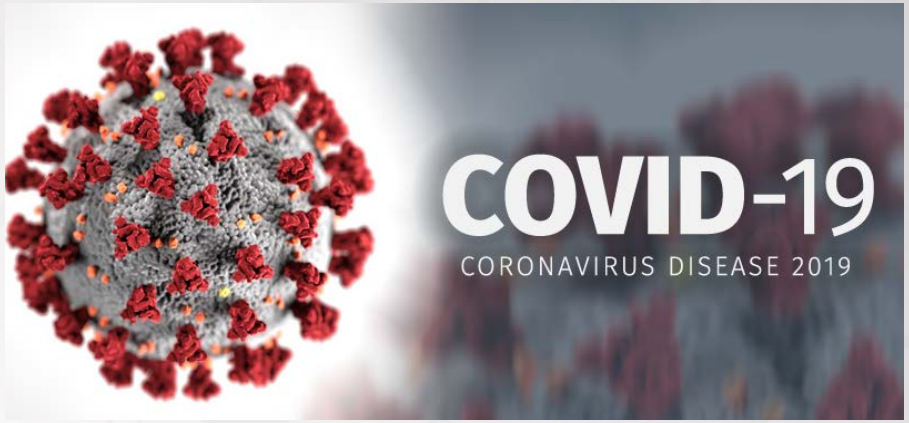
The nonhuman primate model of SARS-COV-2 to test therapeutic strategies: overcoming challenges and obstacles towards proof of concept.



Koen Van Rompay, DVM. PhD.

UCDAVIS
CALIFORNIA NATIONAL
PRIMATE RESEARCH CENTER

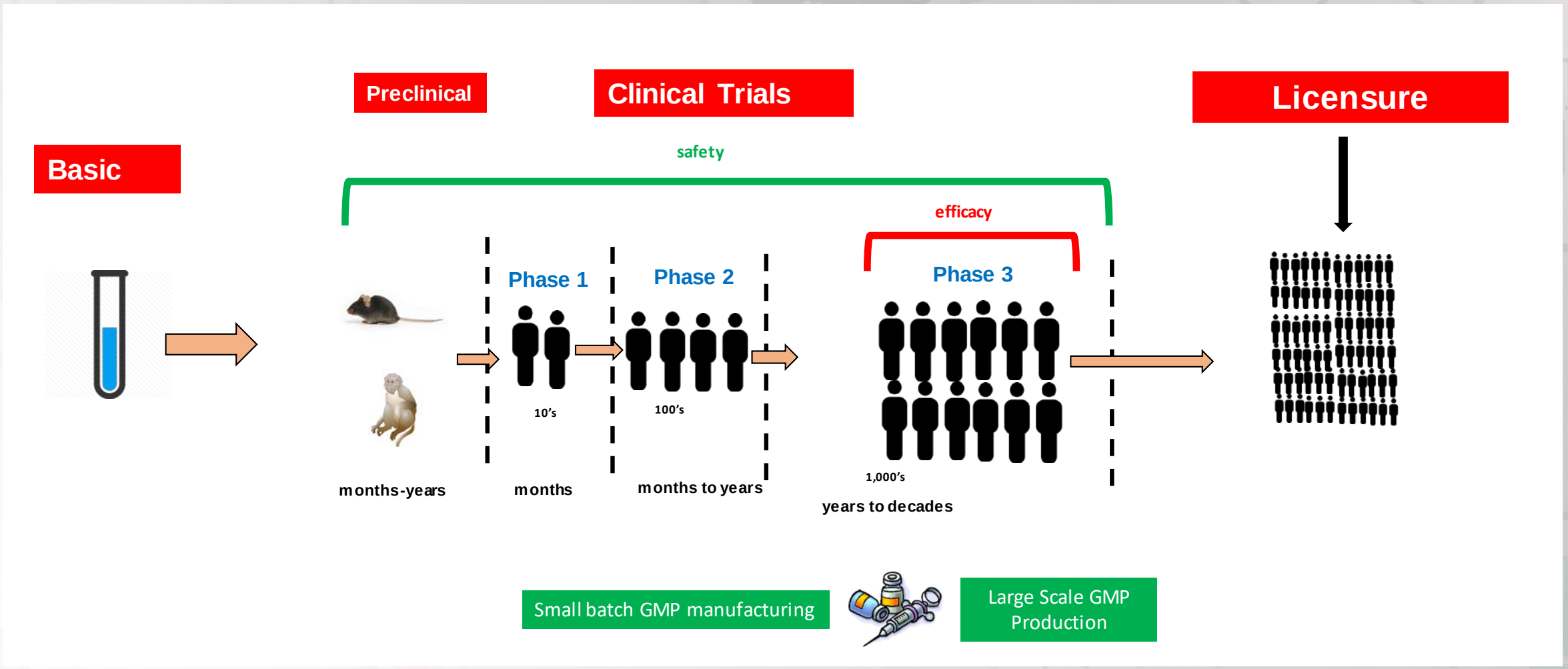
The National Academies of | SCIENCES ENGINEERING MEDICINE

RAPID RESPONSE BY
LABORATORY ANIMAL RESEARCH INSTITUTIONS
DURING THE COVID-19 PANDEMIC: LESSONS LEARNED
MARCH 9-10, 2021
A Virtual Workshop

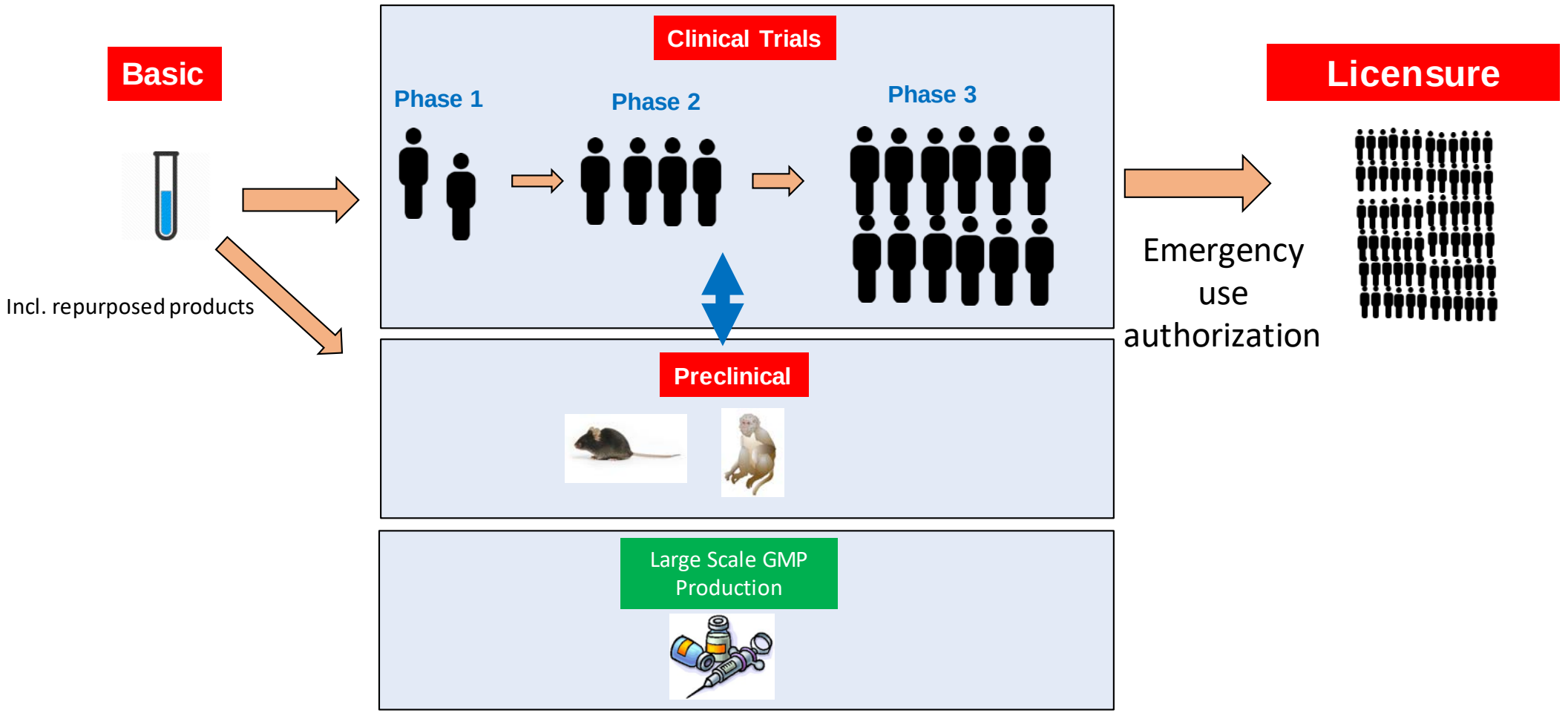
Overview

- Development of the NHP model: challenges & obstacles
- Examples of NHP studies: proof-of-concept

Typical clinical timeline (10-15 years)



COVID-19: Accelerated timeline



“normal times”

