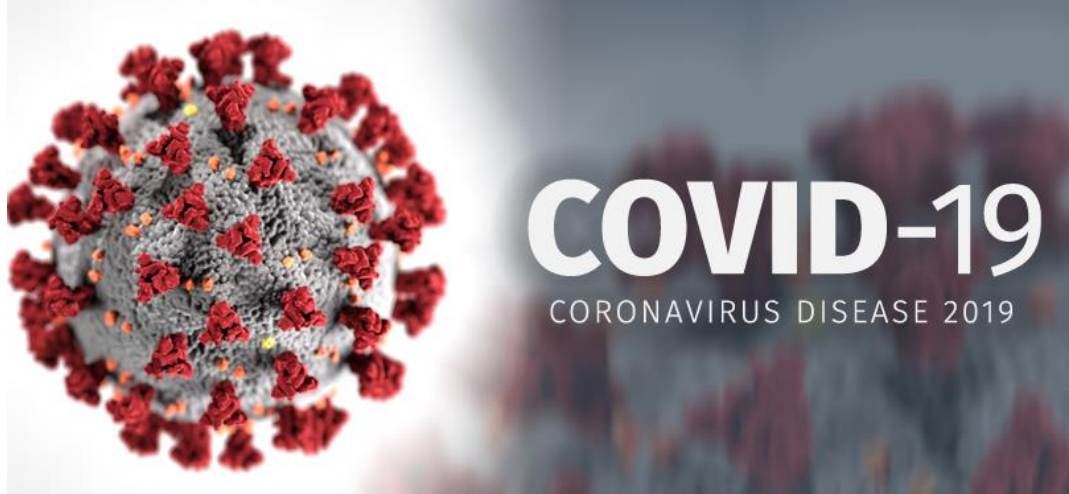


Pros and cons of different animal models of SARS-CoV-2 infection

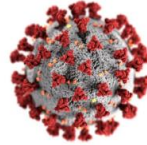


Koen Van Rompay, DVM, PhD
California National Primate Research Center
kkvanrompay@ucdavis.edu

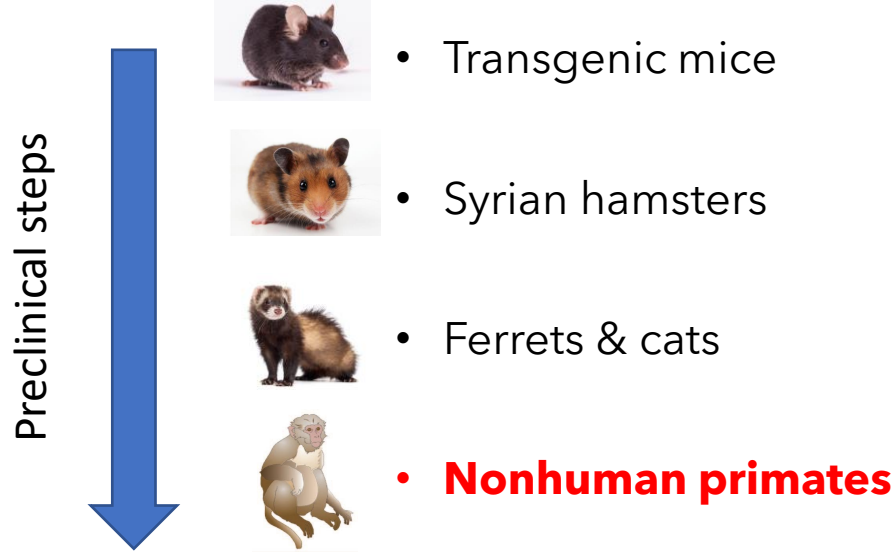


Ideal animal model of human viral diseases

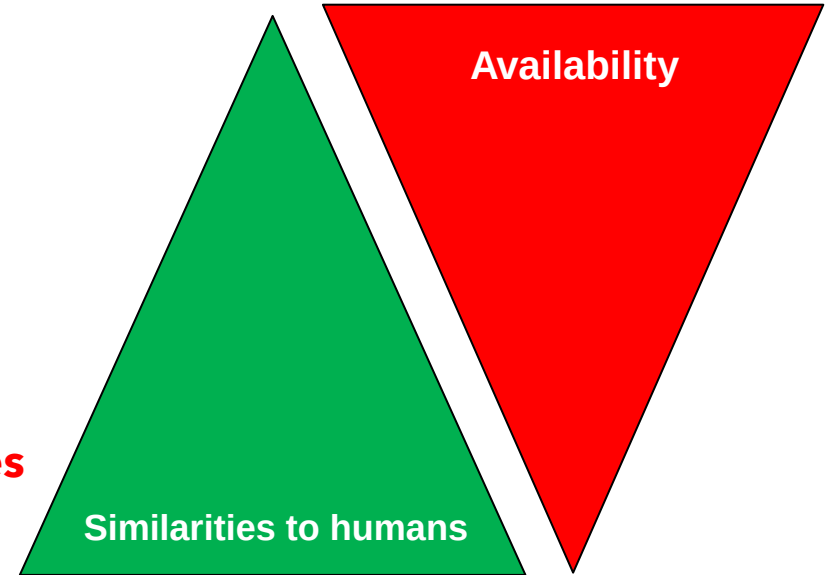
- Similarities in **host**
- Same (or similar) **virus**
- Similar **disease**
& surrogate markers



