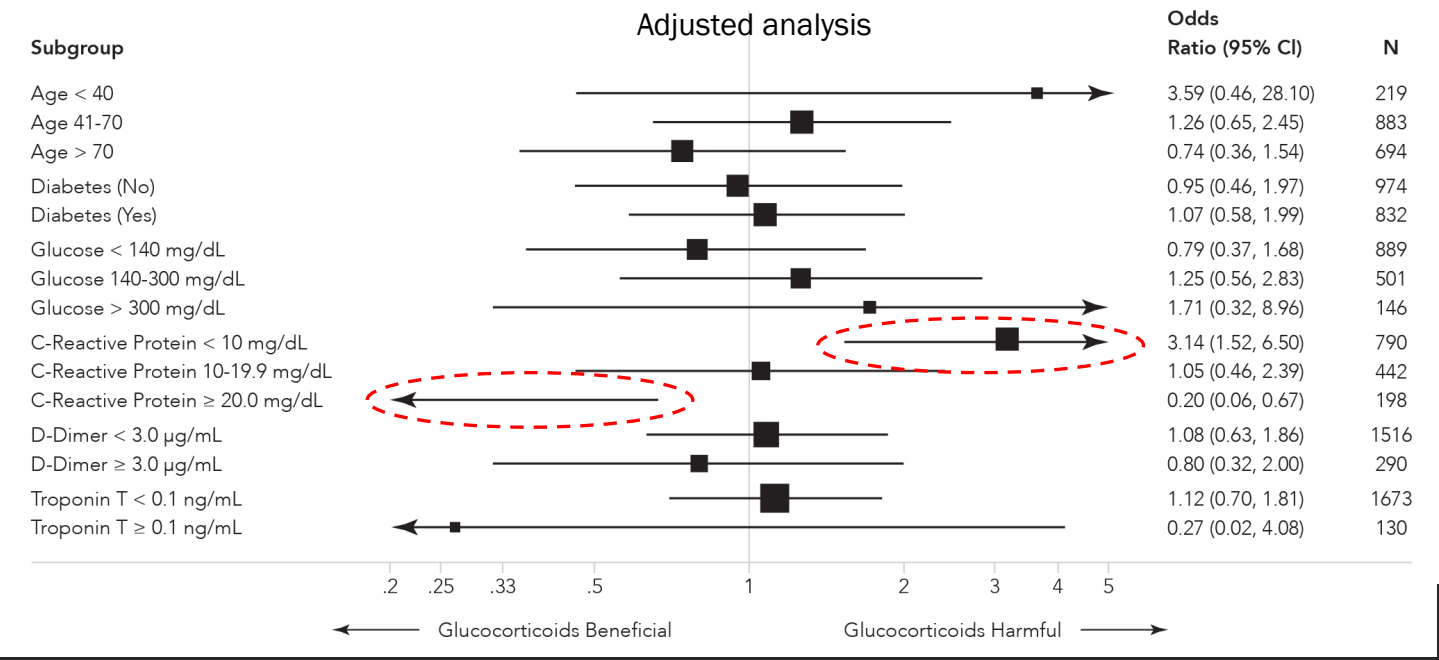
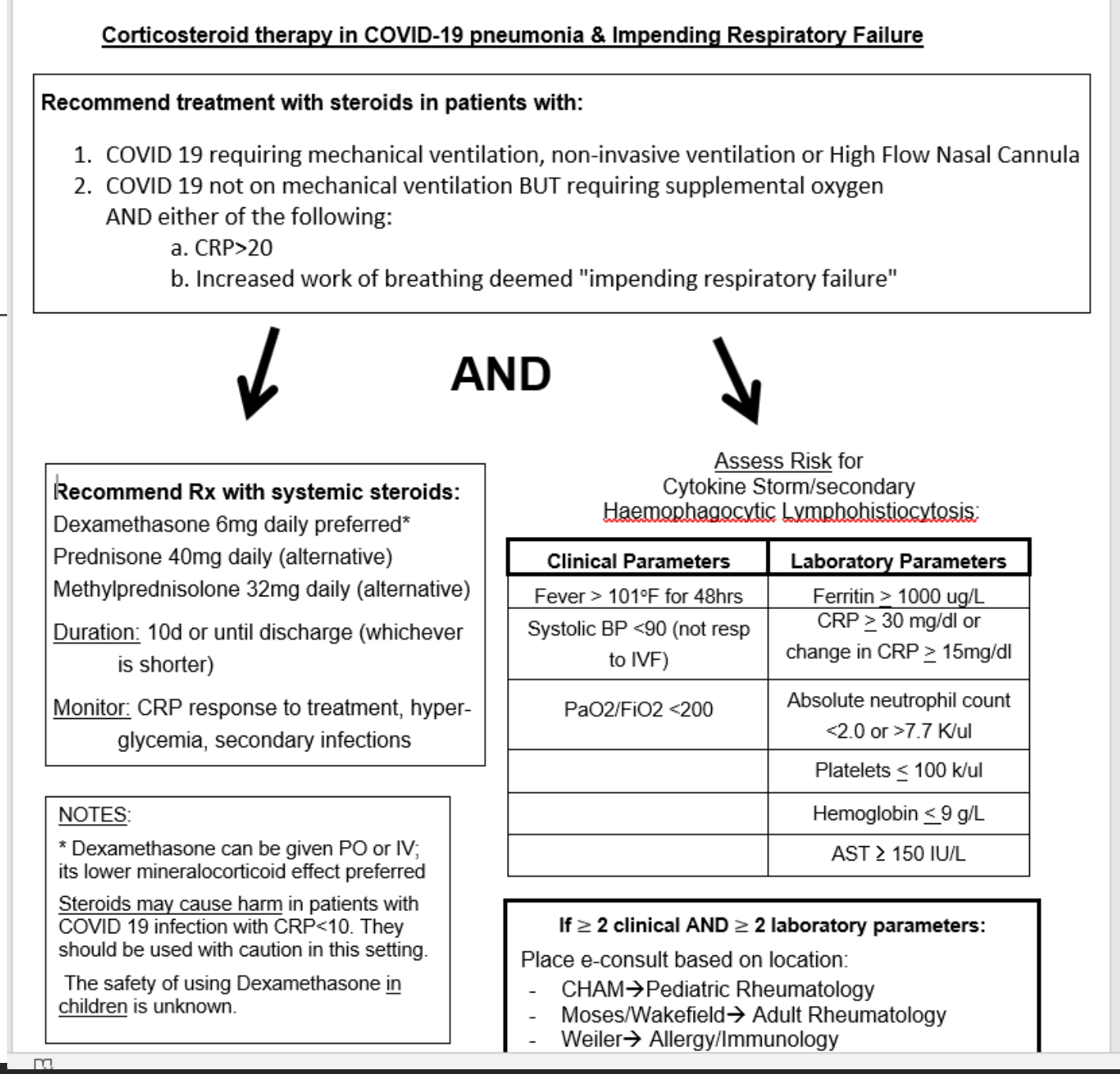


Montefiore Steroids/CRS Treatment Protocol

Revised 7/7/2020



Corticosteroid therapy in COVID-19 pneumonia & Impending Respiratory Failure

Recommend treatment with steroids in patients with:

1. COVID 19 requiring mechanical ventilation, non-invasive ventilation or High Flow Nasal Cannula
2. COVID 19 not on mechanical ventilation BUT requiring supplemental oxygen
   AND either of the following:
   a. CRP>20
   b. Increased work of breathing deemed "impending respiratory failure"

AND

Recommend Rx with systemic steroids:
Dexamethasone 6mg daily preferred*
Prednisone 40mg daily (alternative)
Methylprednisolone 32mg daily (alternative)

Duration: 10d or until discharge (whichever is shorter)

Monitor: CRP response to treatment, hyperglycemia, secondary infections

NOTES:

* Dexamethasone can be given PO or IV; its lower mineralocorticoid effect preferred

Steroids may cause harm in patients with COVID 19 infection with CRP<10. They should be used with caution in this setting.

The safety of using Dexamethasone in children is unknown.

Assess Risk for Cytokine Storm/secondary Haemophagocytic Lymphohistiocytosis:

Clinical Parameters	Laboratory Parameters
Fever > 101°F for 48hrs	Ferritin ≥ 1000 ug/L
Systolic BP <90 (not resp to IVF)	CRP ≥ 30 mg/dl or change in CRP ≥ 15mg/dl
PaO2/FiO2 <200	Absolute neutrophil count <2.0 or >7.7 K/ul
	Platelets ≤ 100 k/ul
	Hemoglobin ≤ 9 g/L
	AST ≥ 150 IU/L

If ≥ 2 clinical AND ≥ 2 laboratory parameters:

Place e-consult based on location:

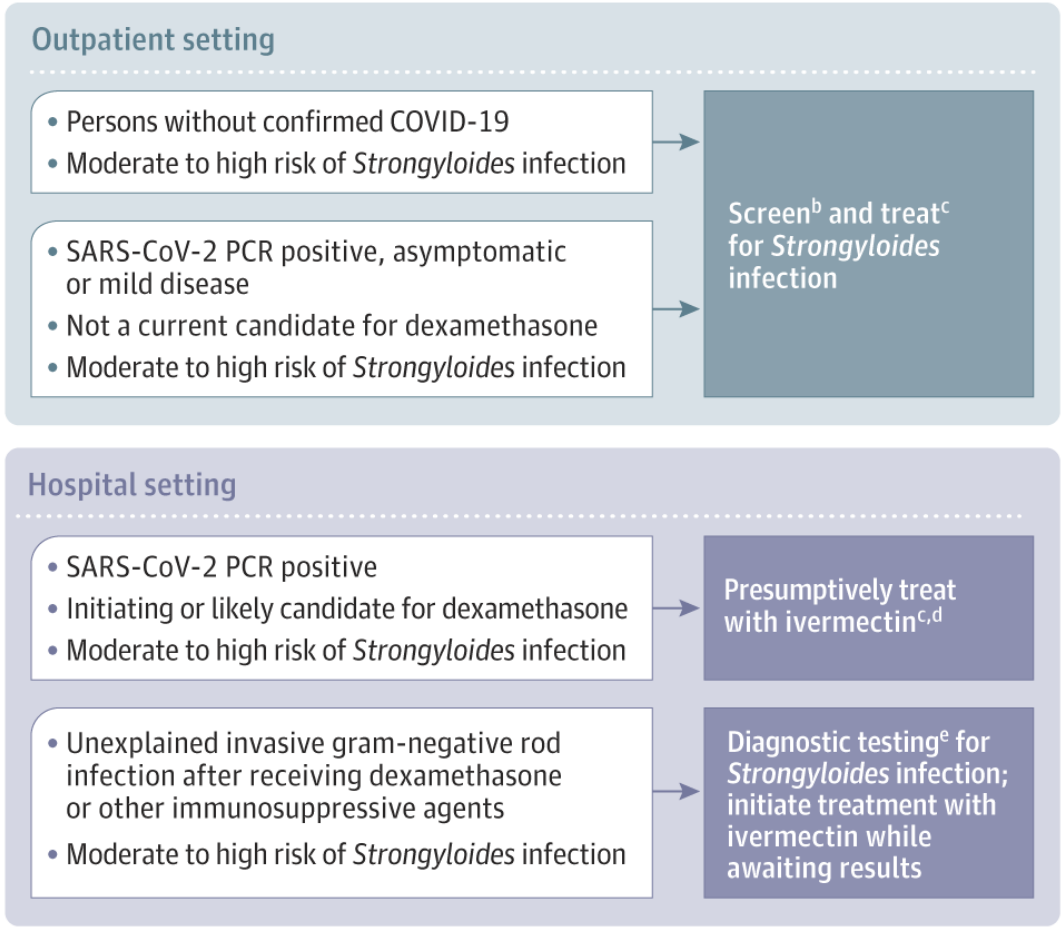
- CHAM→Pediatric Rheumatology
- Moses/Wakefield→ Adult Rheumatology
- Weiler→ Allergy/Immunology

