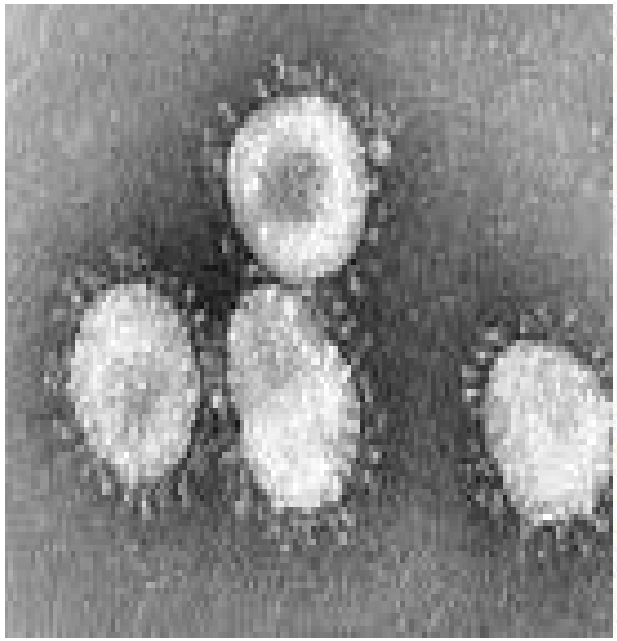
2019-nHCoV

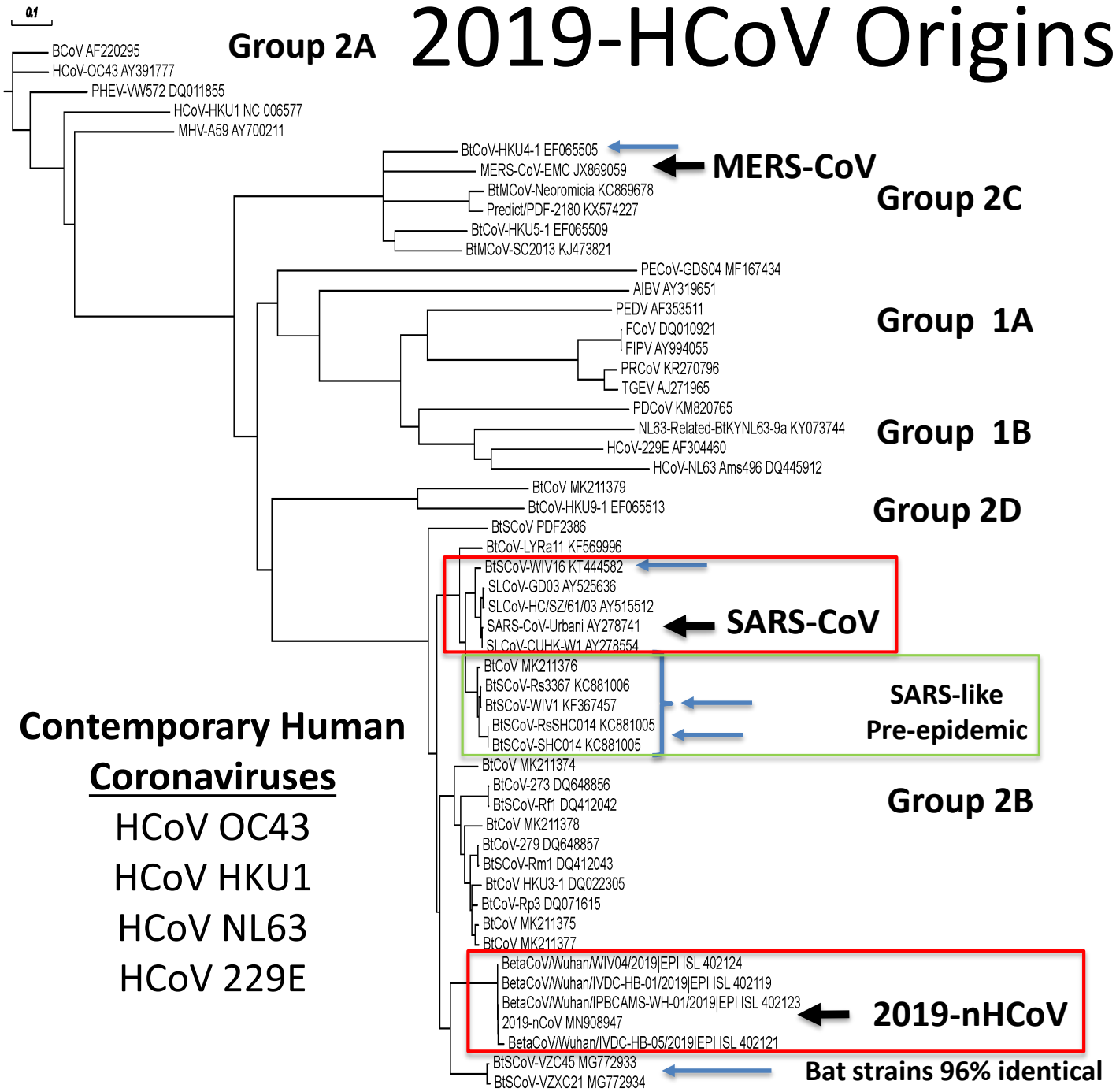
Baric Laboratory
University of North Carolina