COVID-19

COVID lockdown

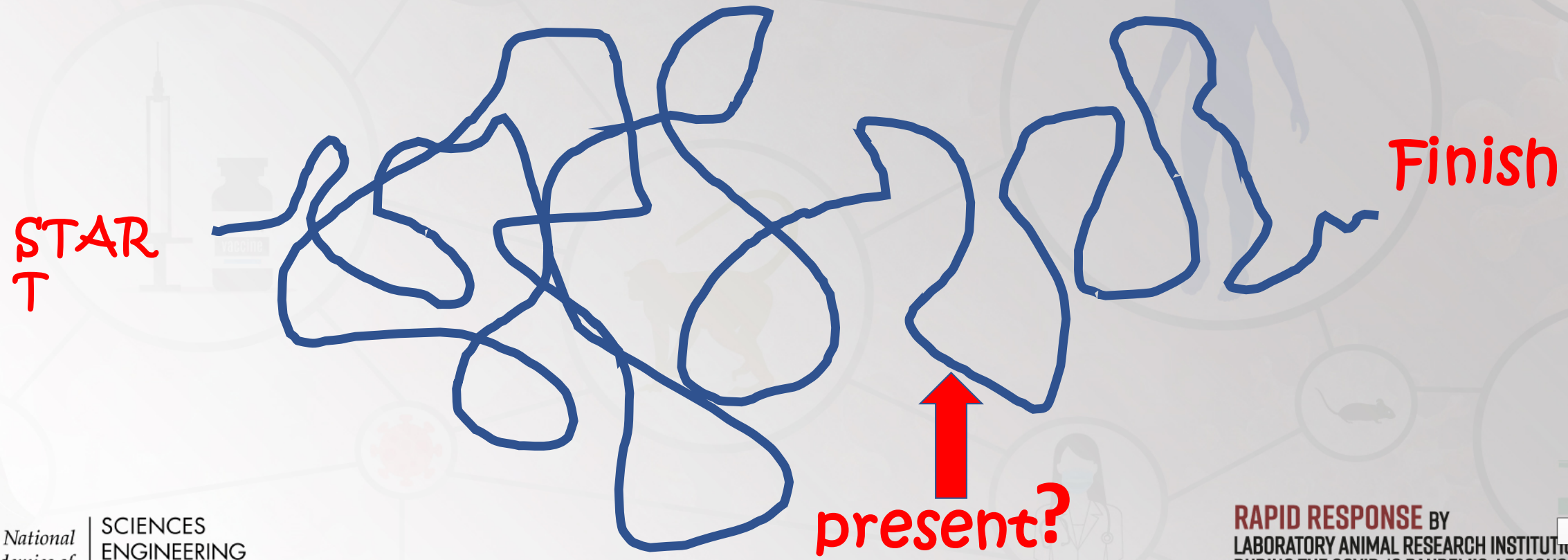
Supply shortage

Politics

Time pressure

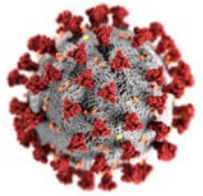
Funds?

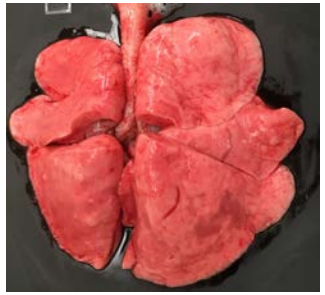
Shortage of monkeys



Ideal animal model of HUMAN VIRAL diseases

- Similarities in host
- Same (or similar) virus
- Similar disease



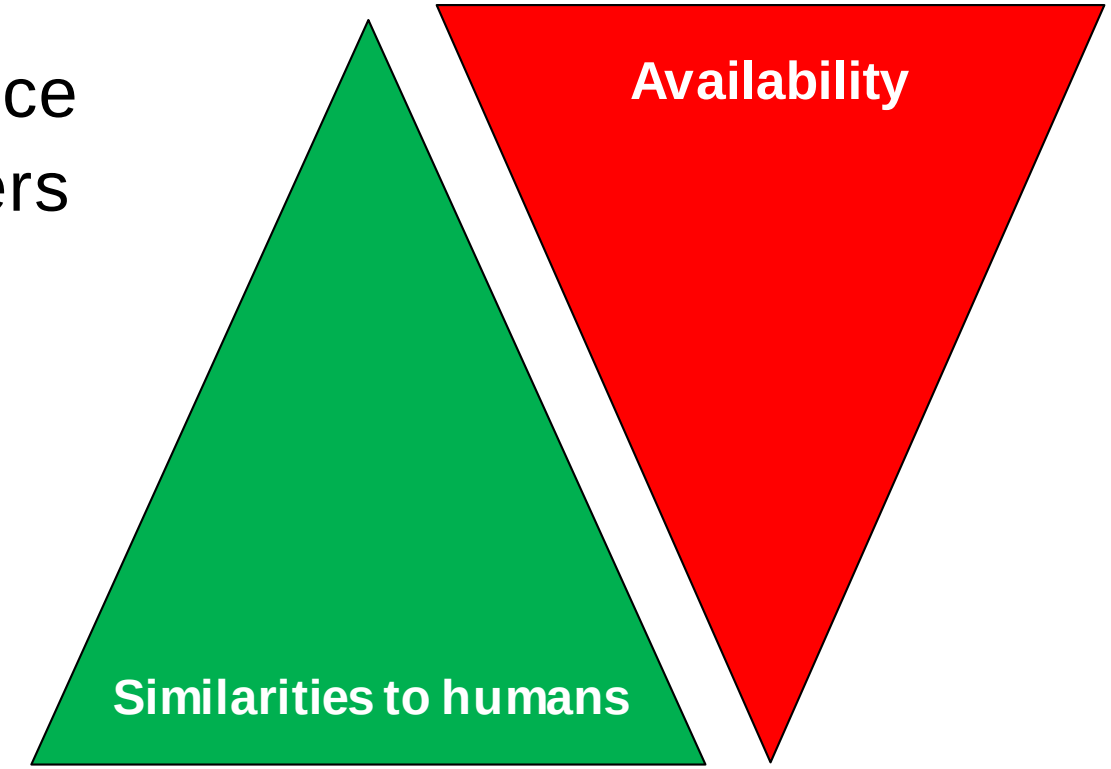


Animal models of SARS-CoV-2

- Transgenic mice
- Syrian hamsters
- Ferrets & cats
- **Nonhuman primates**

Macaques

AGM, Baboons, marmosets,….

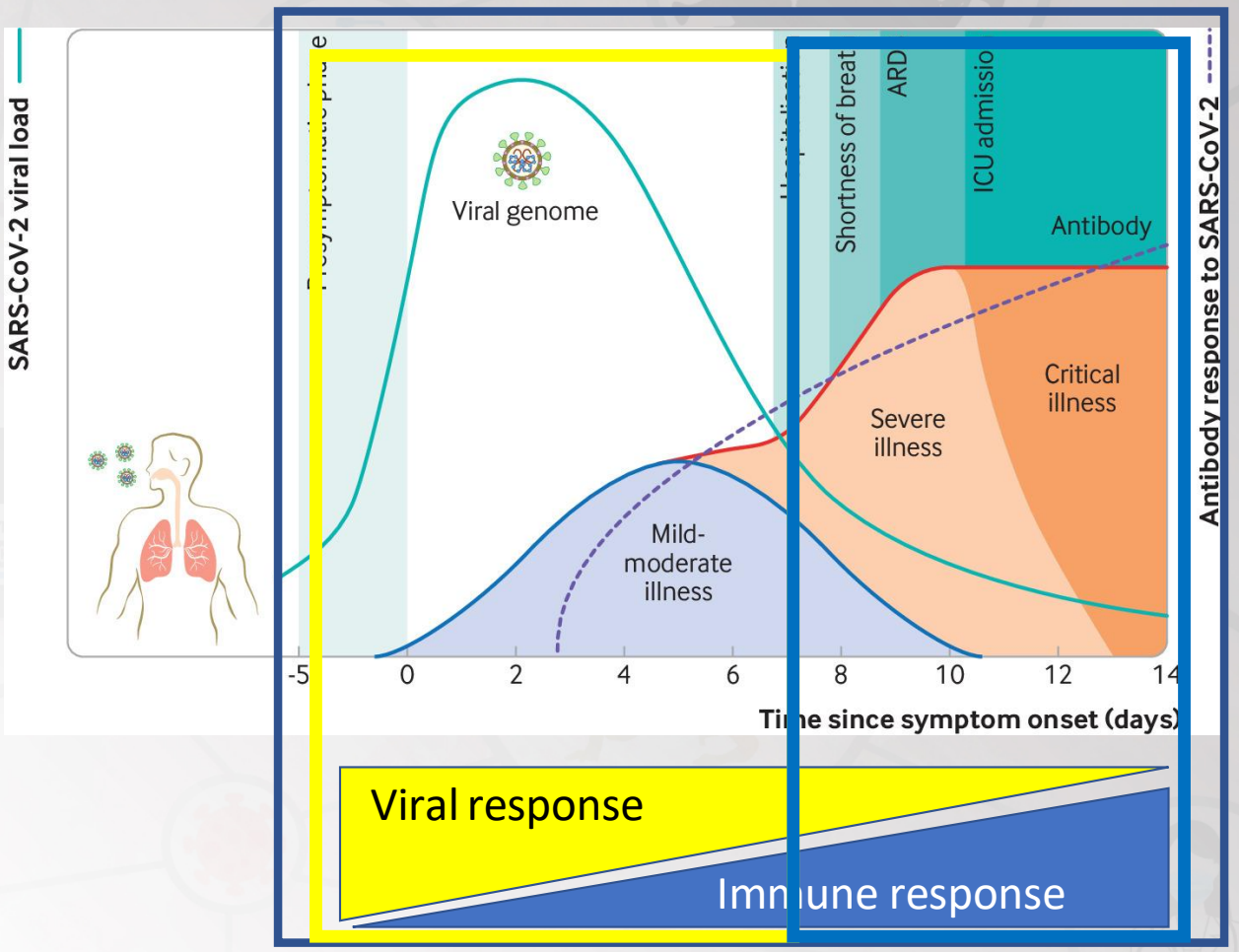


SARS-Cov-2 infection of Macaques: recapitulates majority of human covid-19 cases

- Clinical signs: mild-moderate
- Replication in upper & lower respiratory tract
- Innate & inflammatory responses
- Radiology & histology: pneumonia
- Antiviral immune responses, incl. neut. antibodies
- Immune to rechallenge

Model to test interventions

Natural History of SARS-CoV-2 infection



bmj | BMJ 2020;371:m3862 | doi:10.1136/bmj.m3862

Scientific challenges

?