Animal models of SARS-CoV-2



***Proof of concept
(vaccines, treatments)***



Mice



Pros

- Easy to work with
- ~Inexpensive
- Well-defined genetics
- Reagent availability
- Inbred and outbred genetics available *

Cons

- Ace2 biologically incompatible
 - requires modification of mouse or virus
 - Example: hAce-2 (K18)
- Artificial disease phenotype
 - More lethal
 - Different distribution

* Multiple genetic backgrounds available with mouse-adapted SARS-CoV-2

Hamster



Pros

- Easy to work with
- Inexpensive
- Can be infected with WT SARS-CoV-2
- Moderate to severe disease
 - Non-lethal
 - Transient weight loss
 - Lung pathology (interstitial pneumonia)

Cons

- Fewer immunology reagents
- USDA-protected species (AWA)
- Larger (more space, fewer animals per cage)



Nonhuman Primate models

Macaques, AGM, Baboons, marmosets,....

Pros

- Easier monitoring of infection (incl. samples)
- Routes of administrations ~ humans
- Better mimics human infection:
 - Clinical signs: mild-moderate
 - Virus replication (upper & lower respiratory tract)
 - Innate & adaptive immune responses
 - Lung pathology



Cons

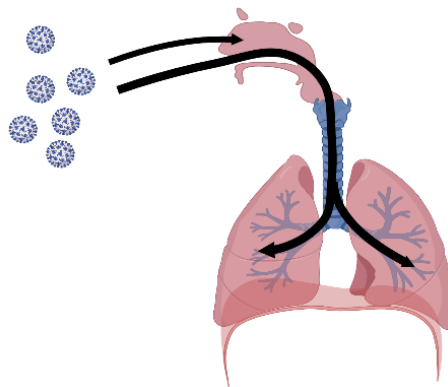
- Limited availability (rhesus > cynos)
- High expenses
- Outbred species: variability
- Clinical signs: mild-moderate



To test interventions with small “n”:
- Reduce variability
- Surrogate markers of disease

Optimizing NHP models to test interventions

- High-dose of virus: **intranasal + intratracheal**
- Early peak of virus replication (~ 1-2 days)