Steroids and Strongyloides

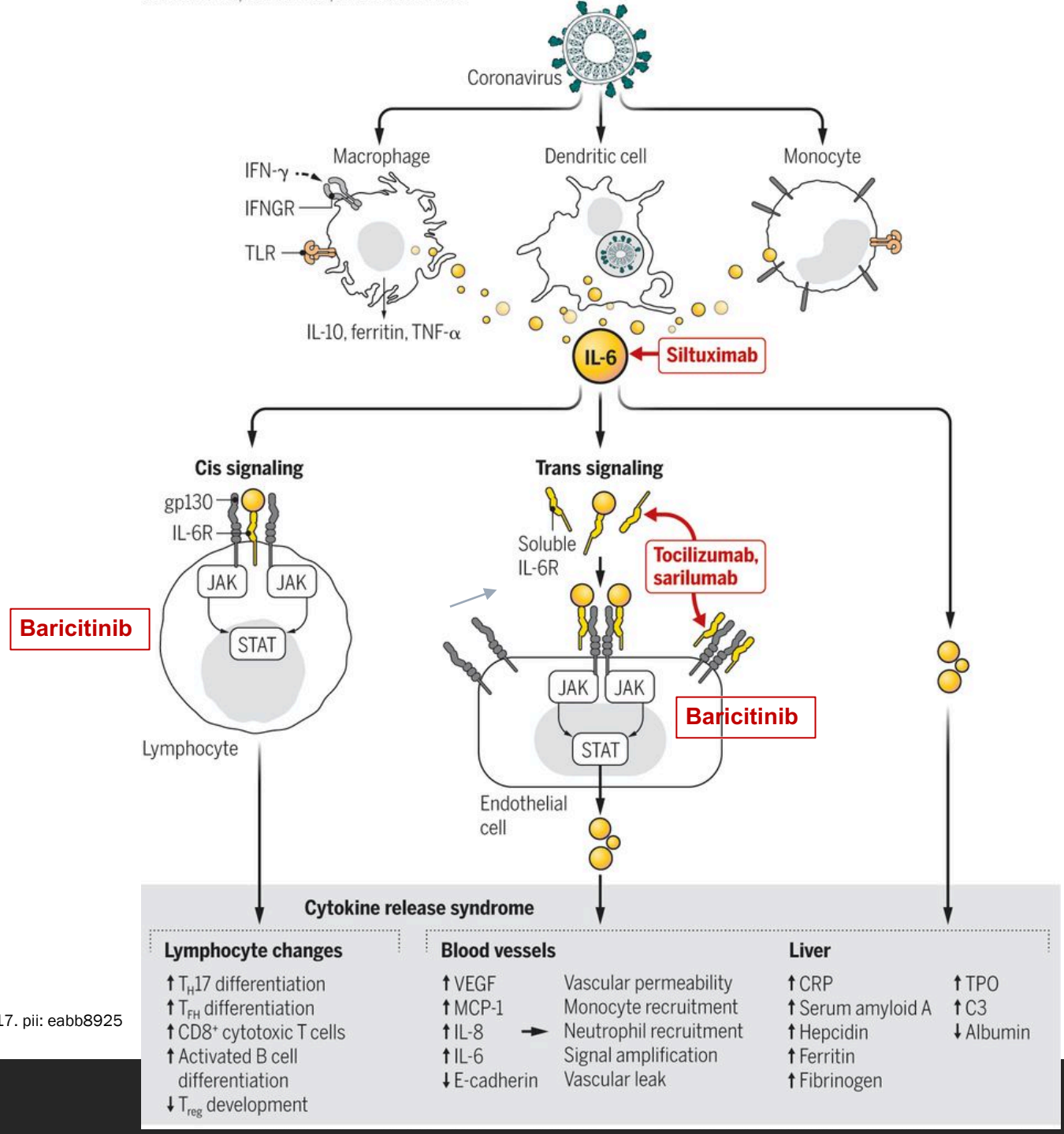
10-40% Strongyloides prevalence in tropical/subtropical areas, typically 10-20%

- Strongyloides hyperinfection syndrome increased with immune suppressants
- 83% of hyperinfection associated with prednisone at average 40 mg/day, but can occur with less and with few doses *(Geri et al, Infection 2015)*

Dexamethasone 6 mg = 40 mg prednisone



JAMA. Published online July 30, 2020. doi:10.1001/jama.2020.13170



Science. 2020 Apr 17. pii: eabb8925

IL-6 inhibitors (tocilizumab; sarilumab, others)

IL-1r inhibitors (anakinra)

JAK/STAT inhibitors (baricitinib, others)

CCR5 inhibitors (leronlimab)

GM-CSF inhibitors

TNF-alpha inhibitors

CTLA-4 inhibitors (immune checkpoint inhibitors)

CCR2/5 inhibitor

Host Targeted/Immune Modulators: IL-6 directed

Tocilizumab

- Recombinant humanized anti-IL-6 receptor IgG1 antibody
- Many positive observational studies

Tocilizumab

Press Release, April 27, 2020:

CORIMUNO-TOCI trial (NCT04331808)

- open-label, randomized, hospitalized patients (n = 129, 7 French sites)
- tocilizumab (n = 65) or standard of care alone (n = 64).
- Preliminary results: % who died or who needed ventilation (NIV or mechanical) lower in toci group
- DSMB resigned after press release issued

Press Release, June 17, 2020, Italian study, 24 sites:

- RCT, toci in early COVID pneumonia on LFO2 at most: no benefit

https://covid19treatmentguidelines.nih.gov/

Host Directed/Immune Modulators: IL-6 directed

Sarilumab

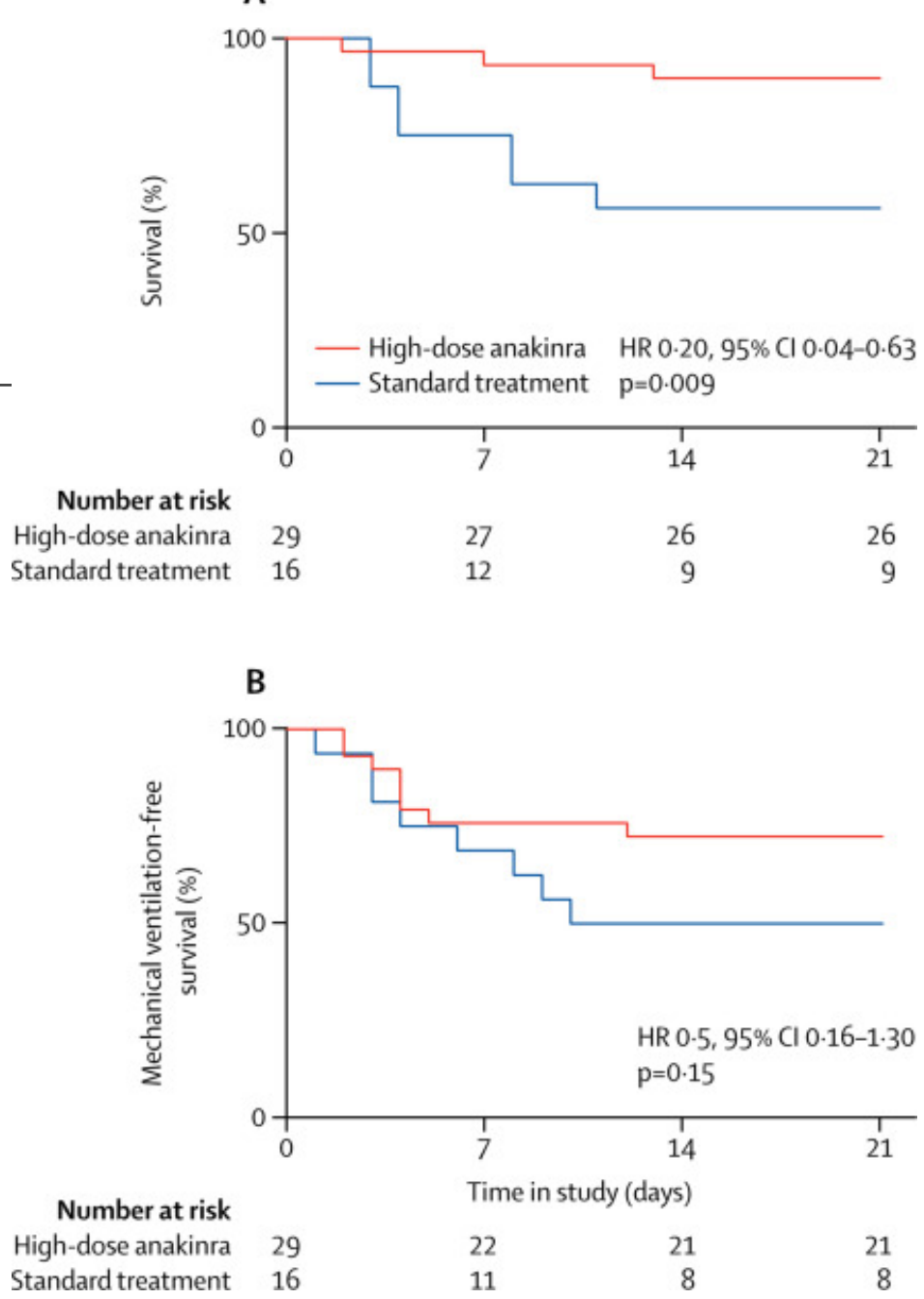
- RCTs vs placebo
  - **Phase 2, severe disease arm:** stopped; trends to worsening
  - **Phase 3, Critical disease arm:** stopped 7/2020; minor positive trends in vent'd patients; negative trends in others

Regeneron Press Release 4/2020

Host Directed/Immune Modulators: IL-1R antagonist

Anakinra

- **Italian case series; ARDS** *(Cavalli et al)*
  - 29 with moderate-to-severe ARDS; high-dose anakinra vs 16 SOC/similar patients
  - higher survival at 21 days (90% vs. 56% with SOC)
  - mechanical ventilation-free survival similar
  - CRP improved faster
- **Phase 2 RCT ongoing** (NCT04324021)
  - Lower dose
  - Patients with hyperinflammation, not ARDS
- **Some use in MIS-C**



The Lancet Rheumatology DOI: (10.1016/S2665-9913(20)30127-2)

ACTT-2: Study Intervention

- Remdesivir OPEN LABEL: 200 mg IV loading dose Day 1 followed by 100 mg daily IV x 10-days while hospitalized
- Baricitinib/placebo BLINDED: 4 mg PO daily x 14 days while hospitalized