- **Mimic human SARS-CoV-2 infection**
- High variability
- Treatment is only needed for minority (severe cases).

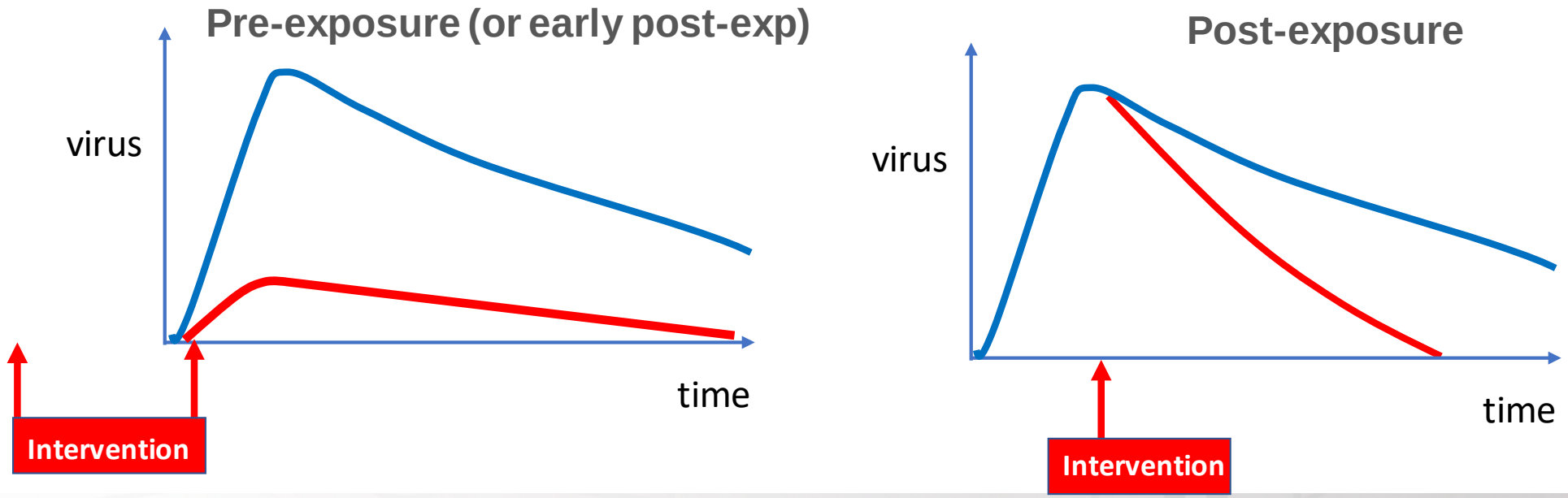
Proof of concept

A practical animal model

- Mostly mild-moderate disease
- Low animal numbers
- Try to reduce variability
- Surrogate markers

Considerations: NHP models for therapeutics

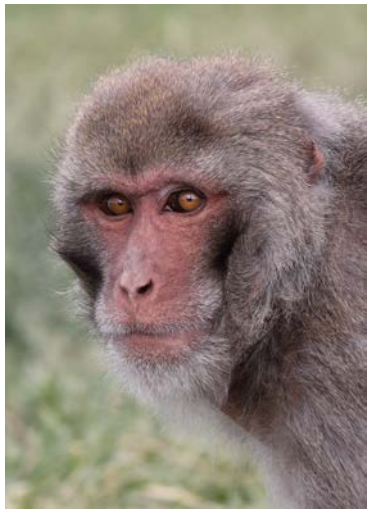
- **High-dose challenge models**: intranasal + intratracheal
- Peak virus replication early (~ 1-2 days)
- Considerable variability (outbred species, inoculation, sampling,…)
- Pre-exposure versus post-exposure



Monitoring SARS-CoV-2 infected animals

Clinical signs

Imaging
(X-ray, PET-CT,...)



Virus replication

- Upper respiratory tract
- Lower respiratory tract

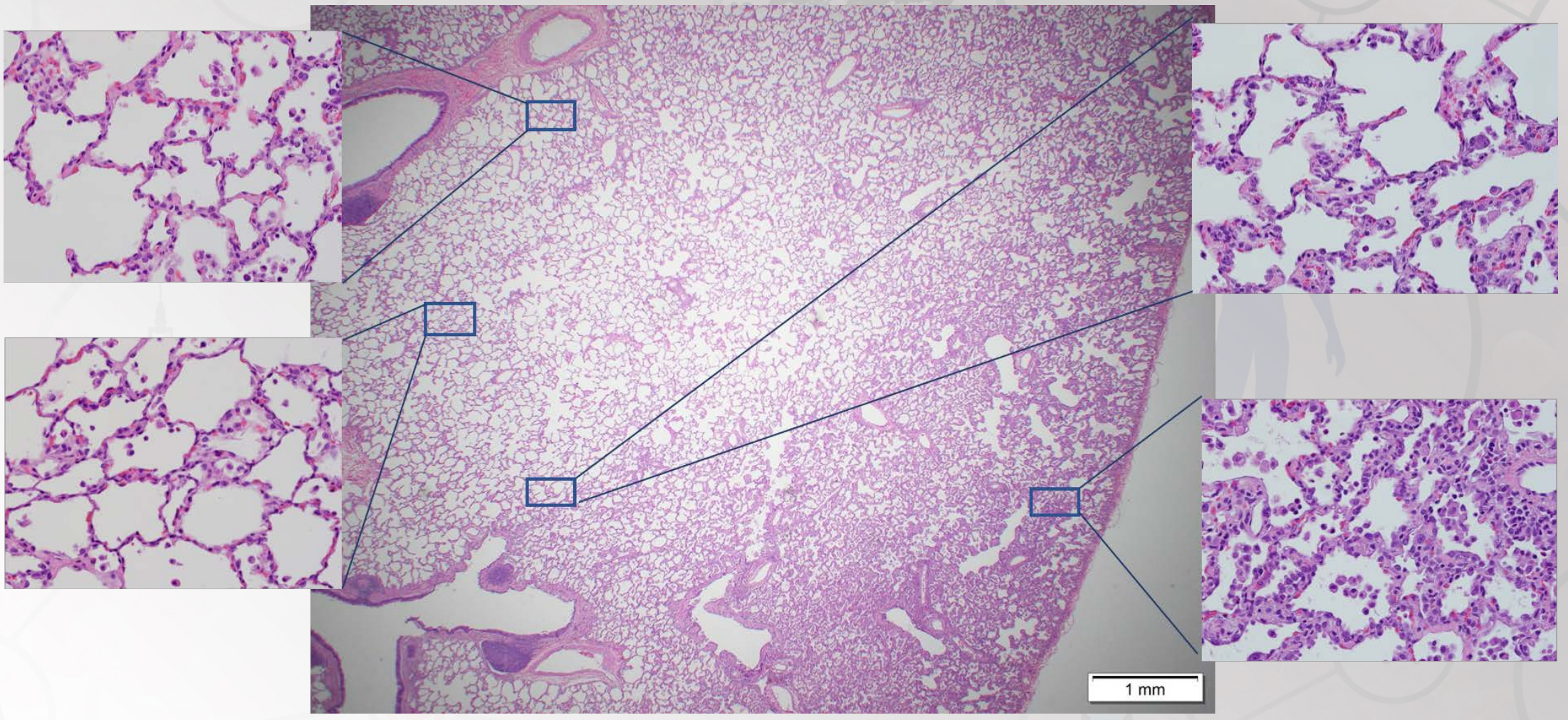
Lung histology

Lung histology scoring

- **Septal cellularity: interstitial pneumonia**
- # alveolar macrophages
- # alveolar neutrophils
- interstitial fibrosis
- type 2 hyperplasia
- pleuritis