Created with BioRender.com

MONITORING



Clinical signs

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

Virus replication

- Upper respiratory tract
- Lower respiratory tract

Lung histology

Surrogate marker of disease

EVALUATION OF LUNG

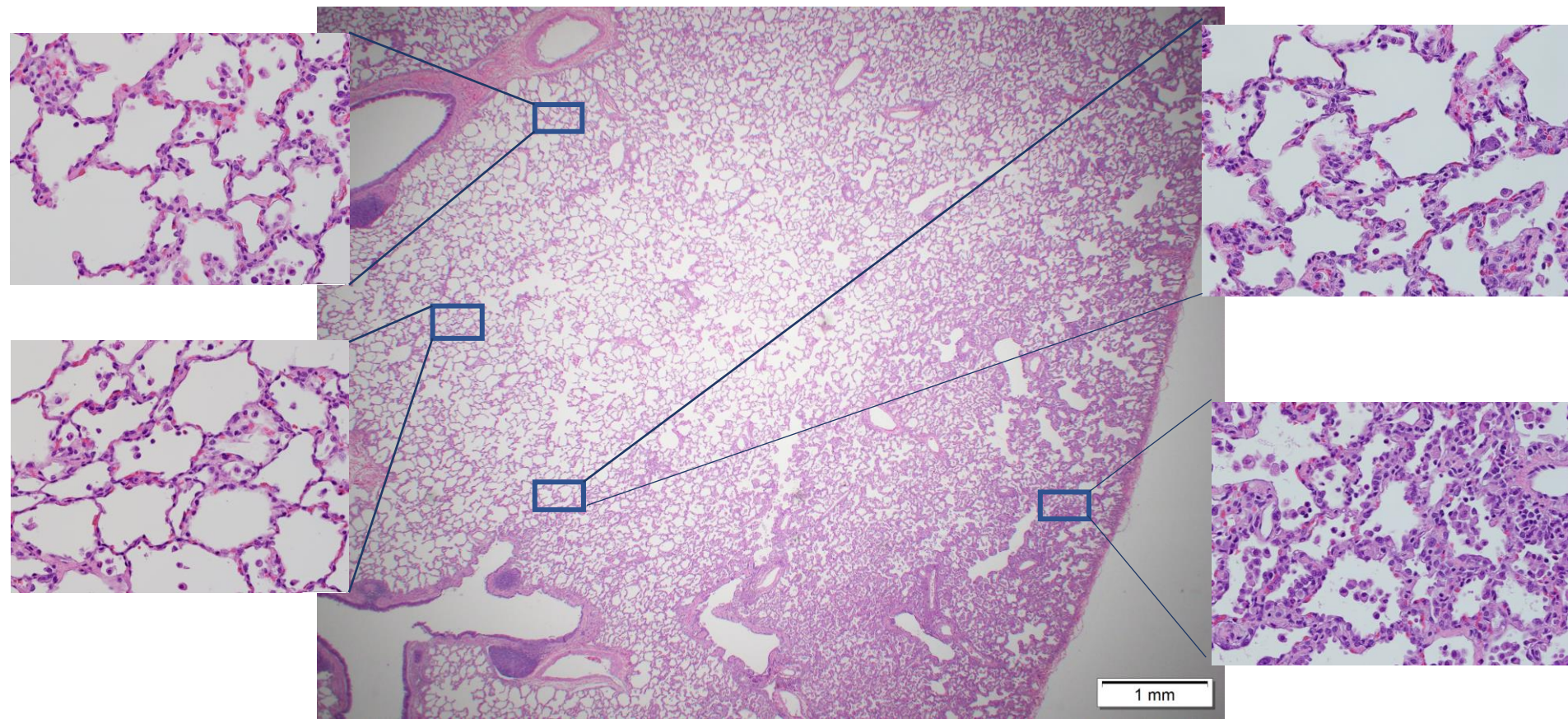


Virus levels

Histology



HISTOLOGY SCORING



Histology at 7 days after infection

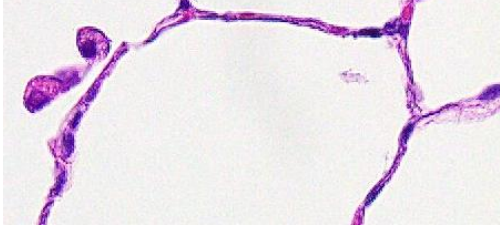
- **Interstitial cellularity: interstitial pneumonia**



- # alveolar macrophages
- # alveolar neutrophils
- interstitial fibrosis
- type 2 hyperplasia
- pleuritis

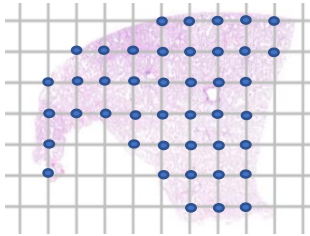
Interstitial Cellularity

Grade 0



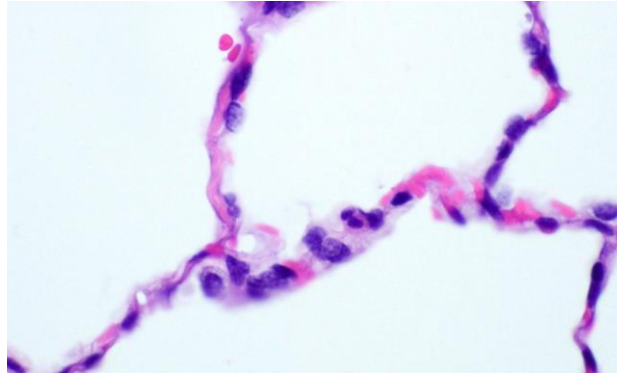
Scoring:

- Each point is scored individually at a 40x field

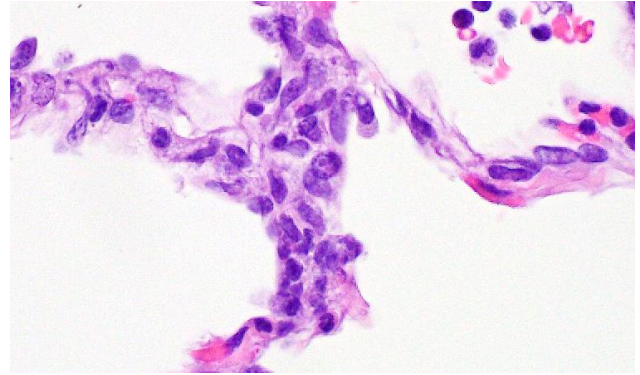


25 random 40x fields/slide
~450 to 1600 fields per animal

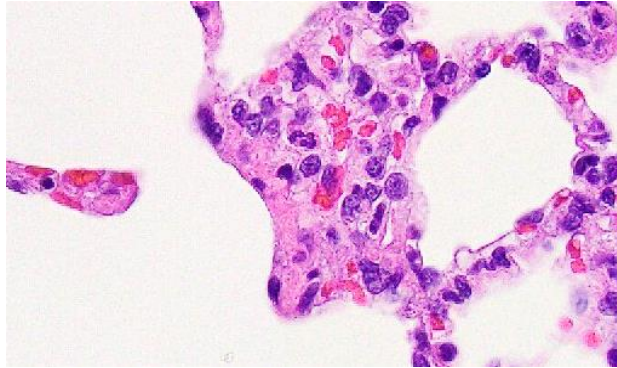
Grade 1 (~1-2 cells thick)