Outline

- **Introduction**
- **Emerging Coronaviruses**
  - SARS-CoV, MERS-CoV
  - Pre-pandemic SARS-like Bat-CoV
  - 2019-HCoV
    - **Genome Organization and relatedness**
- **The Outbreak**
  - **Origins**
  - **Disease**
  - **Human to Human Spread**
- **Countermeasures**
  - Broad based CoV nucleoside inhibitors
- **Summary**

2019-HCoV Origins



Contemporary Human Coronaviruses

HCoV OC43
HCoV HKU1
HCoV NL63
HCoV 229E

Emerging Human Coronaviruses

SARS-CoV 2003
MERS-CoV 2012
2019-nHCoV 2019

Origins

Bat Coronaviruses

Not Snakes

Timeline: Emerging Nidoviruses

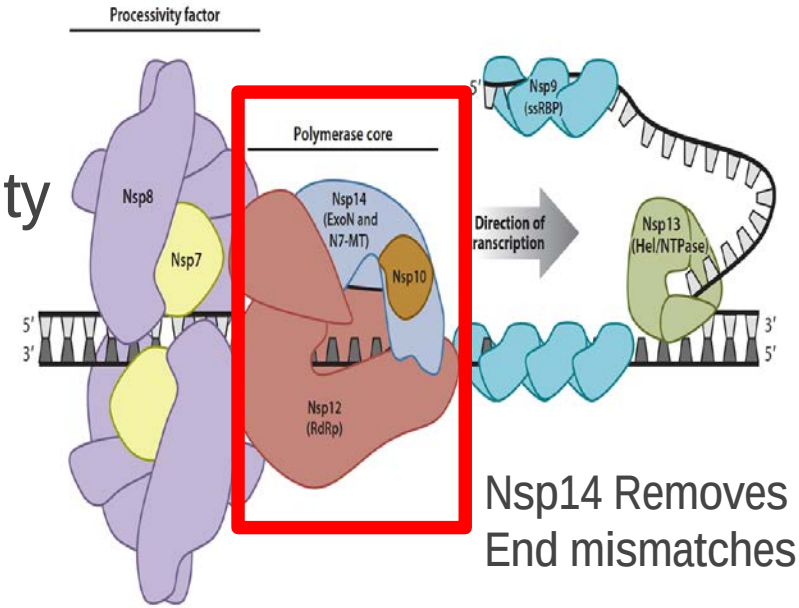
Virus	Species	Emergence	
HCoV-NL63	**Human**	500-800 years	
HCoV-229E	**Human**	200-300 years	
HCoV-OC43	**Human**	~120 years	
PEDV	Porcine	~25 years	← 2012 in US
PRRSV	Porcine	~25 years	
BCoV	Bovine	~20 years	
SARS-CoV	**Human**	~16 years	Accelerating Cross Species Movement
MERS-CoV	**Human**	~7 years	
SADS-CoV (HKU2)	Porcine	~2 years	
2019-nHCoV	Human	2 months	