Formalin drip infusion of lung

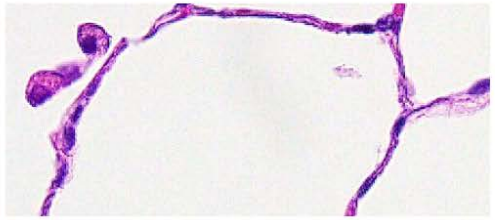
Challenges of lung Histology scoring



Lung HISTOLOGY scoring

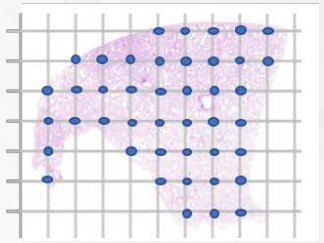
Septal Cellularity

Grade 0



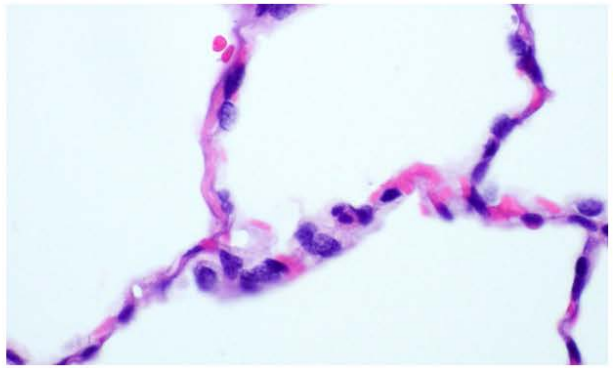
Scoring:

- Each point is scored individually at a 40x field

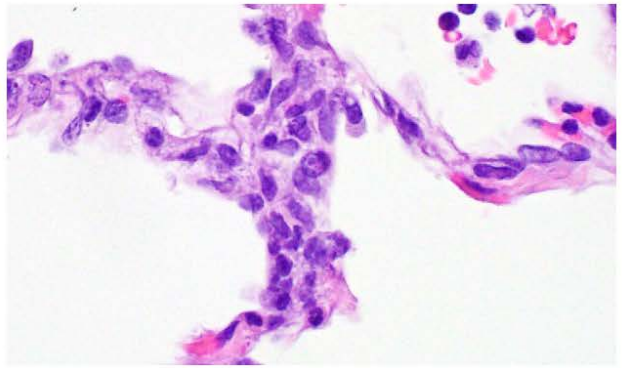


25 random 40x fields/slide
450 to 675 fields per animal

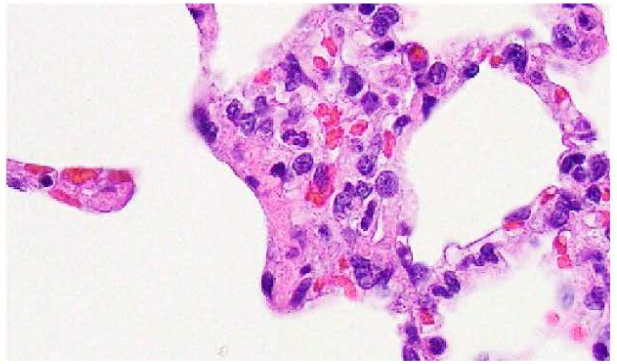
Grade 1 (~1-2 cells thick)



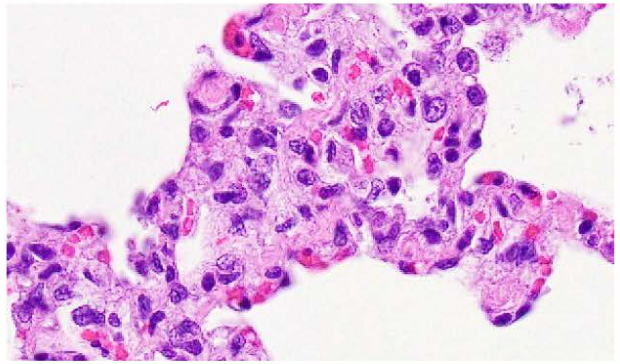
Grade 2 (~2-4 cells thick)



Grade 3 (~4-6 cells thick)



Grade 4 (~>6 cells thick)

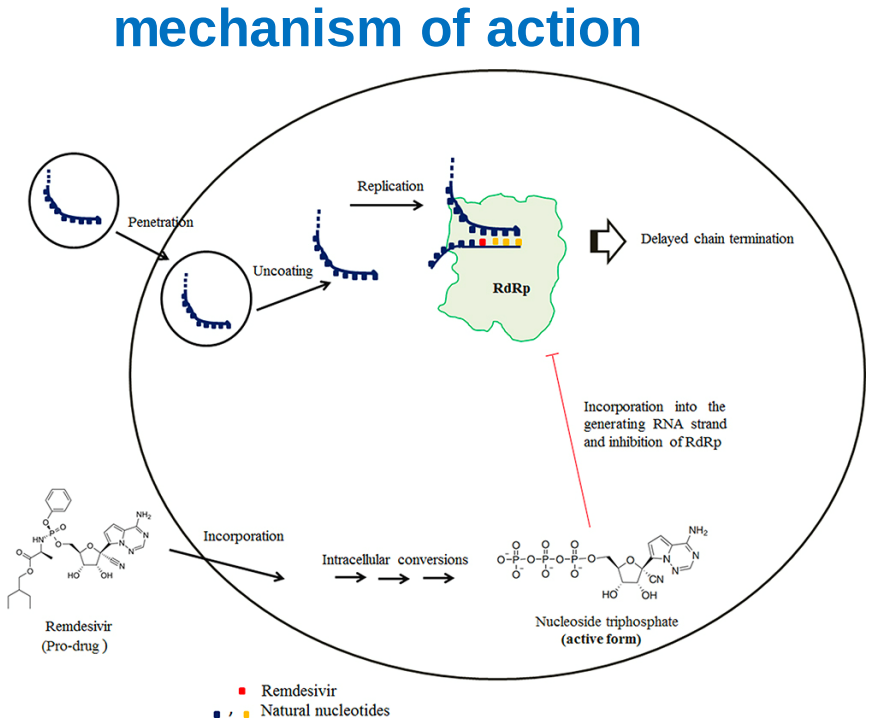


Therapeutic interventions against SARS-CoV-2

- Antiviral drugs
- Antiviral antibodies:
  - Convalescent plasma
  - Monoclonal antibodies
- Anti-inflammatory

Antiviral: Remdesivir

Remdesivir: phosphorylated, incorporated, then causes RNA chain termination



Hashemian SM, Farhadi T, Velayati AADove Medical Press
Nature, Sept. 2020

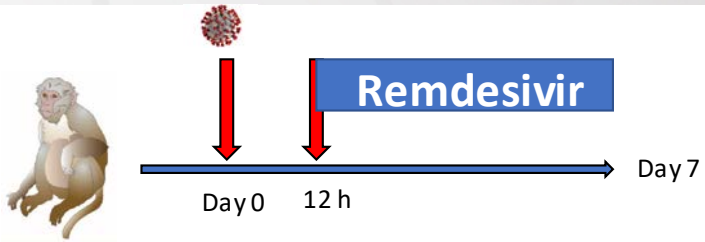
Therapeutic efficacy of remdesivir

Article

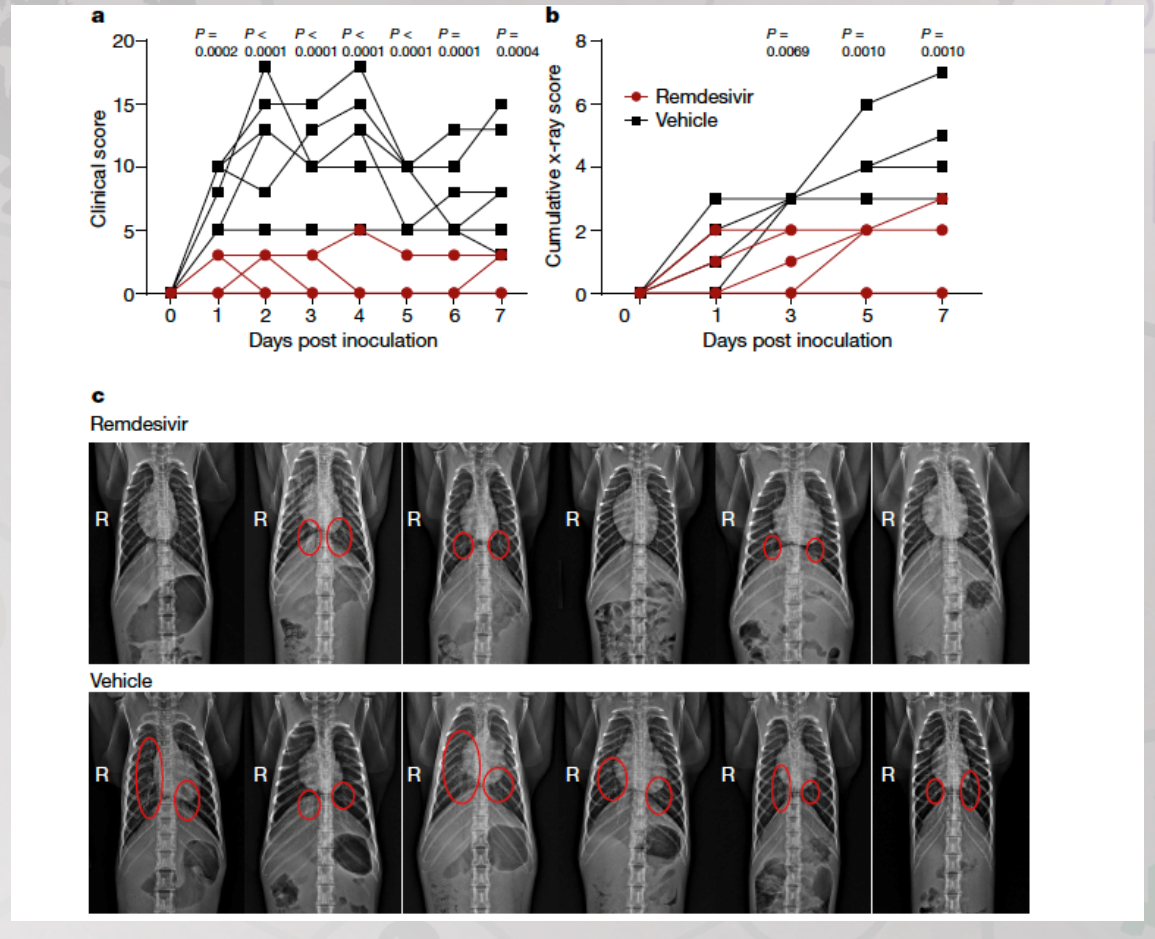
Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2

https://doi.org/10.1038/s41586-020-2423-5
Received: 23 April 2020
Accepted: 2 June 2020
Published online: 9 June 2020
Check for updates