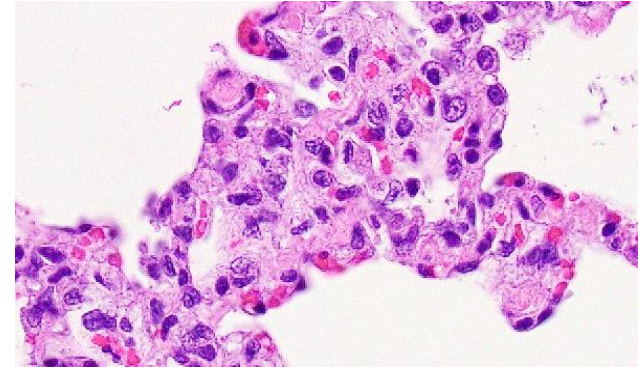
Grade 2 (~2-4 cells thick)



Grade 3 (~4-6 cells thick)



Grade 4 (~>6 cells thick)



Examples of neutralizing antibody-based therapies in NHP

2 studies with antibody at 1 day after SARS-CoV-2 (Wa)



Monoclonal antibodies

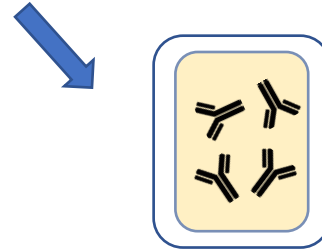
PLOS PATHOGENS 2021



RESEARCH ARTICLE

Early treatment with a combination of two potent neutralizing antibodies improves clinical outcomes and reduces virus replication and lung inflammation in SARS-CoV-2 infected macaques

Koen K. A. Van Rompay^{1,2,3}, Katherine J. Olatad^{1,2}, Rebecca L. Sammak¹, Joseph Dutra¹, Jennifer K. Watanabe¹, Jodie L. Usachenko¹, Ramya Immareddy¹, Anil Verma¹, Yashavanth Shaan Lakshmanappa¹, Brian A. Schmidt¹, Jamin W. Roh¹, Sonny H. Elzaidi¹, A. Mark Allen¹, Frauke Muecke-Scholz¹, Julio C. G. Lorendi¹, Sarah Lockwood¹, Rachel E. Pollard¹, JoAnn L. Yee¹, Peter B. Nham¹, Amir Ardehsir¹, Jesse D. Deere¹, Jean Patterson¹, Que Dang¹, Theodora Hatziioannou¹, Paul D. Blierstein^{1,2,3}, Smita S. Iyer^{1,2,3}, Dennis J. Hartigan-O'Connor^{1,2}, Michel C. Nussenzweig^{1,2,3}, J. Rachel Reader^{1,2,3}



COVID Convalescent plasma (CCP)

PLOS PATHOGENS 2022

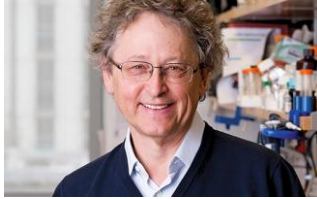


RESEARCH ARTICLE

Early post-infection treatment of SARS-CoV-2 infected macaques with human convalescent plasma with high neutralizing activity had no antiviral effects but moderately reduced lung inflammation

Koen K. A. Van Rompay^{1,2,3}, Katherine J. Olatad^{1,2}, Rebecca L. Sammak¹, Joseph Dutra¹, Jennifer K. Watanabe¹, Jodie L. Usachenko¹, Ramya Immareddy¹, Jamin W. Roh¹, Anil Verma¹, Yashavanth Shaan Lakshmanappa¹, Brian A. Schmidt¹, Clara Di Germanio¹, Nabeela Rizvi¹, Hongwei Liu¹, Zhong-Min Ma¹, Mary Stone¹, Graham Simmons¹, Larry J. Dumont¹, A. Mark Allen¹, Sarah Lockwood¹, Rachel E. Pollard¹, Rafael Ramiro de Assis¹, JoAnn L. Yee¹, Peter B. Nham¹, Amir Ardehsir¹, Jesse D. Deere¹, Anil Jain¹, Philip L. Felgner¹, Lark L. Coffey¹, Smita S. Iyer^{1,2,3}, Dennis J. Hartigan-O'Connor^{1,2}, Michael P. Busch^{1,2,3}, J. Rachel Reader^{1,2,3}