Fu et al., 2018 Infect Genetic Evolution; Peiris JS et al., Lancet 2003, Huynh J et al., J.Virol 2012; Zaki AM et al., N Engl J Med. 2013, Mole B. Nature. 2013; Zhou P et al., Nature 2018

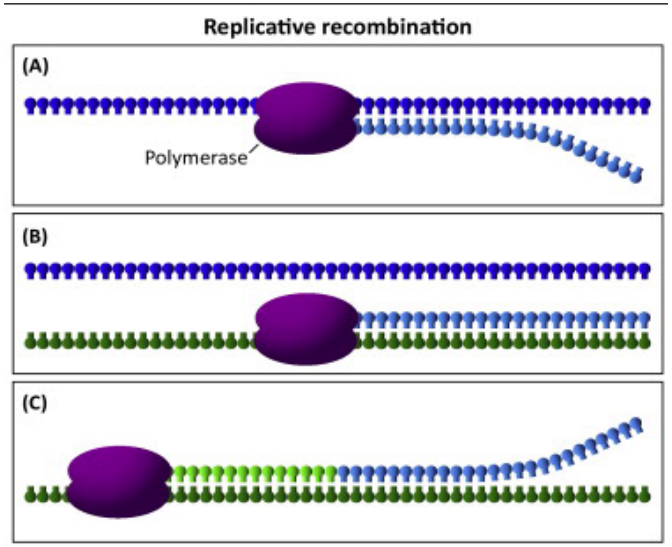
Drivers of CoV Evolution

- CoV Genome Size: 32Kb
- CoV Mutation Rate
  - 10^{-6} → Regulated Fidelity (nsp14: ExoN)
  - Environmental Change
    - Fidelity rates change
- High Rates RNA Recombination
  - 25% during mixed infections
  - Modular evolution

CoV Replicase Complex



Nsp14 Removes 3' End mismatches



Position Piece: CoV: An RNA Proofreading Machine Regulates Replication and Fidelity (RNA Biol, 2011), Dudas G. Virus Evolution 2016; Eckerle et al., Plos Pathogens 2010; Graham et al., Nature Medicine 2012; Smith et al., Plos Path 2014

Drivers of CoV Evolution

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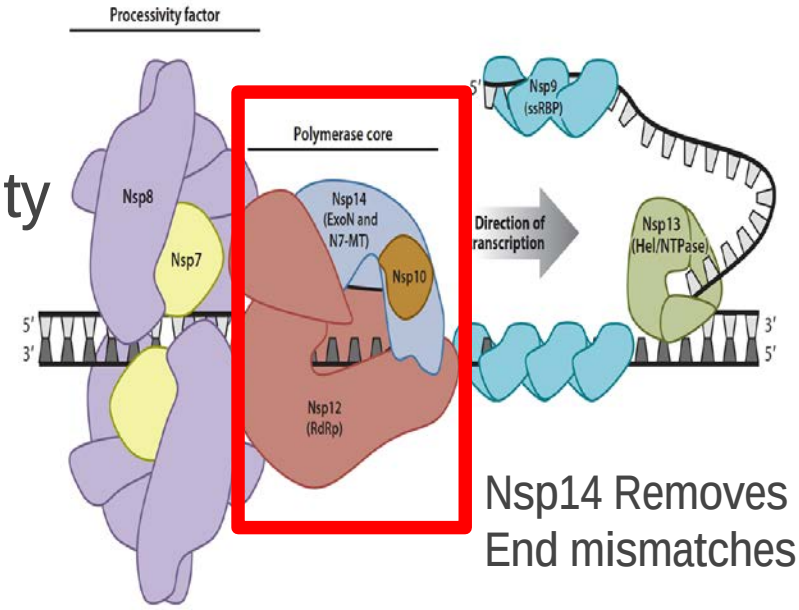
    - Fidelity rates change
- High Rates RNA Recombination
  - 25% during mixed infections
  - Modular evolution
- Plastic Surface Glycoprotein
  - Tolerates high rates of mutation
  - Deletions and Insertions (tropism, antigenicity)
  - Recombination (modular evolution)