Brandi N. Williamson[1], Friederike Feldmann[2], Benjamin Schwarz[3], Kimberly Meade-White[1], Danielle P. Porter[4], Jonathan Schulz[1], Neeltje van Doremalen[1], Ian Leighton[3], Claude Kwe Yinda[1], Lizzette Pérez-Pérez[1], Atsushi Okumura[1], Jamie Lovaglio[2], Patrick W. Hanley[2], Greg Saturday[2], Catharine M. Bosio[3], Sarah Anzick[5], Kent Barbian[5], Tomas Cihlar[4], Craig Martens[5], Dana P. Scott[2], Vincent J. Munster[1] & Emmie de Wit[1]✉

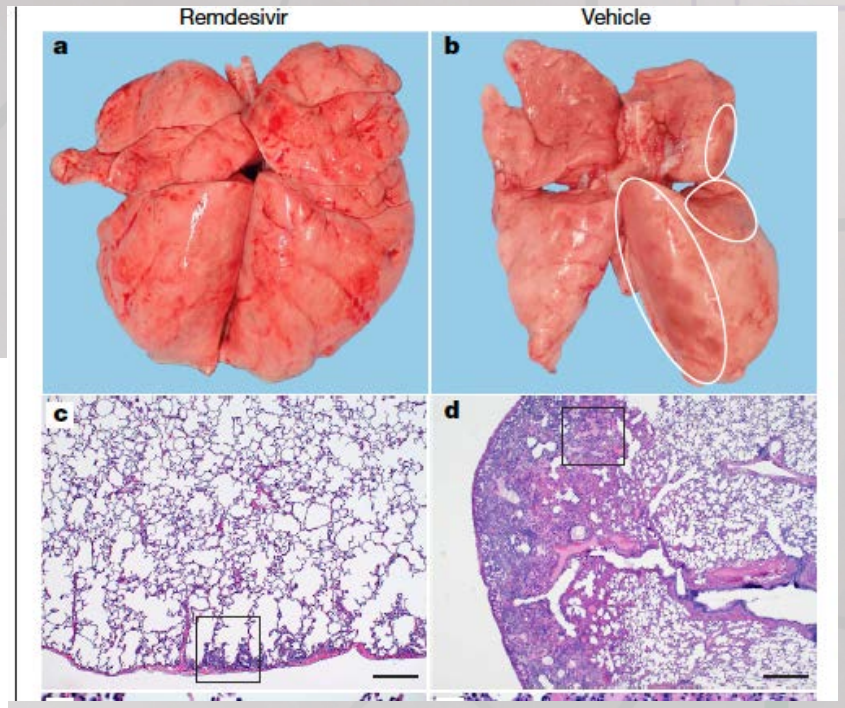


- Infection with SARS-Cov-2
- Treatment with remdesivir (10 mg/kg IV) starting 12 h post SARS-CoV-2 infection
- Reduced clinical scores
- Reduces radiographic scores



Therapeutic efficacy of remdesivir

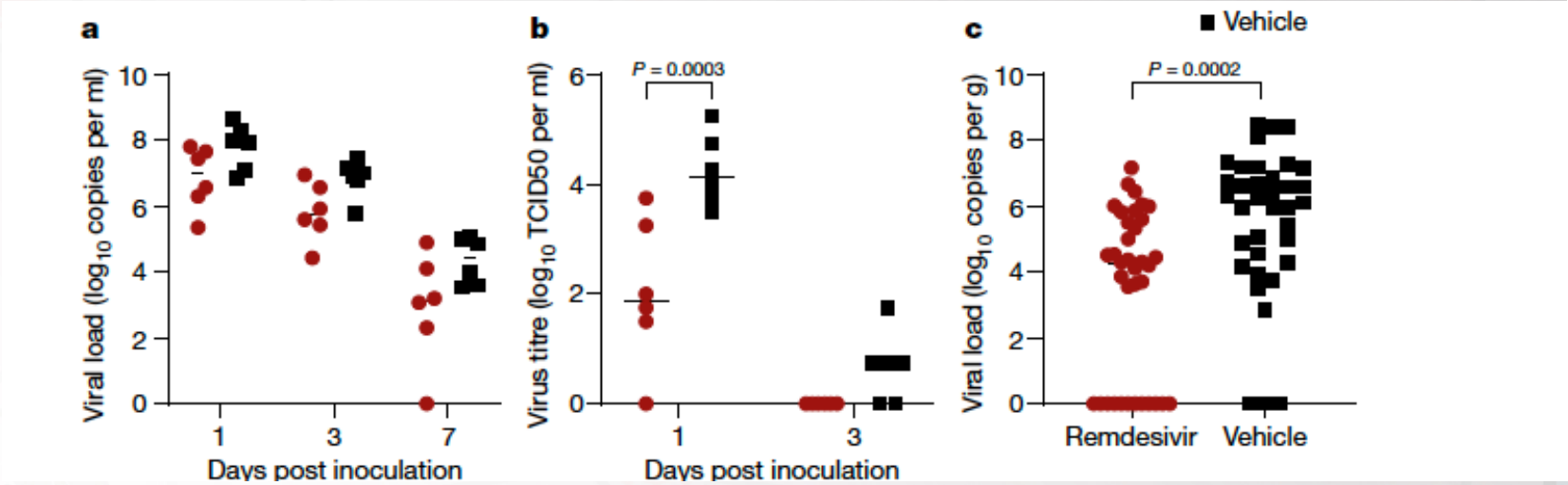
- Reduced virus replication in lung
- Reduced pneumonia