Study 1: Monoclonal antibodies



Michel Nussenzweig et al, Rockefeller University

Nature, Aug 20, 2020

Article

Convergent antibody responses to SARS-CoV-2 in convalescent individuals

<https://doi.org/10.1038/s41586-020-2456-9>

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Check for updates

Davide F. Robbiani^{1,4,10,12}, Christian Gaebler^{1,10}, Frauke Muecksch^{2,10}, Julio C. C. Lorenz^{1,10}, Zijun Wang^{1,10}, Alice Cho^{1,10}, Marianna Agudelo^{1,10}, Christopher O. Barnes^{2,10}, Anna Gazumyan^{1,10}, Shlomo Fink^{1,10}, Thomas Hägglöf^{1,10}, Thiago Y. Oliveira^{1,10}, Charlotte Viant^{1,10}, Arlene Hurley⁴, Hans-Heinrich Hoffmann⁵, Katrina G. Millard⁴, Rhonda G. Kost⁴, Melissa Cipolla⁴, Kristie Gordon⁴, Filippo Bianchini⁴, Spencer T. Chen⁴, Victor Ramos⁴, Roshni Patel⁴, Juan Dizon⁴, Irina Shmellovich⁴, Pilar Mendoza⁴, Harald Hartweger⁴, Lillian Nogueira⁴, Maggi Pack⁴, Jill Horowitz⁴, Fabian Schmidt⁴, Yiska Weisblum², Eleftherios Michailidis⁵, Alison W. Ashbrook⁶, Eric Waltari⁷, John E. Pak⁷, Kathryn E. Huey-Tubman⁸, Nicholas Koranda⁸, Pauline R. Hoffman⁸, Anthony P. West Jr⁸, Charles M. Rice⁹, Theodora Hatziloannou⁹, Pamela J. Bjorkman¹⁰, Paul D. Bieniasz^{2,4,12}, Marina Caskey¹⁰ & Michel C. Nussenzweig^{1,4,12}

During the coronavirus disease-2019 (COVID-19) pandemic, severe acute respiratory