ACTT-2	Baricitinib	Placebo
Remdesivir	Arm 1 Baricitinib tabs + remdesivir IV	Arm 2 Placebo tabs + remdesivir IV

Host Targeted/Immune Modulators: anti-CCR5

Leronlimab (PRO 140)

- Humanized IgG4 mAb to the C-C chemokine receptor CCR5
- Emergency use IND program
  - CytoDyn Press Release 4/30/20; 49 patients
    - Encouraging, uncontrolled results: including 11 in a NYC hospital
- RCT in mild-moderate dz (no/mild/mod pneumonia; SpO_2 >93% on RA)
  - 9 US sites (Montefiore/Einstein)

https://www.cytodyn.com/newsroom/press-releases/detail/424/cytodyn-reports-strong-results-from-eind-covid-19-patients

Host Targeted/Immune Modulators: CytoSorb®

"Reducing the Fuel to the Fire of Inflammation"

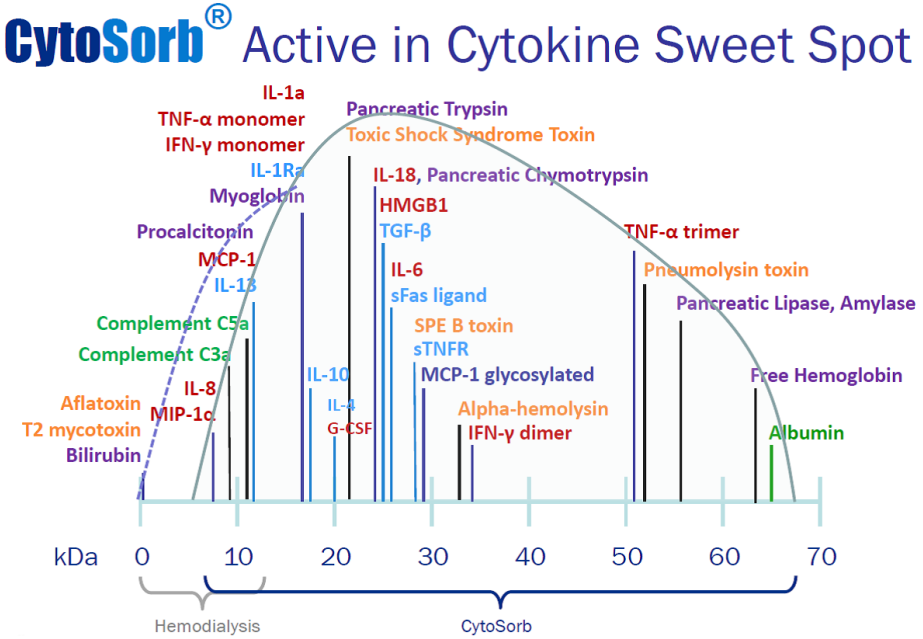
Extracorporeal cytokine adsorber cartridge aimed at "cytokine storm and other inflammatory mediators in the blood"

Cartridge compatible with most hemodialysis, CRRT, heart-lung, ECMO and other blood pumps and machines

Minimal evidence of efficacy
- 2 ongoing single-site German studies, 1 an RCT of ECMO +/- CytoSorb

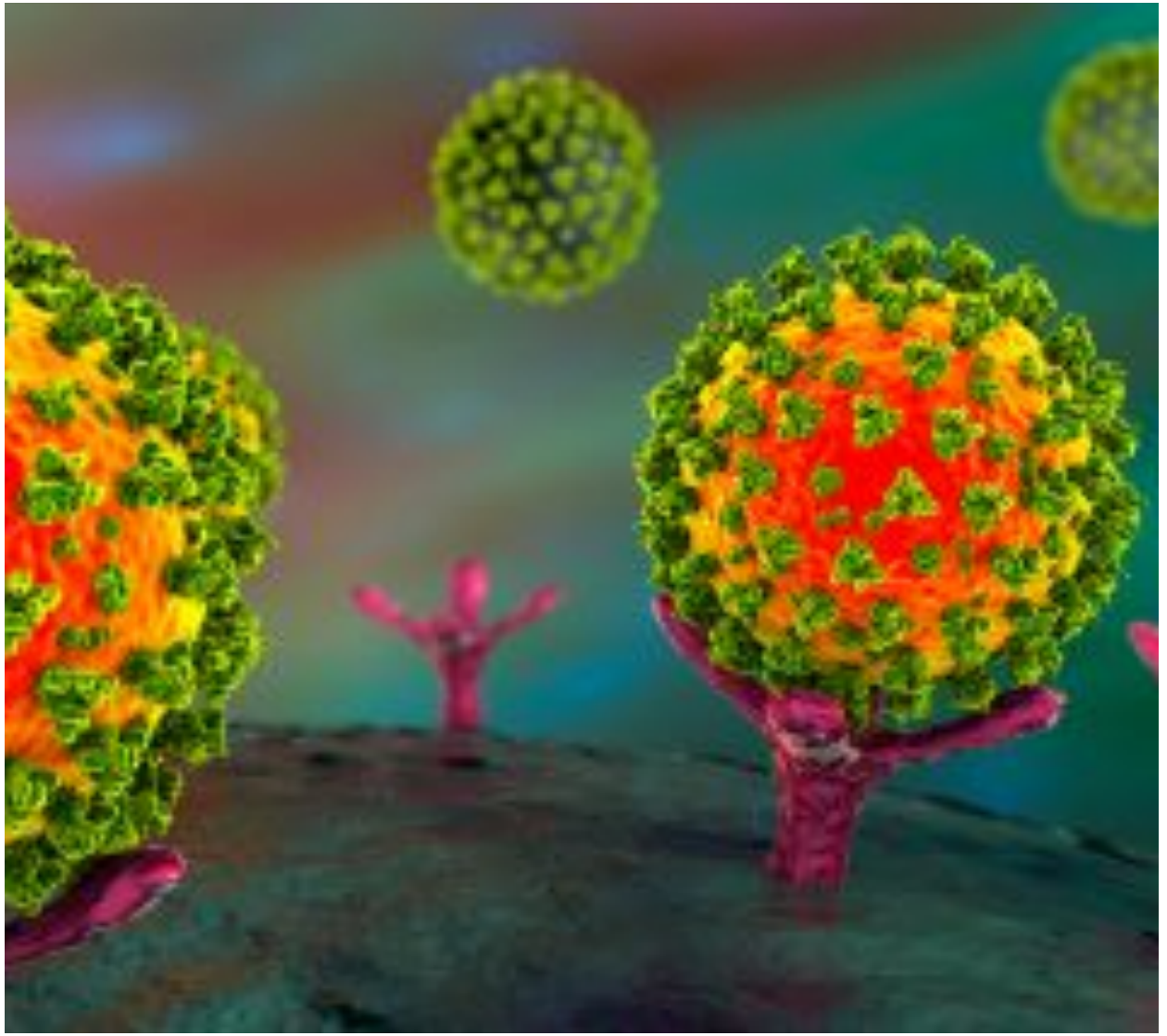
What else does it adsorb? Remdesivir? Antibiotics? Anticoagulants?

FDA granted EUA April 10, 2020
- 18 or older; confirmed COVID-19; ICU admit; confirmed or imminent respiratory failure



Transfus Apher Sci. 2020 Jun 25 : 102855; Lancet Respir Med. 2020 Mar; 8(3): 240–241; https://cytosorb-therapy.com/en-us/;

Mixed Mechanism

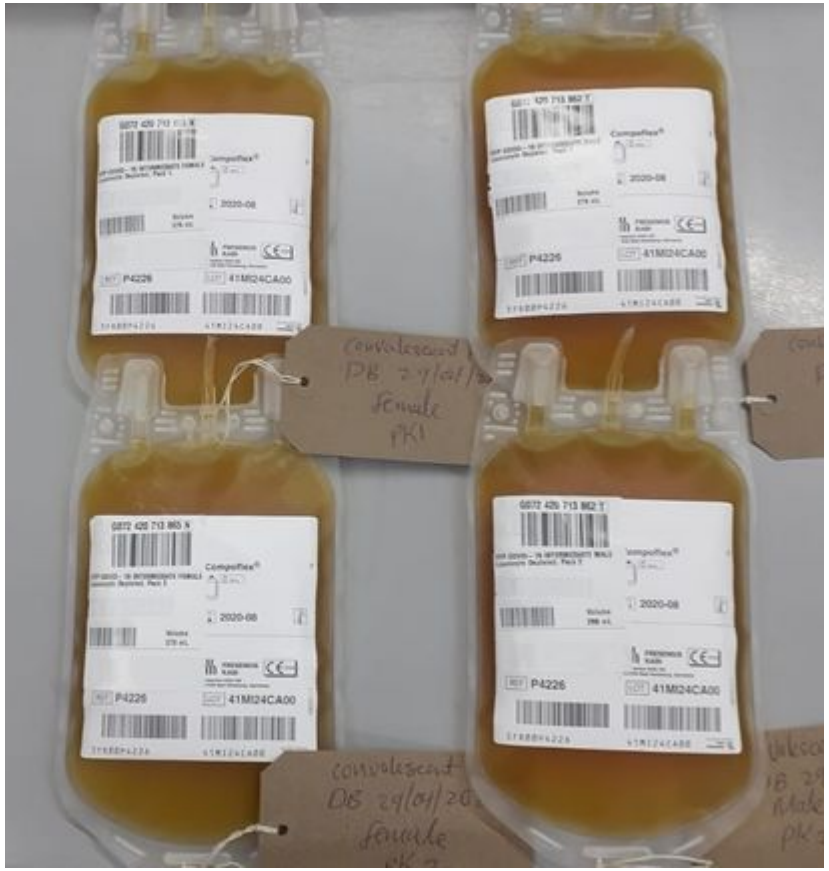


SARS-CoV-2 virus binding to an ACE2 receptor on a human cell. (Image: © Shutterstock)

Convalescent Plasma

75 studies on clinicaltrials.gov

- Some encouraging uncontrolled results
- Joyner, J Clin Invest. https://doi.org/10.1172/JCI140200 Mayo IND, 5000 pts
  - Well tolerated; 36 SAEs, 25 related, 2 definitely
    - mortality (*n*=4); severe allergic transfusion reactions (*n*=3)
    - transfusion-associated circulatory overload (TACO; *n*=7); transfusion-related acute lung injury (TRALI; *n*=11)



Effect of Convalescent Plasma on Mortality among Hospitalized Patients with COVID-19: Initial Three-Month Experience

Michael J. Joyner[1]*, M.D., Jonathon W. Senefeld[1], Ph.D., Stephen A. Klassen[1], Ph.D., John R. Mills[2], Ph.D., Patrick W. Johnson[3], Elitza S. Theel[2], Ph.D., Chad C. Wiggins[1], Ph.D., Katelyn A. Bruno[4], Ph.D., Allan M. Klompas[1], M.B., B.Ch., B.A.O., Elizabeth R. Lesser[3], Katie L. Kunze[5], Ph.D., Matthew A. Sexton[1], M.D., Juan C. Diaz Soto[1], M.D., Sarah E. Baker[1], Ph.D., John R.A. Shepherd[1], M.D., Noud van Helmond[6], M.D., Nigel S. Paneth[7,8#], M.D., M.P.H., Ph.D., DeLisa Fairweather[4#], Ph.D., R. Scott Wright[9,10#], M.D., Rickey E. Carter[3#], Ph.D., Arturo Casadevall[11#], M.D., Ph.D., *the US EAP COVID-19 Plasma Consortium,*