Viral RNA in BAL

Infectious virus in BAL

Viral RNA in lung lobes

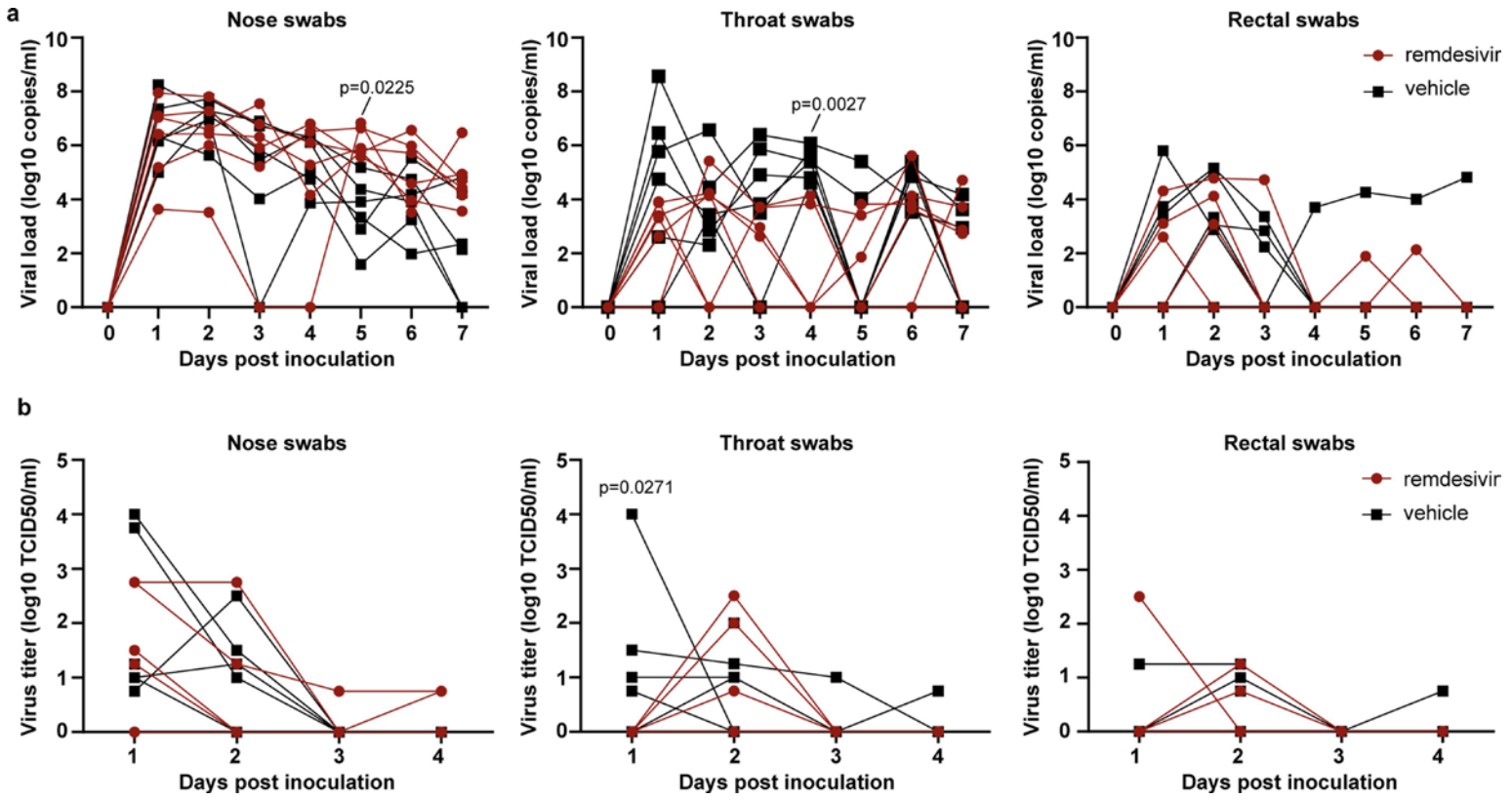


Remdesivir

no effect on viral shedding in mucosal secretions

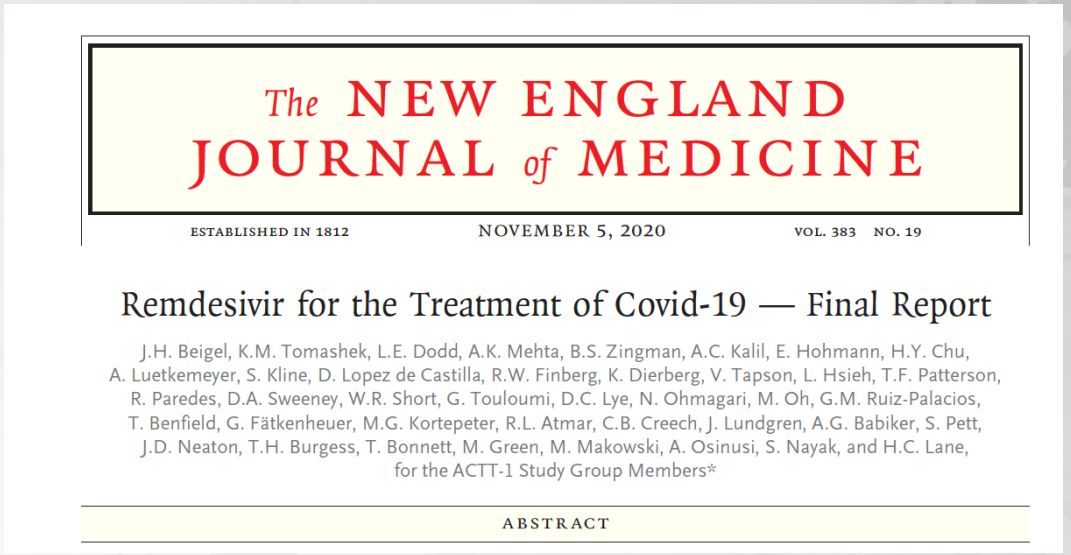
Viral RNA

Infectious virus



"clinical improvement should not be interpreted as a lack of infectiousness"

Remdesivir



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 5, 2020 VOL. 383 NO. 19

Remdesivir for the Treatment of Covid-19 — Final Report

J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, E. Hohmann, H.Y. Chu, A. Luetkemeyer, S. Kline, D. Lopez de Castilla, R.W. Finberg, K. Dierberg, V. Tapson, L. Hsieh, T.F. Patterson, R. Paredes, D.A. Sweeney, W.R. Short, G. Touloumi, D.C. Lye, N. Ohmagari, M. Oh, G.M. Ruiz-Palacios, T. Benfield, G. Fätkenheuer, M.G. Kortepeter, R.L. Atmar, C.B. Creech, J. Lundgren, A.G. Babiker, S. Pett, J.D. Neaton, T.H. Burgess, T. Bonnett, M. Green, M. Makowski, A. Osinusi, S. Nayak, and H.C. Lane, for the ACTT-1 Study Group Members*

ABSTRACT

Hospitalized patients

- Faster median recovery time (10 days versus 15 days)
- Moderate reduction on mortality

May 4, 2020:
FDA Emergency Use Authorization

October 22, 2020

FDA NEWS RELEASE

FDA Approves First Treatment for COVID-19

Share Tweet Linkedin Email Print

For Immediate Release: October 22, 2020

Español

Today, the U.S. Food and Drug Administration approved the antiviral drug Veklury (remdesivir) for use in adult and pediatric patients 12 years of age and older and weighing at least 40 kilograms (about 88 pounds) for the treatment of COVID-19 requiring hospitalization. Veklury should only be administered in a hospital or in a healthcare setting capable of providing acute care comparable to inpatient hospital care. Veklury is the first treatment for COVID-19 to receive FDA approval.

Passive immunization

Neutralizing antibodies

Monoclonal antibodies

Convalescent plasma (CP)

https://www.wired.com/story/trials-of-plasma-from-recovered-covid-19-patients-have-begun/

Monoclonal Antibodies

2 mAbs given either – 3 days or + 1 day

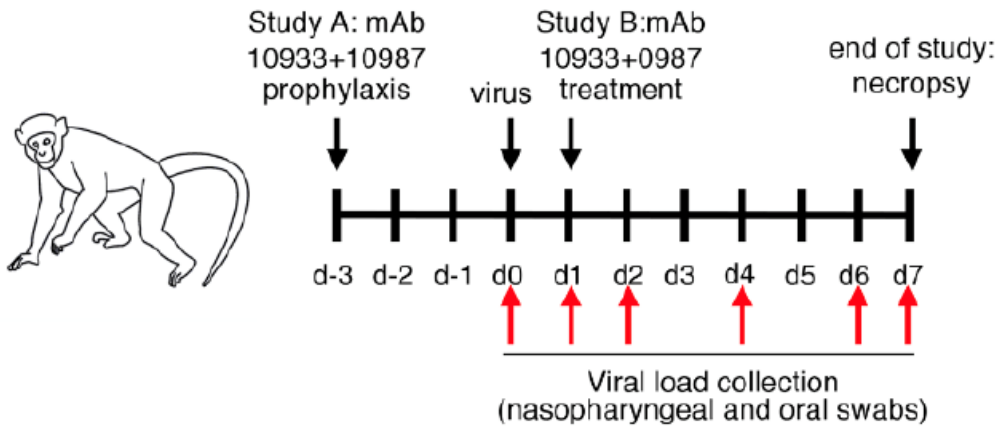
Science REPORTS

Cite as: A. Baum *et al.*, *Science* 10.1126/science.abe2402 (2020).

REGN-COV2 antibodies prevent and treat SARS-CoV-2 infection in rhesus macaques and hamsters

Alina Baum[1], Dharani Ajithdoss[1], Richard Copin[1], Anbo Zhou[1], Kathryn Lanza[1], Nicole Negron[1], Min Ni[1], Yi Wei[1], Kusha Mohammadi[1], Bret Musser[1], Gurinder S. Atwal[1], Adelekan Oyejide[1], Yenny Goez-Gazi[2], John Dutton[2], Elizabeth Clemmons[2], Hilary M. Staples[2], Carmen Bartley[2], Benjamin Klaffke[2], Kendra Alfson[2], Michal Gazi[2], Olga Gonzalez[2], Edward Dick Jr.[2], Ricardo Carrion Jr.[2], Laurent Pessaint[3], Maciel Porto[3], Anthony Cook[3], Renita Brown[3], Vaneesha Ali[3], Jack Greenhouse[3], Tammy Taylor[3], Hanne Andersen[3], Mark G. Lewis[3], Neil Stahl[1], Andrew J. Murphy[1], George D. Yancopoulos[1], Christos A. Kyratsous[1]*

[1]Regeneron Pharmaceuticals, Inc., Tarrytown, NY 10591, USA. [2]Southwest National Primate Research Center, Texas Biomedical Research Institute, San Antonio, TX 78245, USA. [3]BIOQUAL, Rockville, MD 20850, USA.