CoV Replicase Complex



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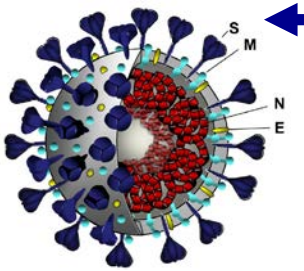

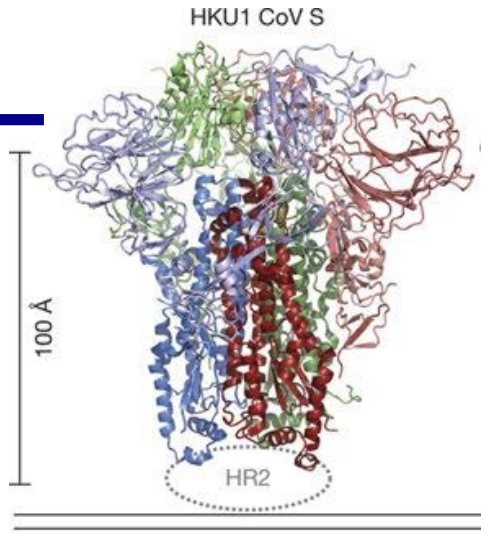

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Origins of the Group 2B SARS and SARS-like CoV

- SARS-CoV Origins
  - bats
  - Open Markets and Civet Intermediate Hosts
- SARS-like bat CoV
  - Pre-epidemic potential
  - Bats, low level seroprevalence in people residing near bat hibernacula
- 2019-nHCoV
  - Bats
  - Open Market Origins?
    - We will discuss

SARS-CoV Emergence in 2002 in China

8,096 cases, 774 deaths, in 32 countries, Nov 1 2002 - July 31 2003

Bat to Human to Civet

evolution towards efficient infection of human cells

Bat to Civet to Human

Wikiwand.com
USAID Flikr page

SARS-CoV Emergence in 2002 in China

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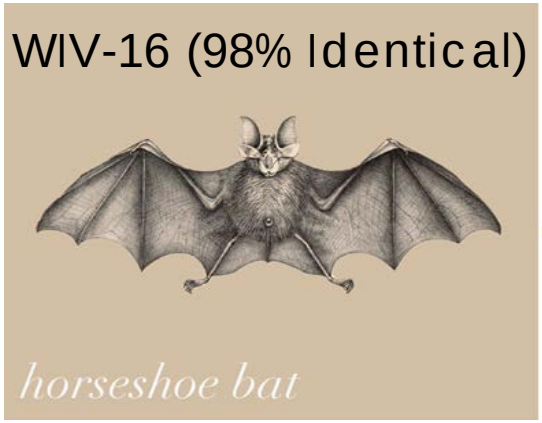
Most Likely Model

Epidemic SARS-CoV



Intermediate host

Bat to Human to Civet

Is SARS-CoV Extinct?

BtCoV
Bats
Animals

Threat Level?

Most Emerging Viruses

Zoonotic Reservoirs

SARS-like bat CoV

SARS-CoV

MERS-CoV

Heterogeneous Pools of related viruses (0-35⁺%)

PrePandemic Strains

SARS-CoV

2003-04

0%

10%

22%

2019-nHCoV

High Risk Emergence Strains

2019-

8,000 cases
774 deaths

Future Outbreak?