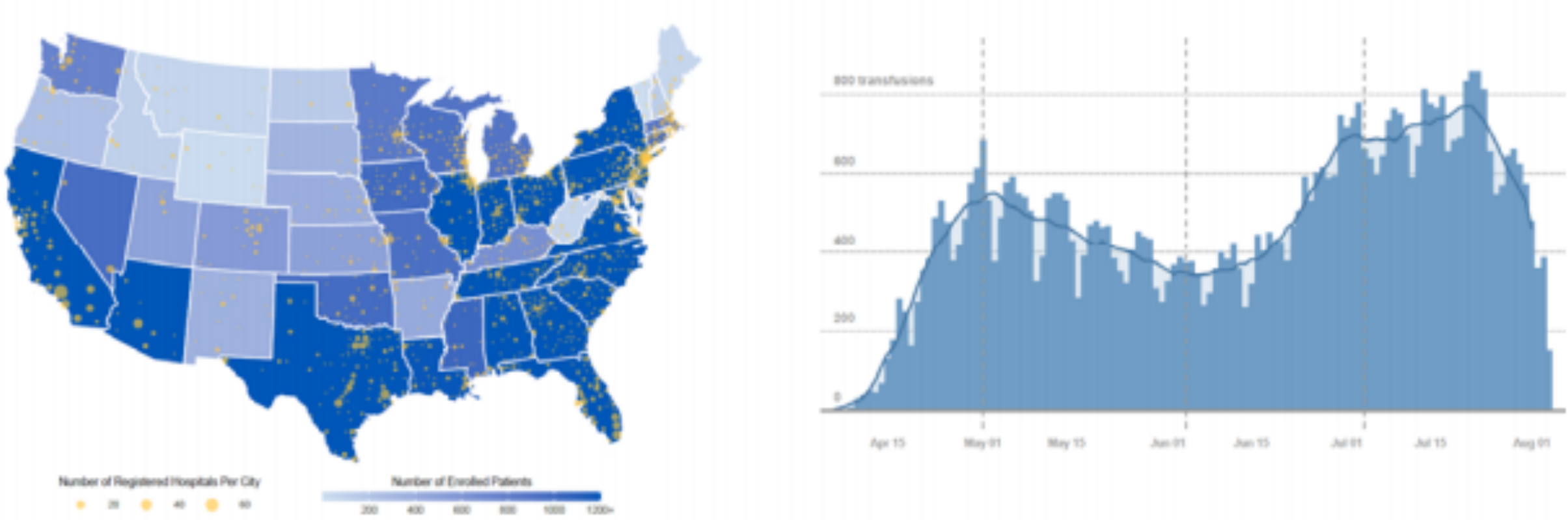


Figure 1. Participation in the US COVID-19 Convalescent Plasma Expanded Access Program (EAP). A. Choropleth map displaying the number of cumulatively enrolled patients in

Joyner et al, pre-print, https://doi.org/10.1101/2020.08.12.20169359

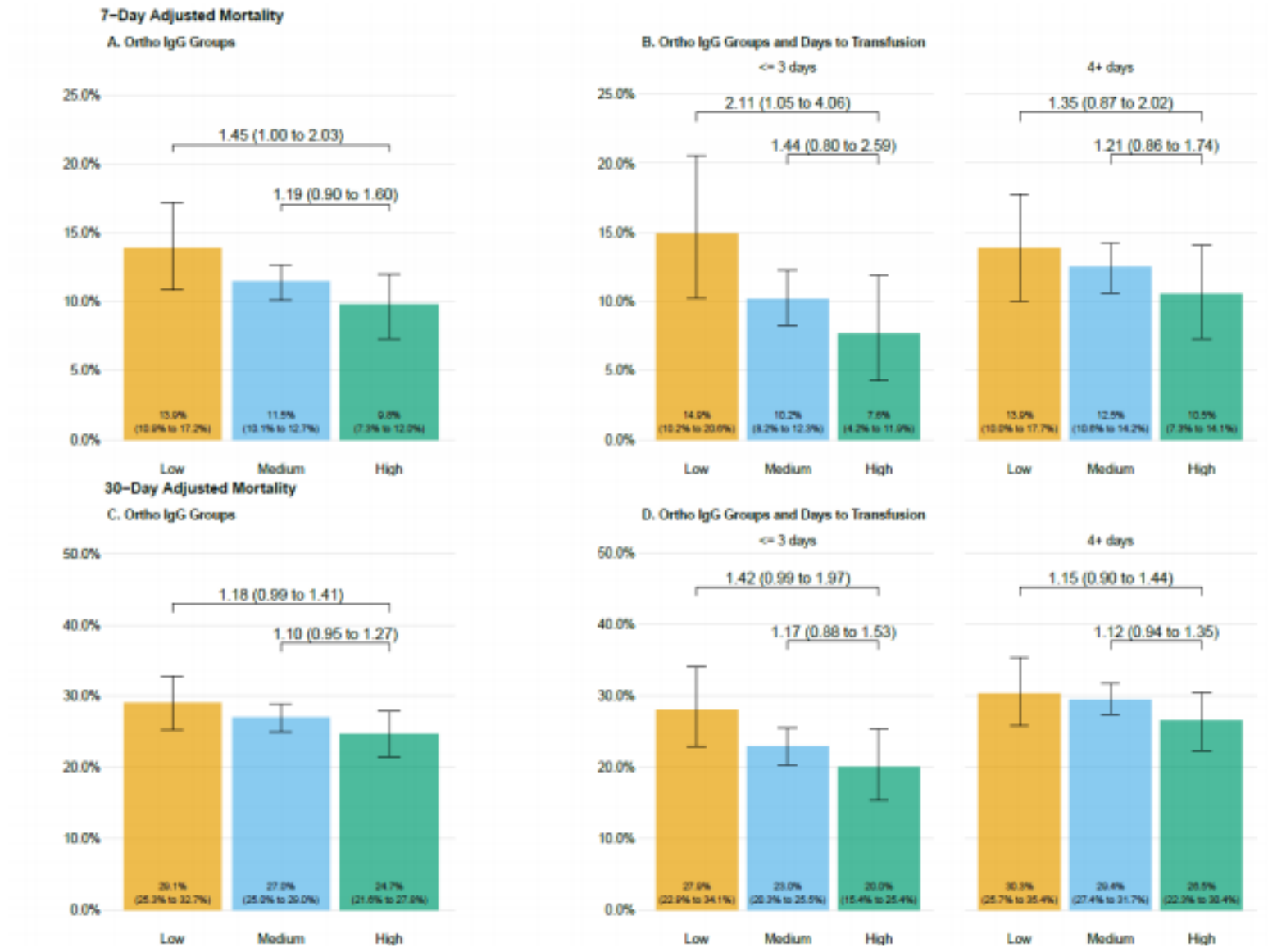


Figure 2. Seven day (A, B) and 30-day (C, D) adjusted mortality stratified by antibody groupings in patients transfused with COVID-19 convalescent plasma. Adjusted mortality

Joyner et al, pre-print, https://doi.org/10.1101/2020.08.12.20169359

Convalescent Plasma RCTs

RCT, China (Li et al, JAMA 6/3/2020)

- underpowered, some positive trends esp in severe disease

Multiple ongoing studies, most small

RCT, hospitalized respiratory disease:

- Montefiore/Einstein (Pirofski/Keller), NYU, other sites

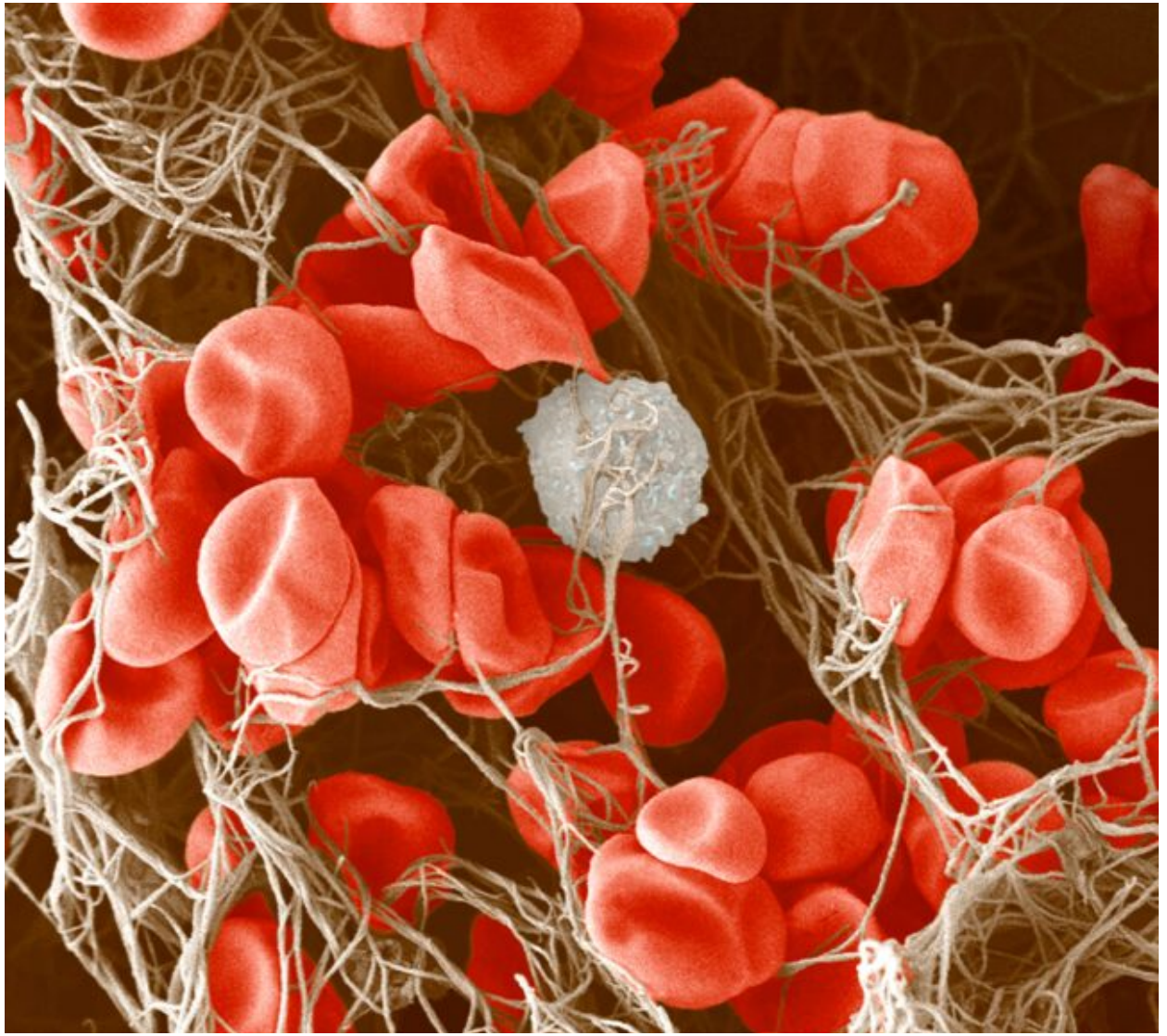
Highly promising; need definitive proof

Possible EUA approval

Joyner et al, pre-print, https://doi.org/10.1101/2020.08.12.20169359

Symptomatic

Supportive



ANNE WESTON/FRANCIS CRICK INSTITUTE VIA WELLCOME

Hypoxia

Positioning

Oxygen and ventilation strategies

Bacterial and Fungal Co-Infection

Little evidence for concurrent bacterial pneumonia on presentation with viral pneumonia