Challenge route	intratracheal/ intranasal
Challenge dose	1.05x10^6 PFU
Study A dose groups (prophylaxis)	0.3,50 (mg/kg)
Study B dose groups (treatment)	25,150 (mg/kg)

- **Reduced virus replication in upper & lower respiratory tract**
- **Reduced lung pathology**

Emergency Use Authorization of MABs

Nov 10, Nov 21, 2020

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

REGN-COV2, a Neutralizing Antibody Cocktail, in Outpatients with Covid-19

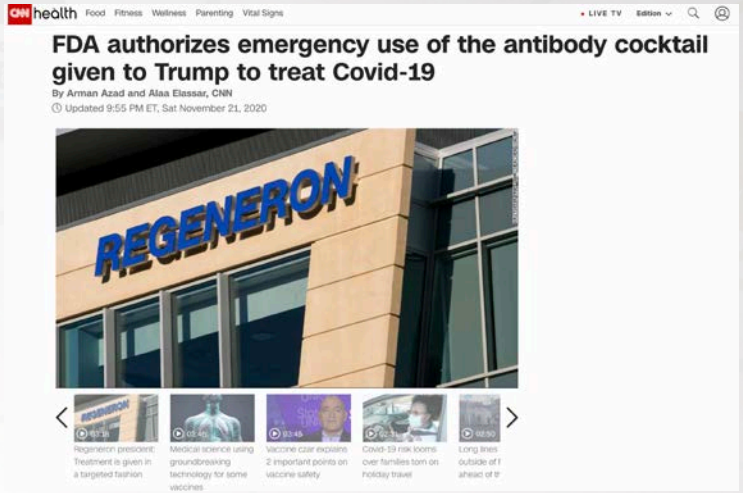
D.M. Weinreich, S. Sivapalasingam, T. Norton, S. Ali, H. Gao, R. Bhore, B.J. Musser, Y. Soo, D. Rofail, J. Im, C. Perry, C. Pan, R. Hosain, A. Mahmood, J.D. Davis, K.C. Turner, A.T. Hooper, J.D. Hamilton, A. Baum, C.A. Kyratsous, Y. Kim, A. Cook, W. Kampman, A. Kohli, Y. Sachdeva, X. Graber, B. Kowal, T. DiCioccio, N. Stahl, L. Lipsich, N. Braunstein, G. Herman, and G.D. Yancopoulos, for the Trial Investigators*

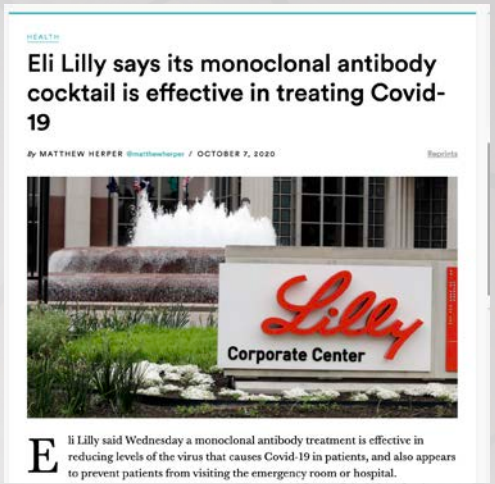
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

SARS-CoV-2 Neutralizing Antibody LY-CoV555 in Outpatients with Covid-19

Peter Chen, M.D., Ajay Nirula, M.D., Ph.D., Barry Heller, M.D., Robert L. Gottlieb, M.D., Ph.D., Joseph Boscia, M.D., Jason Morris, M.D., Gregory Huhn, M.D., M.P.H.T.M., Jose Cardona, M.D., Bharat Mocherla, M.D., Valentina Stosor, M.D., Imad Shawa, M.D., Andrew C. Adams, Ph.D., Jacob Van Naarden, B.S., Kenneth L. Custer, Ph.D., Lei Shen, Ph.D., Michael Durante, M.S., Gerard Oakley, M.D., Andrew E. Schade, M.D., Ph.D., Janelle Sabo, Pharm.D., Dipak R. Patel, M.D., Ph.D., Paul Klekotka, M.D., Ph.D., and Daniel M. Skovronsky, M.D., Ph.D., for the BLAZE-1 Investigators*



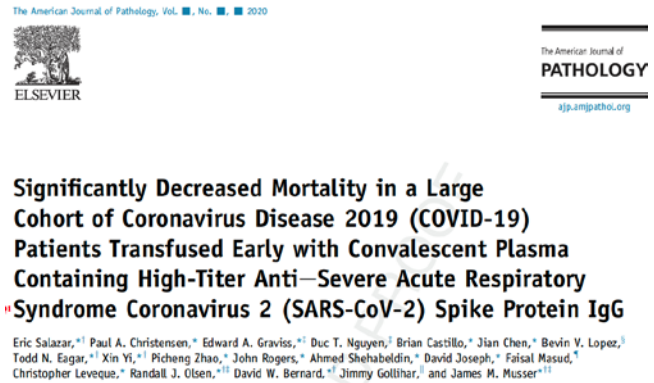


Convalescent plasma

Early treatment with CP with high neut titers provides benefits

(unpublished NHP data)

+



The American Journal of Pathology, Vol. ■, No. ■, ■ 2020

ELSEVIER

The American Journal of PATHOLOGY

ajp.amjpathol.org

Significantly Decreased Mortality in a Large Cohort of Coronavirus Disease 2019 (COVID-19) Patients Transfused Early with Convalescent Plasma Containing High-Titer Anti—Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Spike Protein IgG

Eric Salazar,*† Paul A. Christensen,* Edward A. Graviss,*‡ Duc T. Nguyen,‖ Brian Castillo,* Jian Chen,* Bevin V. Lopez,‖ Todd N. Eagar,*† Xin Yi,*† Picheng Zhao,* John Rogers,* Ahmed Shehabeldin,* David Joseph,* Faisal Masud,¶ Christopher Leveque,* Randall J. Olsen,*†‖ David W. Bernard,*† Jimmy Gollihar,‖ and James M. Musser*†‖

August 23, 2020
FDA Emergency Use Authorization

FDA NEWS RELEASE

FDA Issues Emergency Use Authorization for Convalescent Plasma as Potential Promising COVID-19 Treatment, Another Achievement in Administration's Fight Against Pandemic

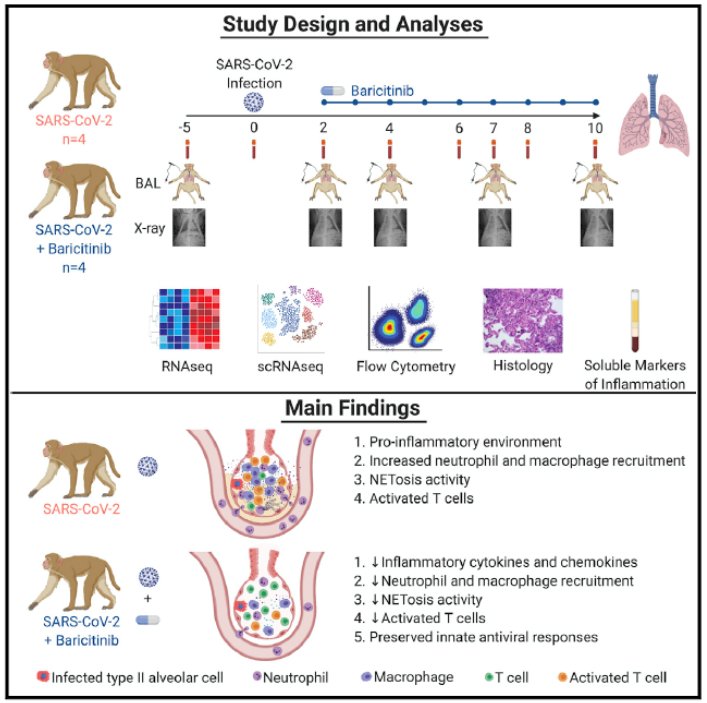
Share Tweet LinkedIn Email Print

For Immediate Release: August 23, 2020

Anti-inflammatory treatment: Baricitinib

Baricitinib treatment resolves lower-airway macrophage inflammation and neutrophil recruitment in SARS-CoV-2-infected rhesus macaques

Graphical Abstract



Authors

Timothy N. Hoang, Maria Pino, Arun K. Boddapati, ..., Raymond F. Schinazi, Steven E. Bosinger, Mirko Paiardini

Correspondence

rschina@emory.edu (R.F.S.), steven.bosinger@emory.edu (S.E.B.), mirko.paiardini@emory.edu (M.P.)

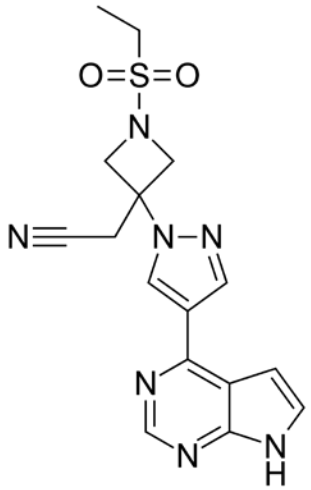
In Brief

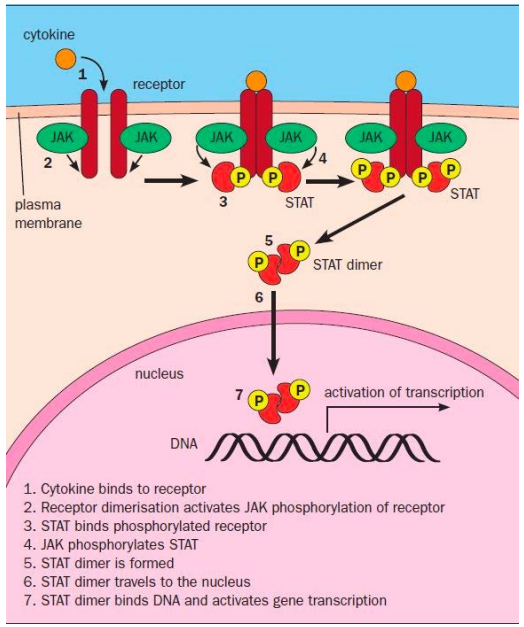
Using a rhesus macaque infection model, it is shown that baricitinib treatment started early after infection effectively resolves inflammatory signatures in airway macrophages, with decreased lung pathology and neutrophil infiltration.