C135-LS and C144-LS

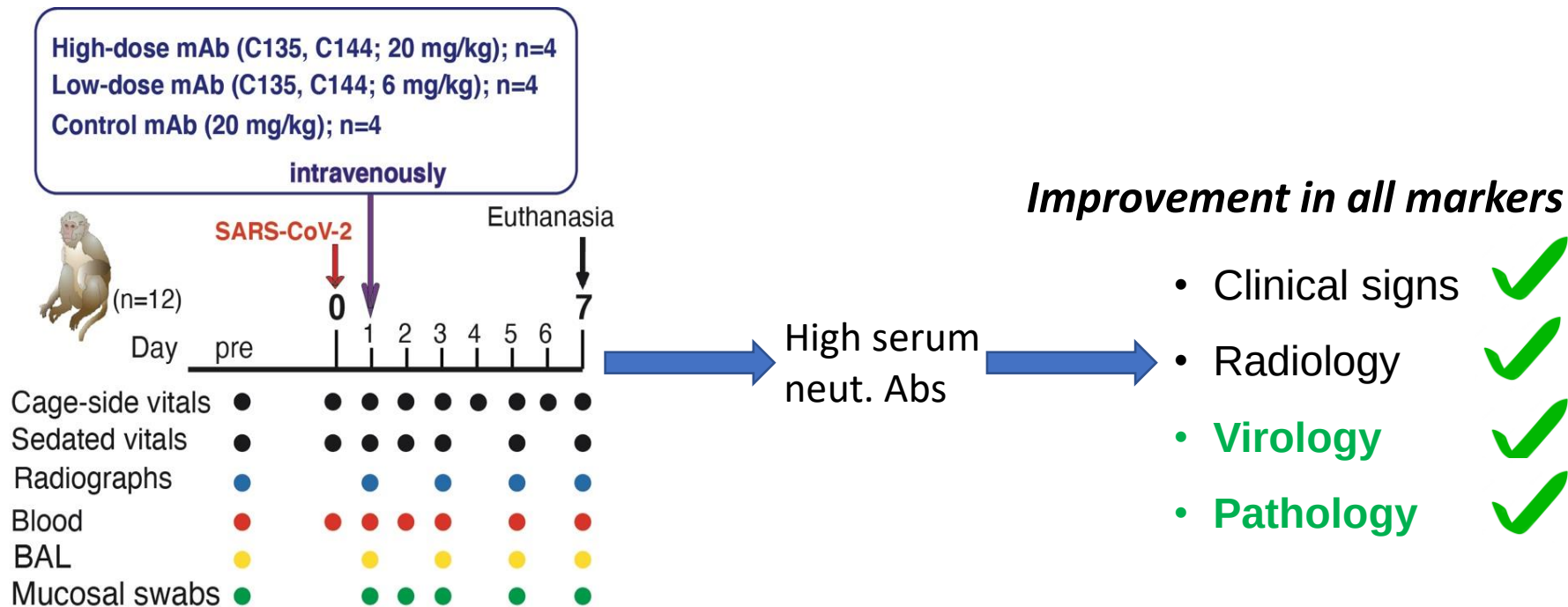


In vitro EC ~ 5 ng/ml

LS: Fc portion engineered to have prolonged half-life

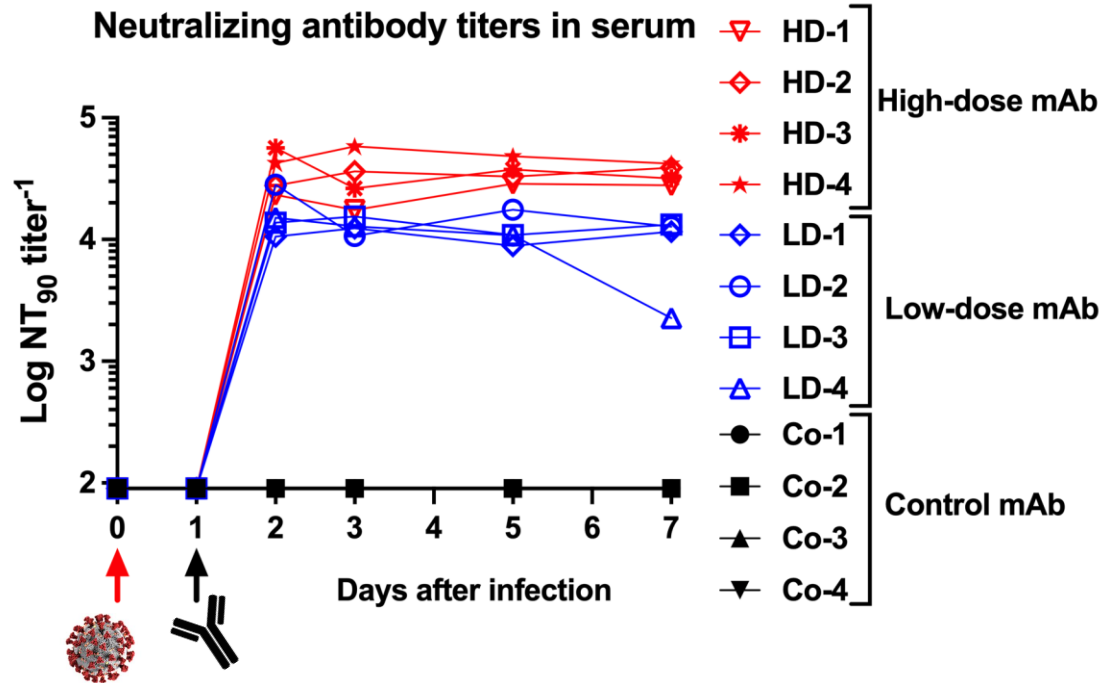
Combination is active in vitro against variants of concern

Experimental design: mAb therapy 1 day after virus inoculation



High neutralizing activity in serum of recipient macaques

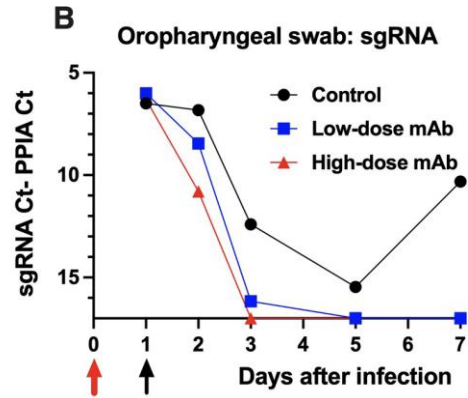
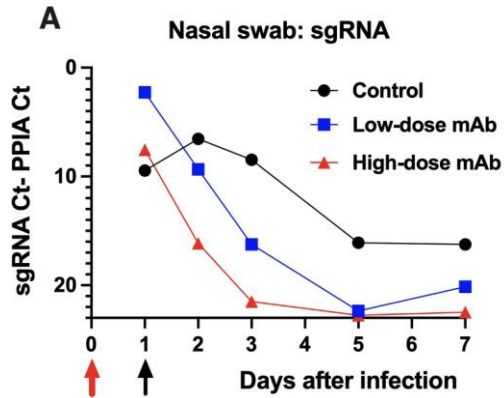
(pseudotype neut assay)



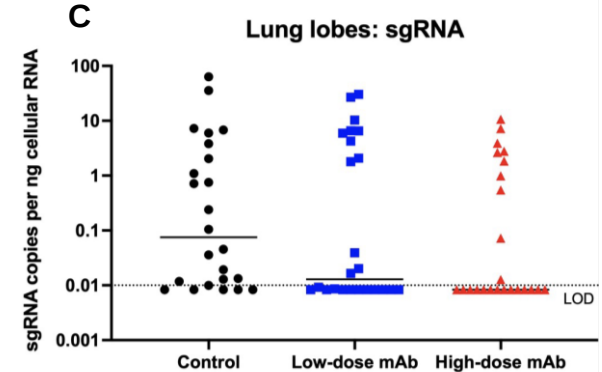
NT₅₀ titers $\geq 13,525$
NT₉₀ titers $\geq 2,257$

throughout observation period

- ## Monoclonal antibodies accelerated clearance of sgRNA in:



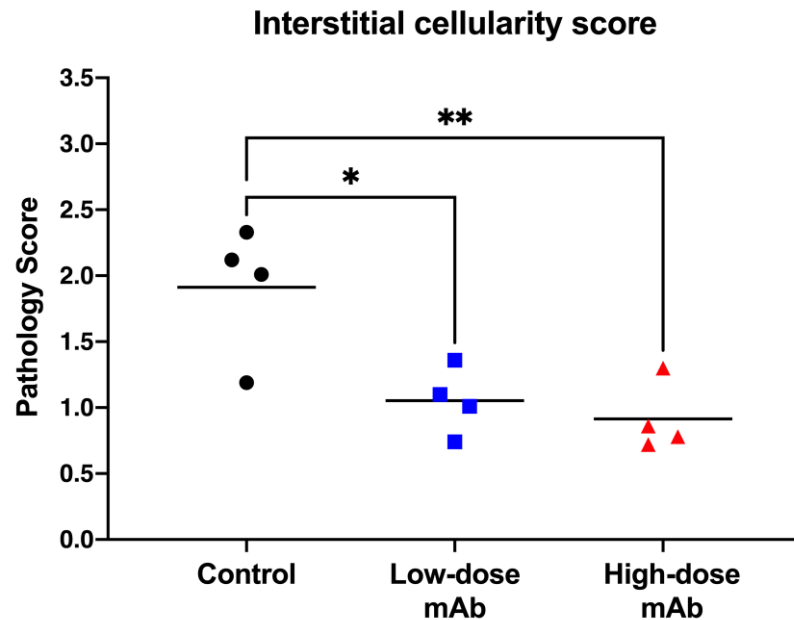
Symbols: median values



Each symbol is one lung lobe



mAb reduce interstitial pneumonia



~ 50% reduction

COVID Convalescent Plasma (CCP)

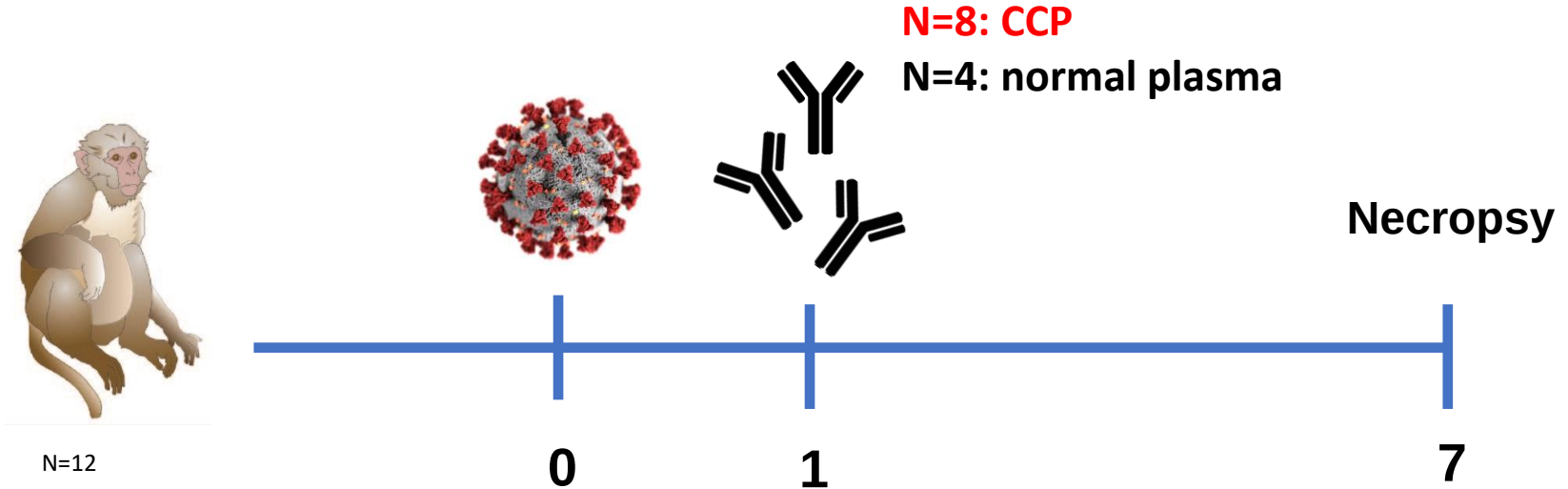
- High enthusiasm to use CCP in clinic
- **August 2020: EUA of CCP**
- Further studies (controlled trials, meta-analyses):
 - mixed results
 - at best mild-to-moderate if high-titer CCP early in infection
- Problem: low% of COVID survivors made high-titer CCP!
- **February 2021: revision of EUA**
 - high-titer CCP
 - only hospitalized patients early in the disease course or impaired humoral immunity



Study 2 (Fall 2020):