- Empiric antibiotics commonly given
- Cultures, urine antigens rarely positive
- Leukocytosis and high CRP or procalcitonin are markers of COVID severity; nonspecific for bacterial infection

Significant risk for nosocomial bacterial and fungal infection as later complications

Bacterial and fungal coinfections in COVID-19 patients hospitalized during the New York City pandemic surge

Priya Nori [a1], Kelsie Cowman [a1], Victor Chen [a2], Rachel Bartash [a1], Wendy Szymczak [a3], Theresa Madaline [a1], Chitra Punjabi Katiyar [a1], Ruchika Jain [a1], Margaret Aldrich [a4], Gregory Weston [a1], Philip Gialanella [a3], Marilou Corpuz [a1], Inessa Gendlina [a1] and Yi Guo [a2]

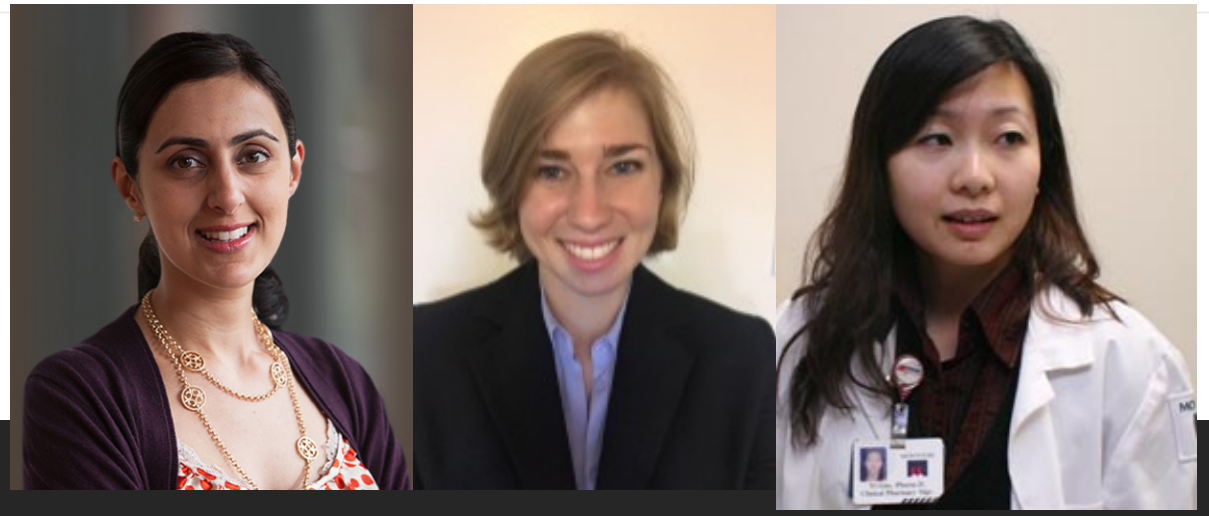
(a1) 1 Division of Infectious Diseases, Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York

(a2) 2 Department of Pharmacy, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York

(a3) 3 Department of Pathology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York

(a4) 4 Department of Pediatrics, Division of Infectious Diseases, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, New York

DOI: https://doi.org/10.1017/ice.2020.368 Published online by Cambridge University Press: 24 July 2020



Wei et al, medRxiv, DOI: 10.1101/2020.06.16.20133181

Venous and Arterial Thromboembolic Diseases

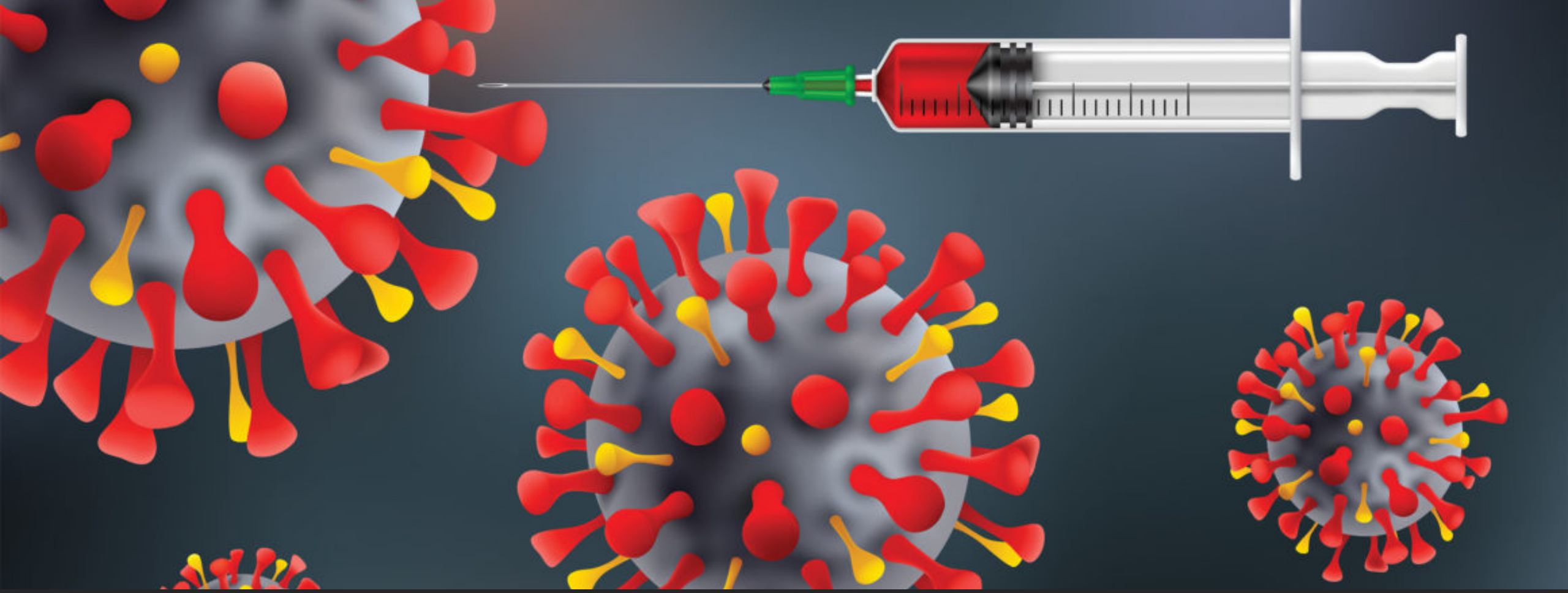
Approaches to anticoagulation; in situ thrombosis

- Prophylactic or therapeutic
- Timing and duration
- Unfractionated heparin, LMWH, Factor Xa inhibitors, thrombolytics
- Combination therapy

Many ongoing studies

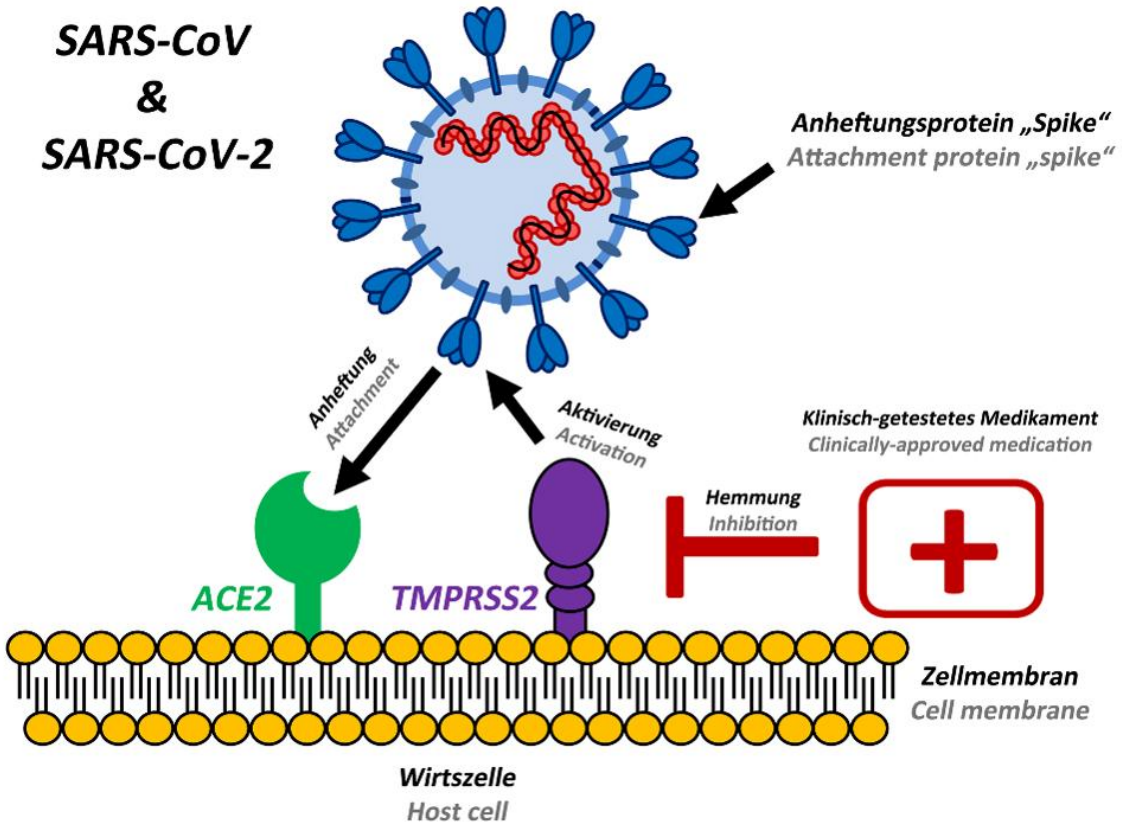
ATTACC study: Montefiore/Einstein *(Billet/Chekuri/Galen)*