Cell, 2021

Baricitinib

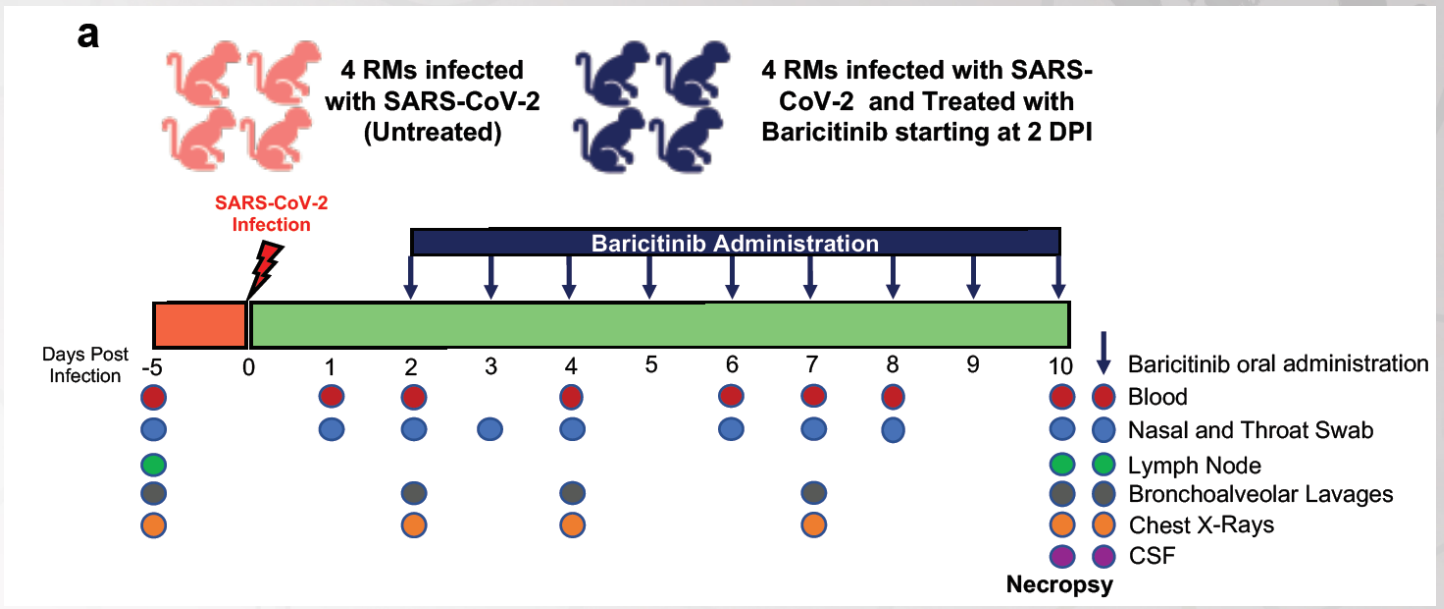
- JAK1/2 inhibitor: anti-inflammatory; reduces hypercytokinemia
- Oral tablet
- Used to treat rheumatoid arthritis



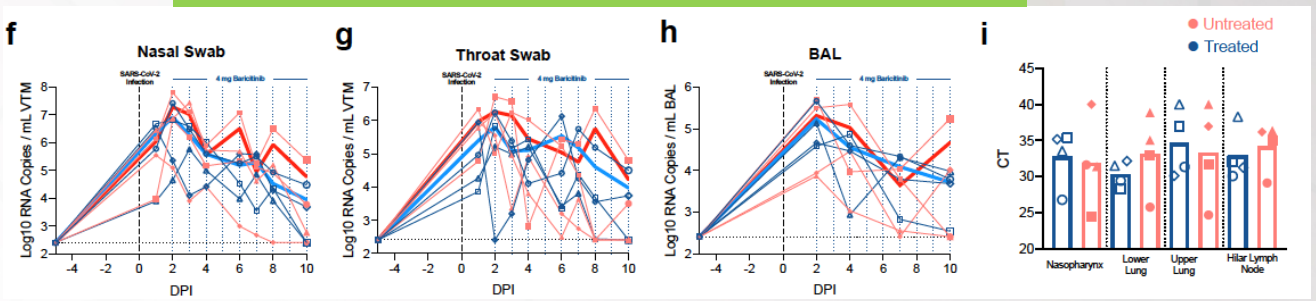


https://www.prescriber.co.uk/article/janus-kinase-inhibitors-autoimmune-disorders/

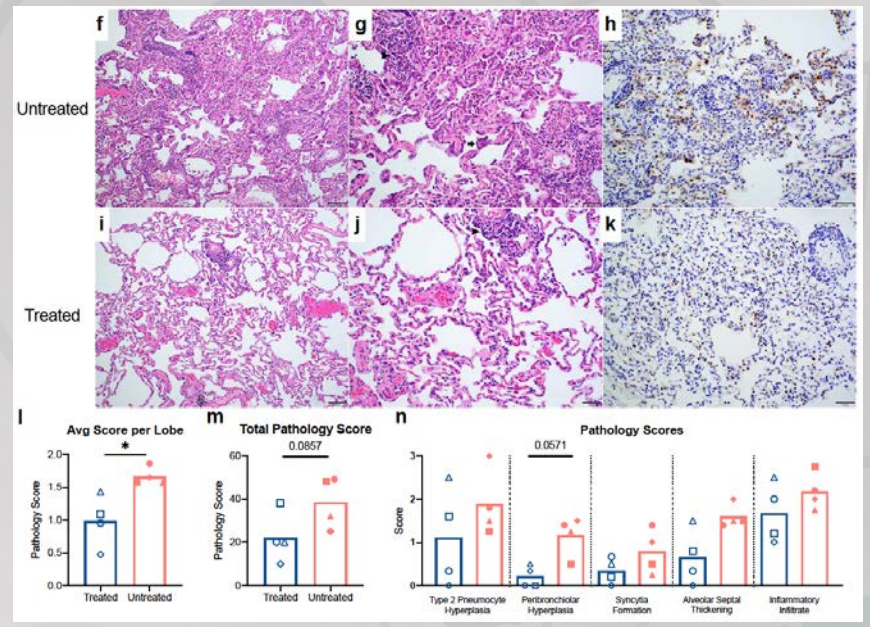
Baricitinib: Experimental design & Results



No difference in viral replication



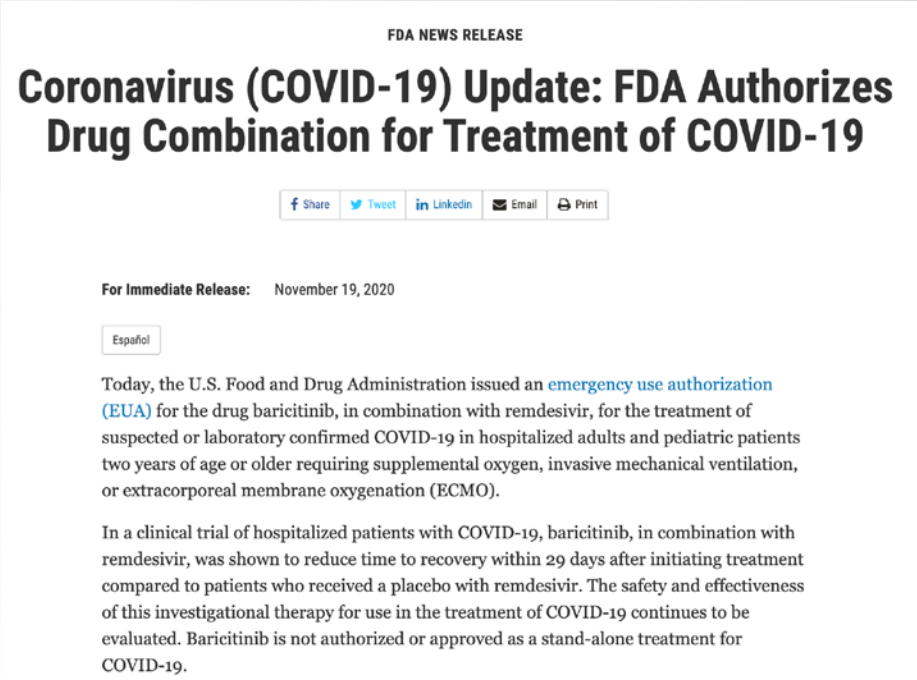
Reduced lung inflammation



Baricitinib + Remdesivir

November 19, 2020

Efficacy of baricitinib + remdesivir > remdesivir alone



FDA NEWS RELEASE

Coronavirus (COVID-19) Update: FDA Authorizes Drug Combination for Treatment of COVID-19

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Español

Today, the U.S. Food and Drug Administration issued an emergency use authorization (EUA) for the drug baricitinib, in combination with remdesivir, for the treatment of suspected or laboratory confirmed COVID-19 in hospitalized adults and pediatric patients two years of age or older requiring supplemental oxygen, invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

In a clinical trial of hospitalized patients with COVID-19, baricitinib, in combination with remdesivir, was shown to reduce time to recovery within 29 days after initiating treatment compared to patients who received a placebo with remdesivir. The safety and effectiveness of this investigational therapy for use in the treatment of COVID-19 continues to be evaluated. Baricitinib is not authorized or approved as a stand-alone treatment for COVID-19.

Hospitalized patients

- Faster median recovery time
- Reduction on mortality

Conclusions + Future directions

- NHP model: proof-of-concept
- Other antiviral & anti-inflammatory & other compounds
- Combination therapy
- Inhalation therapy:
  - Lower cost
  - Self-administered inhaler devices
  - Likely to be effective for prevention & early treatment

Thank you