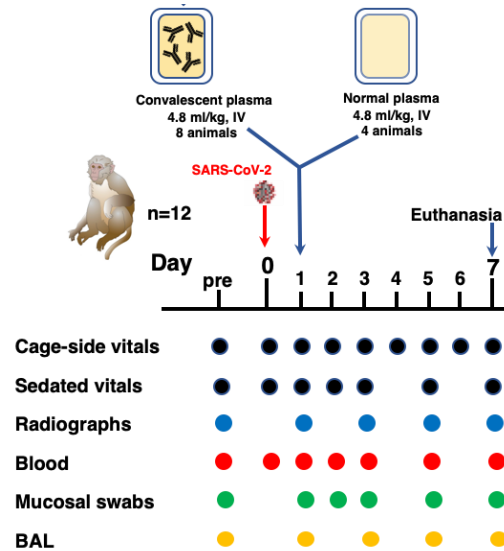
CCP with HIGH neutralization titer

- **Pooled CCP** with NT_{50} neut titer of $\sim 3,000$ (Vitalant).
- **Post-exposure** at 24 h: 4.8 ml/kg



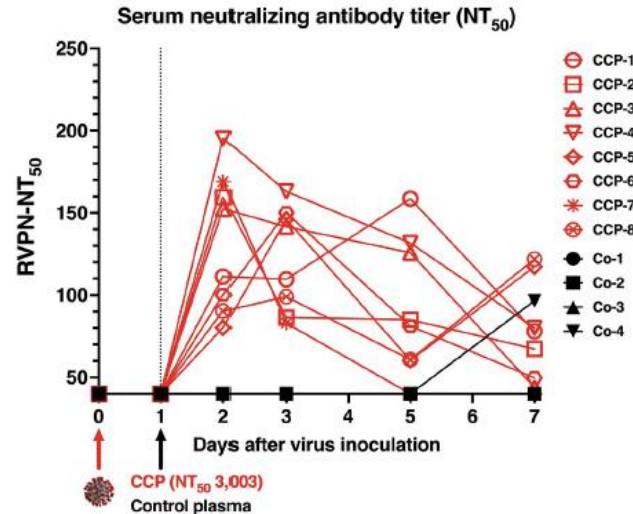
Experimental design

High-titer pooled CCP: $NT_{50} \sim 3,000$ (Vitalant).



Low serum
neut. Abs

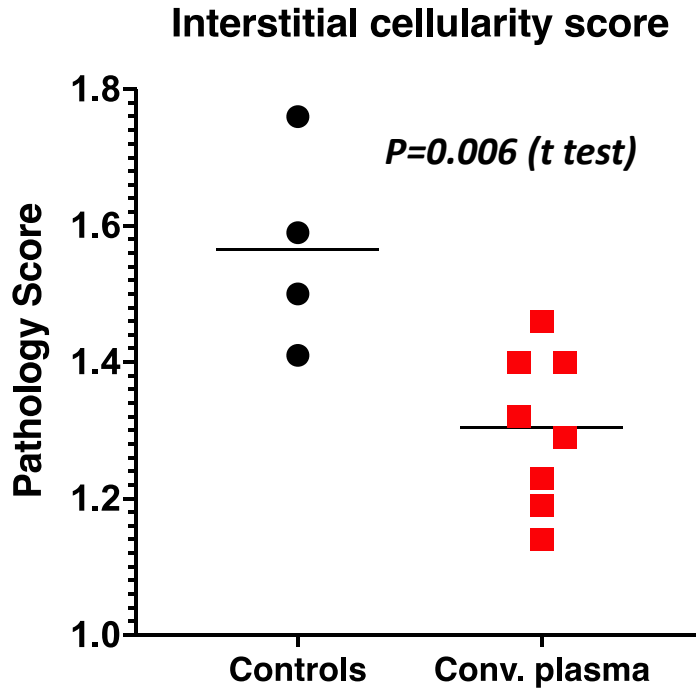
Peak NT_{50} : ~ 150 (99 to 195)



Limited benefit

- Clinical sign
- Radiology
- Virology
- Pathology

Moderate reduction of lung pathology

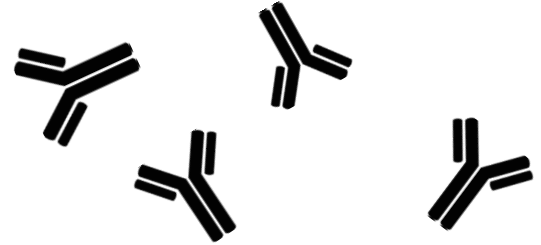


1208 microscopic fields (range: 710-1634) per animal

Mean: 17 % reduction

Conclusions

- Animal models of SARS-CoV-2: useful for **proof of concept**
- Potency: mAbs > CCP
- Future of CCP for future pandemics = ??
 - Needs to be **high titer**
 - **Boosted CCP**: COVID survivors getting vaccinated
 - Purified IgG ?



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Pathology, Microbiology and Immunology

L. Coffey
H. Liu

vitalant.

M. Busch
G. Simmons
C. Di Germanio
M. Stone
N. Rizvi
S. Bakkour
L. Dumont



Rockefeller:

M Nussenzweig
F. Muecksch
J. Lorenzi
T. Hatziioannou
P. Bianiasz

UCI

University of California, Irvine

Philip Felgner
Rafael Ramiro de Assis
Aarti Jain



National Institute
of Allergy and
Infectious Diseases

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Q. Dang
C. Florence
S. Hild

Thank you