ACTIV-4, NHLBI/NINDS: RCTs of at least 3 anticoagulation strategies

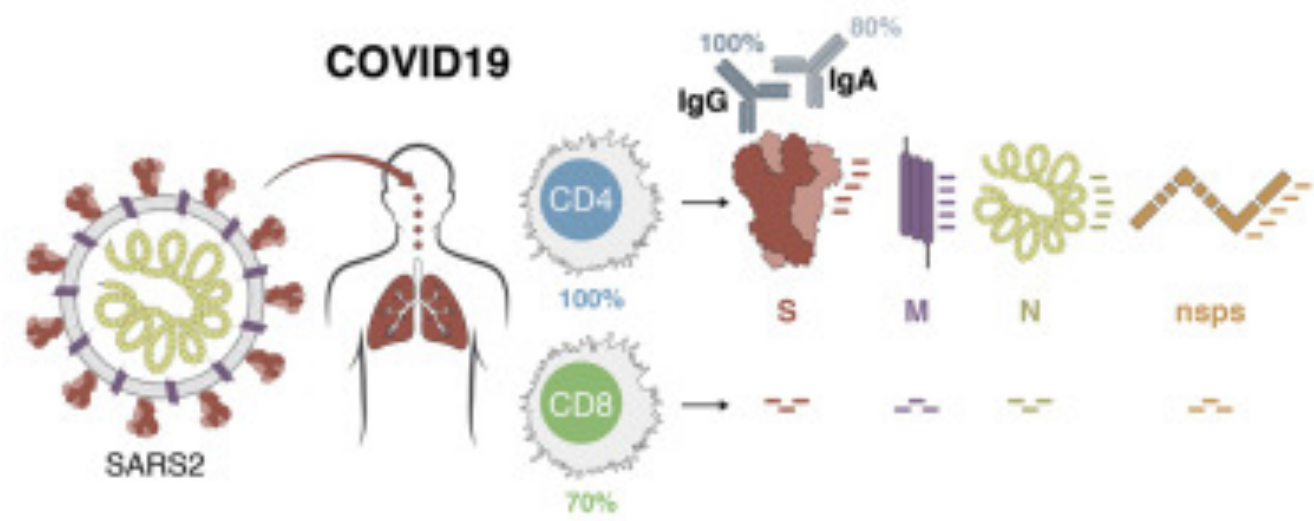


Vaccines

COVID-19 Vaccines



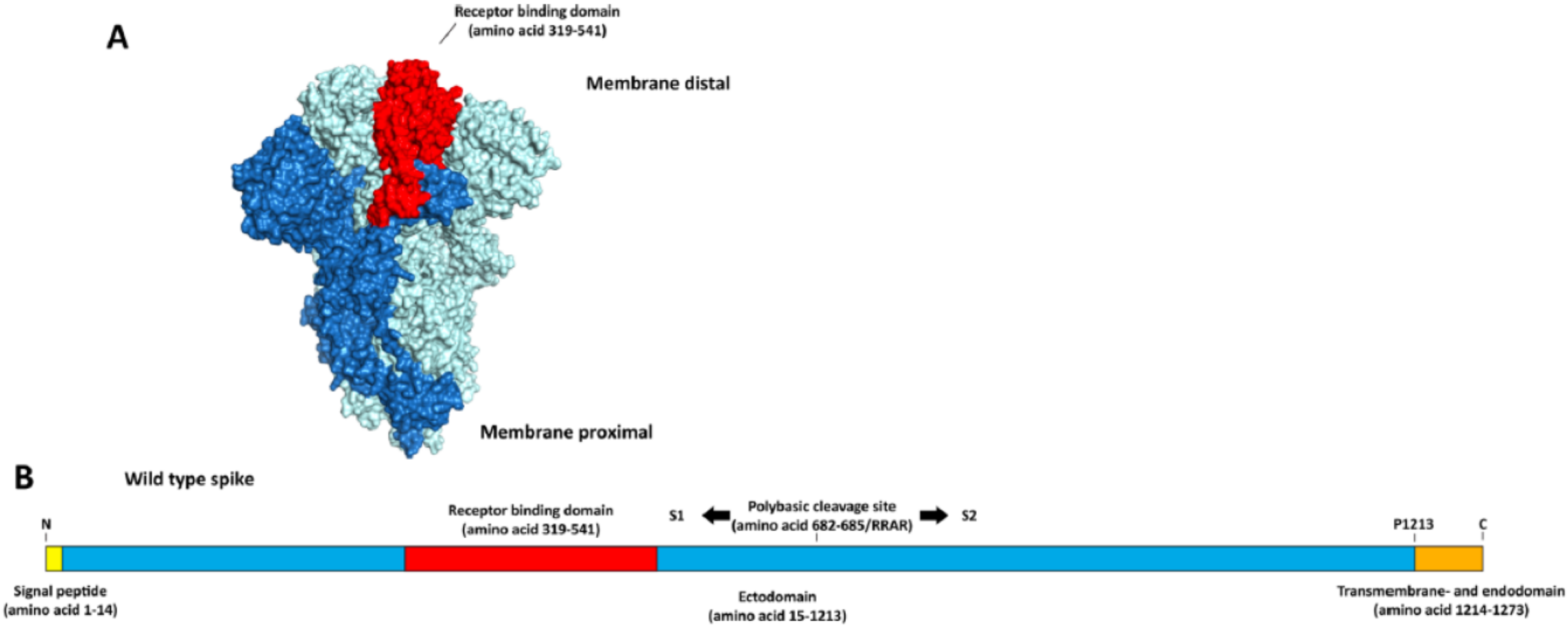
The spike protein of SARS-CoV and SARS-CoV-2 is activated by the protease TMPRSS2 before it binds to the ACE2 receptor.
MARKUS HOFFMANN / GERMAN PRIMATE CENTRE



Grifoni et al, DOI:10.1016/j.cell.2020.05.015

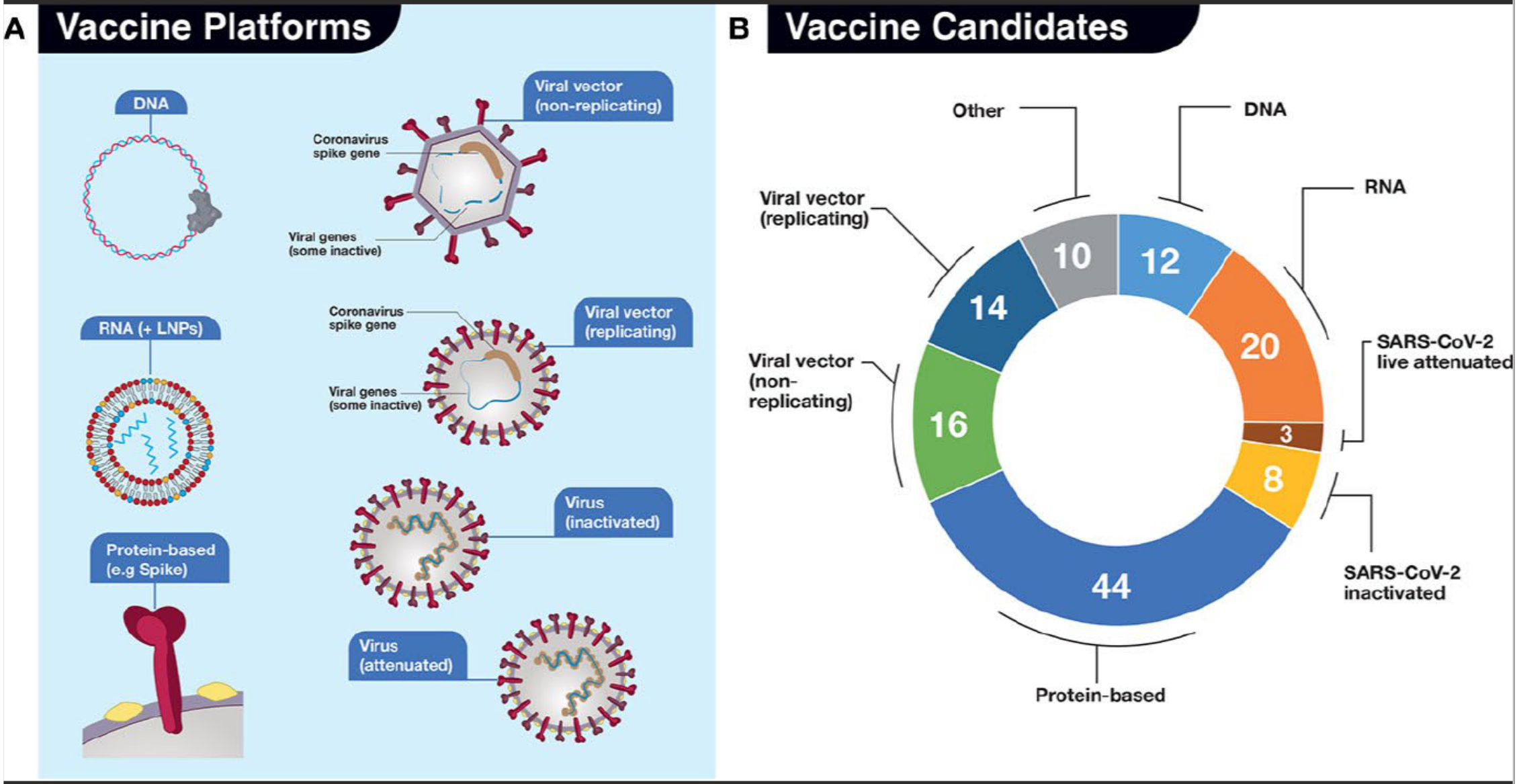
Target of Ab
(and cellular immunity)

Spike Protein, S



Amanat et al, Nat Med 2020

Over 140 Vaccine Candidates in Development



Funk et al, Front Pharmacol 2020

Technology	Attributes				Candidates in Preclinical Development	Candidates in Human Trials
	Single Dose	Licensed Platform	Speed	Current Scale		
DNA	No	No	Fast	Medium	Takis/Applied DNA Sciences/Evvivax Zydus Cadila	Inovio Pharmaceuticals, Phase 1 (NCT04336410)
Inactivated	No	Yes	Medium	Medium to high		Sinovac, Phase 1 (NCT04352608) Inactivated Beijing Institute of Biological Sciences/Wuhan Institute of Biological Sciences, Phase 1 (ChiCTR2000031809)
Live attenuated	Yes	Yes	Slow	High	Codagenix/Serum Institute of India	
Nonreplicating vector	Yes	No	Medium	High	GeoVax/BravoVax Janssen Pharmaceutical Companies Altimmune Greffex Vaxart ExpresS2ion	CanSino Biologics, Phases 1 and 2 (ChiCTR2000030906 and ChiCTR2000031781) University of Oxford/ AstraZeneca, Phase 1/2 (NCT04324606) Shenzhen Geno-Immune Medical Institute, Phase 1/2 (NCT04276896)
Protein subunit	No	Yes	Medium to fast	High	WRAIR/U.S. Army Medical Research Institute of Infectious Diseases Clover Biopharmaceuticals Inc/GSK Vaxil Bio AJ Vaccines Genrex/EpiVax/University of Georgia Sanofi Pasteur Novavax Heat Biologics/University of Miami University of Queensland/GSK/ Baylor College of Medicine iBio/CC-Pharming	
Replicating viral vector	Yes	Yes	Medium	High	Zydus Cadila Institut Pasteur/Themis Tonix Pharma/Southern Research	
RNA	No	No	Fast	Low to medium	Fudan University/Shanghai JiaoTong University/RNACure Biopharma China CDC/Tongji University/Stermina Arcturus/Duke-NUS	Moderna/NIAID (NCT04283461) BioNTech/Pfizer, Phase 1/2 (NCT04368728)

Lurie et al., N Engl J Med 2020; DOI: 10.1056/NEJMp2005630

Vaccines	Advantages	Disadvantages
Viral vectored vaccines	Stimulation of innate immune response; induction of T and B cell immune response.	induction of anti-vector immunity: cell based manufacturing
DNA vaccines	Non-infectious; stimulation of innate immune response; egg and cell free; stable, rapid and scalable production; induction of T and B cell immune response.	Potential integration into human genome; poor immunogenicity in humans.
RNA vaccines	Non-infectious, non-integrating, natural degradation, egg and cell free, rapid and scalable production; stimulation of innate immune response; induction of T and B cell immune response.	Concerns with instability and low immunogenicity.

Zhang et al, Front. Immunol., 27 March 2019 | https://doi.org/10.3389/fimmu.2019.00594

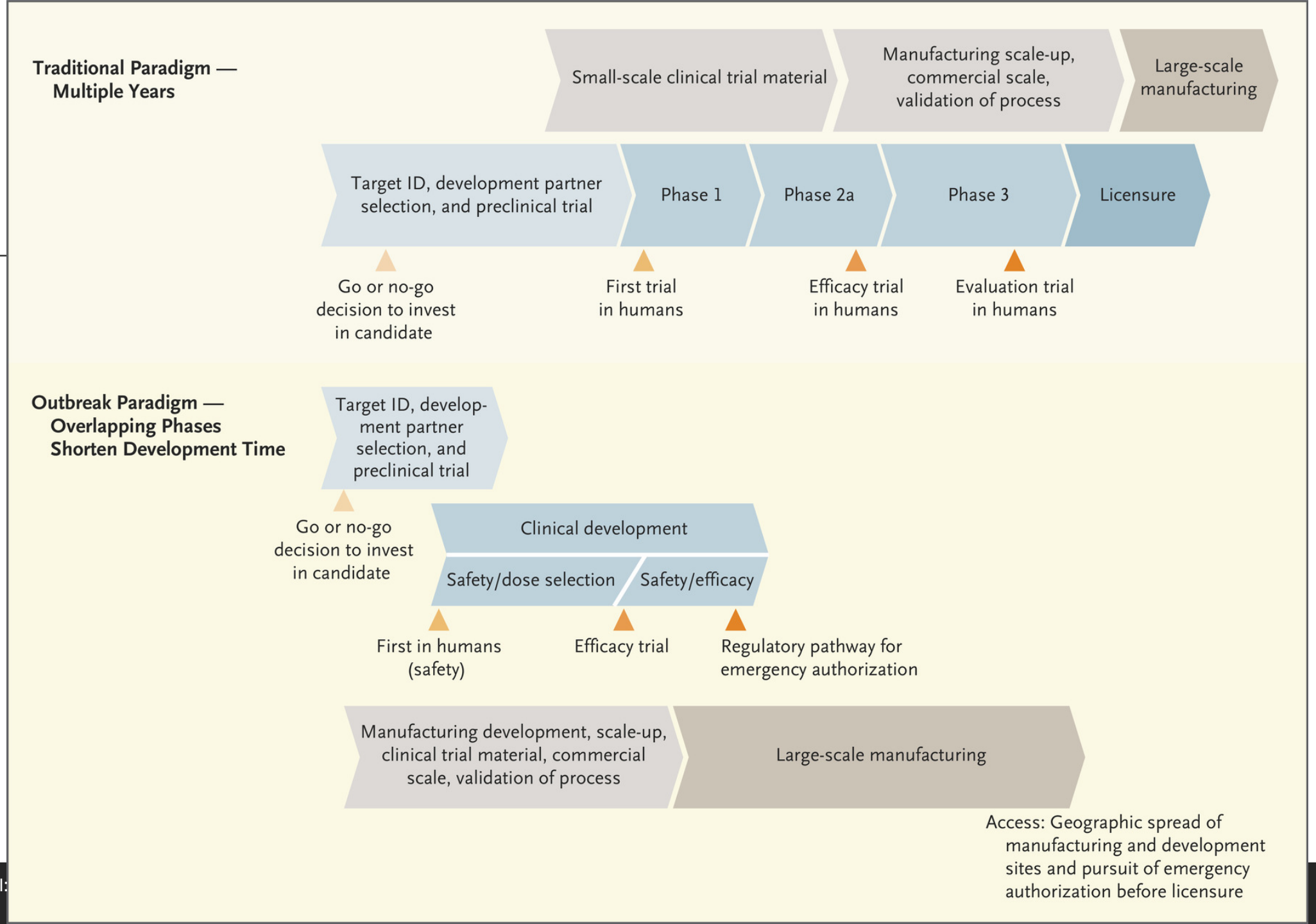
US Public/Private COVID-19 Partnerships

Operation Warp Speed

- US departments (DHHS, Agriculture, Energy, Veterans Affairs) and private sector
- NIH/Industry collaborative: ACTIV

BARDA (Biomedical Advanced Research and Development Authority)

- HHS Office of the Asst Secretary for Preparedness and Response



Lurie et al., N Engl J Med 2020; DOI: 10.1056/NEJMp2005630

Vaccine Candidates with Major Support by US Government

Merck/Int AIDS Vaccine Initiative

- *Live attenuated*, vesicular stomatitis virus-based
- Oral, single dose
- US Phase 1 start August

Sanofi/GSK

- *Peptide-based + adjuvant*
- US Phase 1 September

Novavax

- *Peptide-based*
- US Phase 3 October

University of Oxford & AstraZeneca

- Chimpanzee *adenovirus-based* (ChAdOx1) AZD1222
- UK Phase 3 in progress
- US Phase 3 August/September

Janssen/J & J

- Human *adenovirus-based*, replication defective: Ad26.COV2-S
- US Phase 3 September

Pfizer and BioNTech

- Lipid nanoparticle-encapsulated *mRNA-based* BNT162 a2/b1, b2, c2
- US Phase 2/3 began July

Moderna

- Lipid nanoparticle-encapsulated *mRNA-based*
- US Phase 3 began July

Encouraging monkey, human Phase 1 and/or 2 safety, immune, efficacy data for all

O'Callaghan et al, JAMA, 6 July 2020, doi:10.1001/jama.2020.12190
COVID-19 vaccine current status: Here are the 10 top contenders for coronavirus vaccines adapted from https://bit.ly/2Y6TMSY

COVID-19 Vaccines
FDA guidance 6/30/2020

RCTs, adequate power (n>5000; all plan at least 30,000 enrollees)

Diverse populations in all phases

- Including those most affected, specifically racial and ethnic minorities
- Adequate representation in late phase
  - Elderly
  - Medical comorbidities
  - Studies to support use during pregnancy and in pediatrics

Efficacy benchmark: prevent disease or decrease severity in at least 50% of those vaccinated (lower bound of 95% CI 30%)

Accelerated approval pathway once immune predictors of clinical benefit identified; full approval based on existing legal/FDA standards

Close post-marketing surveillance

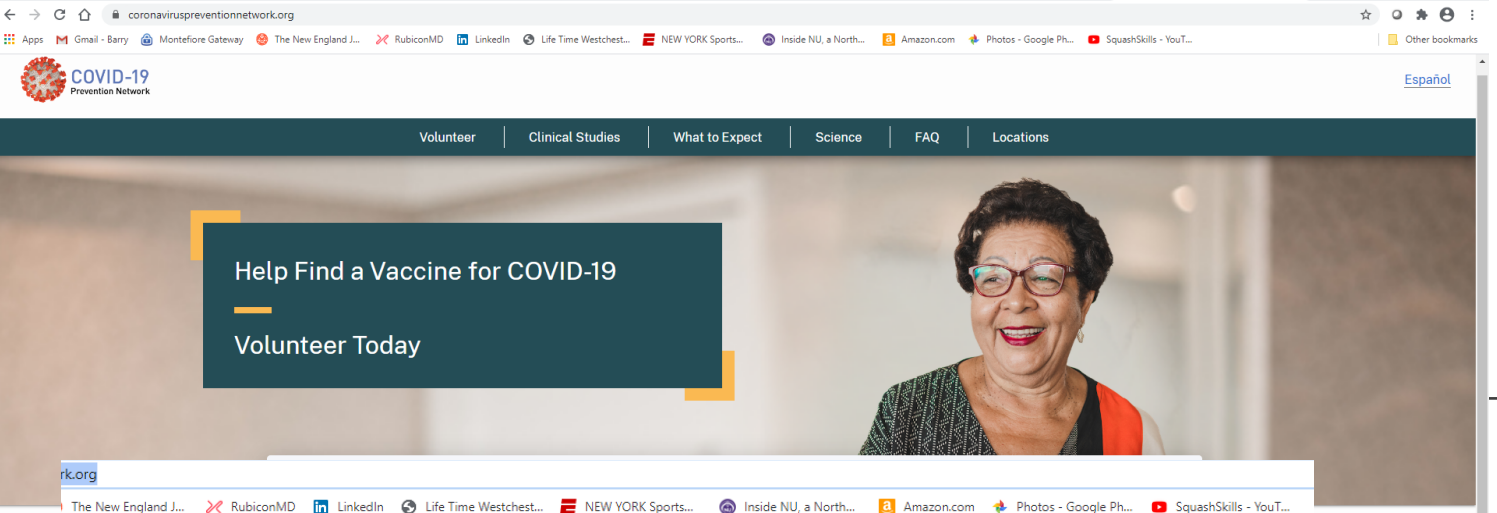
Hahn et al, JAMA. Published online August 7, 2020. doi:10.1001/jama.2020.15725

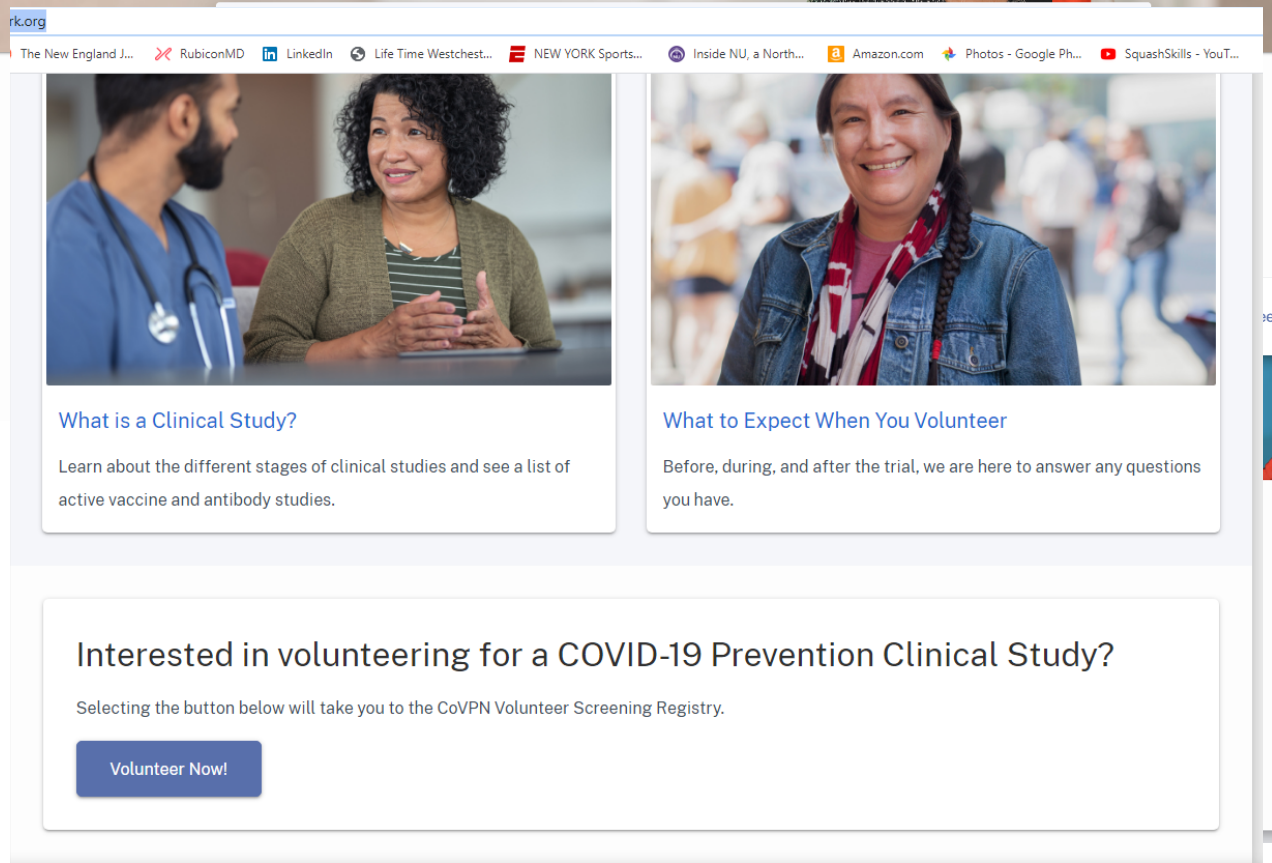
Russian “Sputnik V” adenovirus-based vaccine
Completed Phase 1/2?: no immune, efficacy or safety results released yet

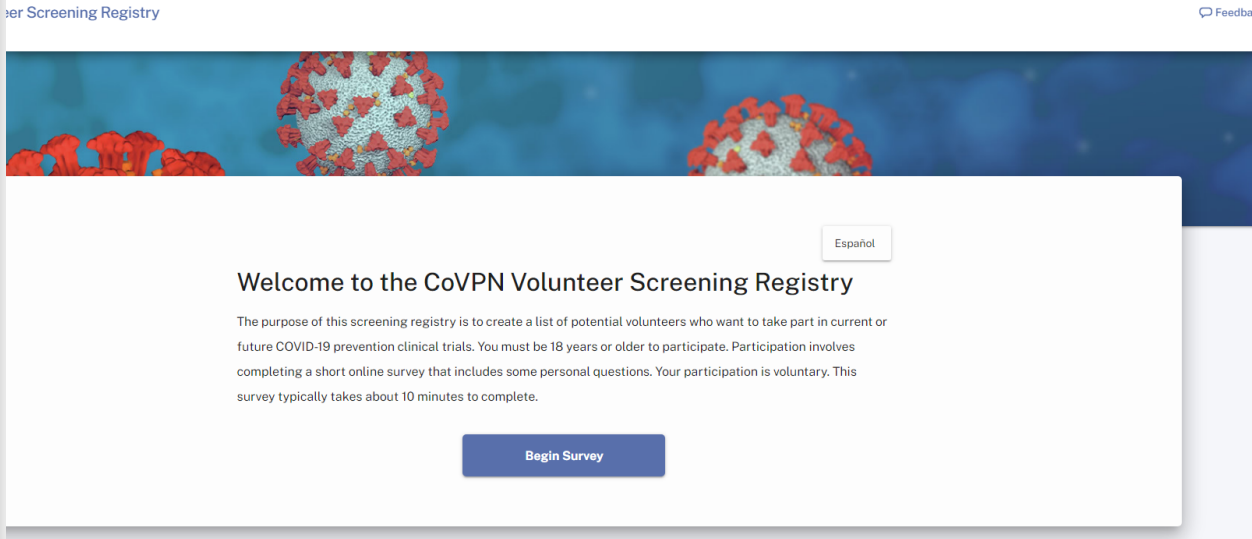
COVID-19 Prevention Network (CoVPN)

NIH/NIAID: Phase 3 vaccine and mAb prevention studies incorporating HIV vaccine, prevention & treatment trials networks and an ID trials network

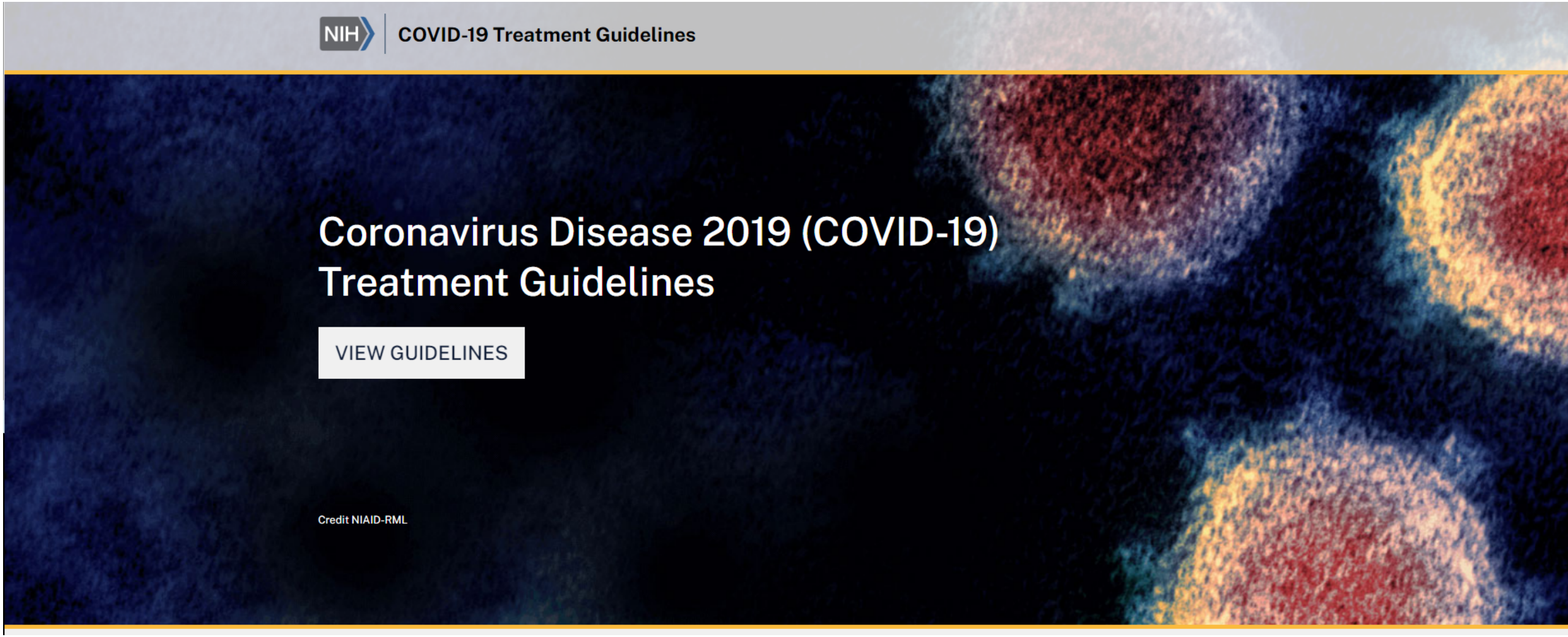
https://www.coronaviruspreventionnetwork.org/



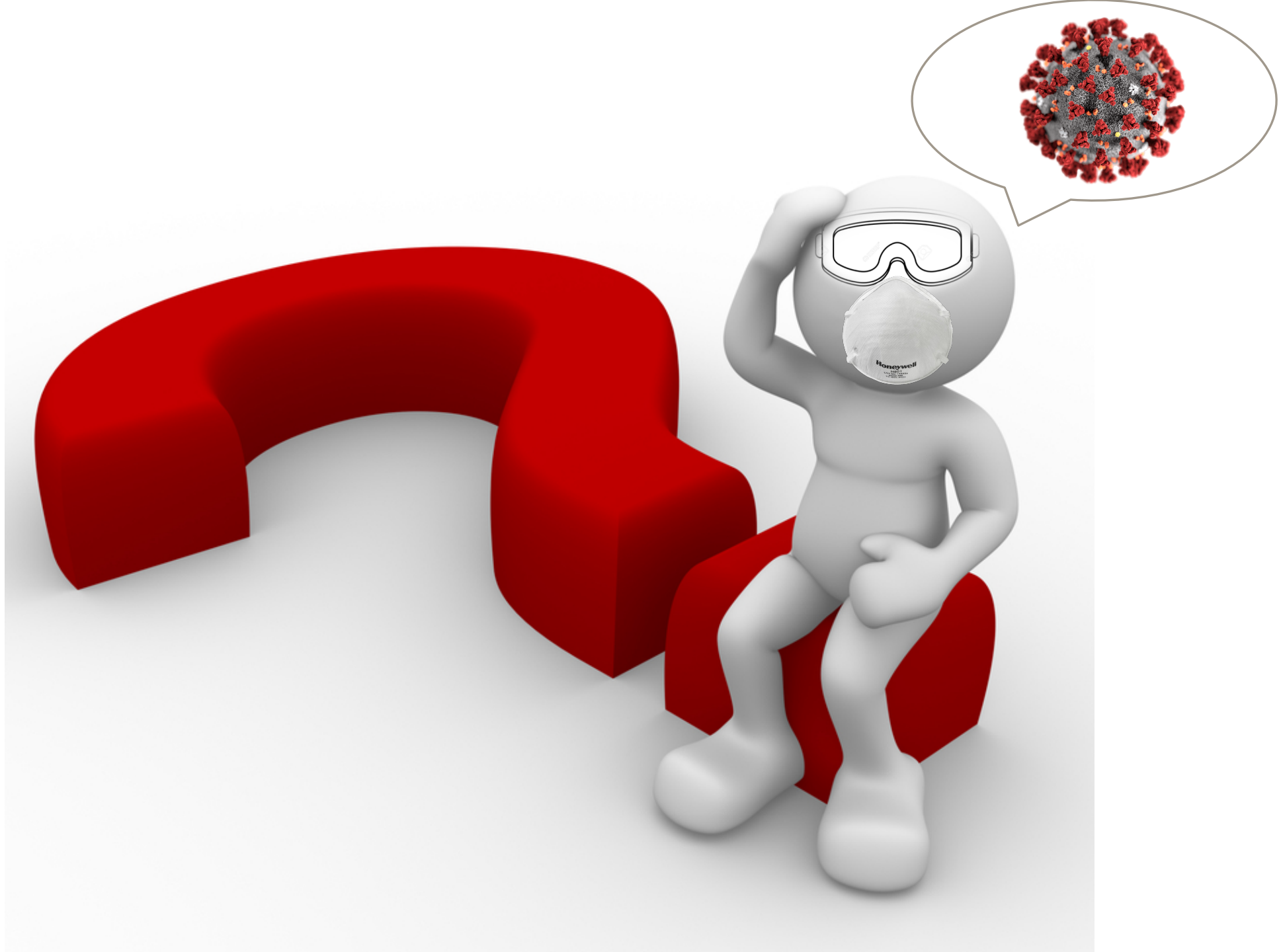




Moderna, Oxford/AstraZeneca, Janssen/J&J, Novavax



https://www.covid19treatmentguidelines.nih.gov/


Honeywell