2019-nHCoV

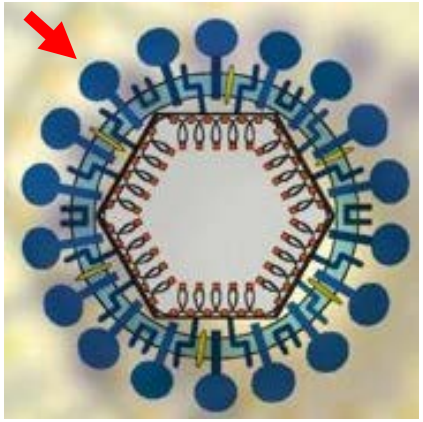
5,934 cases, >1000 serious cases, over 132 deaths, 18 countries

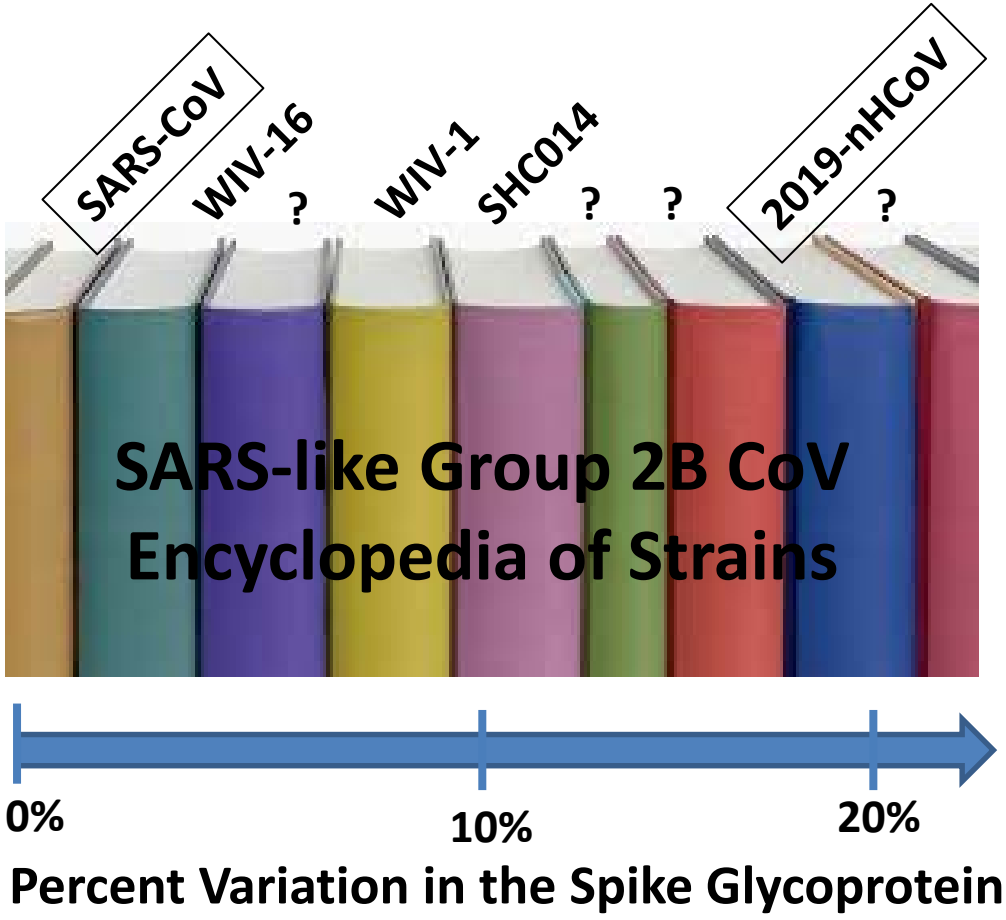
Human transmission: Germany

Z. Shi, Institute of Virology (Discovery Work on the SARS-like bat coronaviruses): Nature. 2013 Nov 28;503(7477):535-8.
Sheahan et al., JV 2008; Becker PNAS 2008; Menachery V et al., Nature Medicine 2015, Menachery PNAS 2016; Simon et al., mBIO 2017

Known Group 2B SARS-like CoV Poised for Human Emergence

SARS-Related Strains





Common Features

Pre-epidemic Group 2B SARS-like CoV

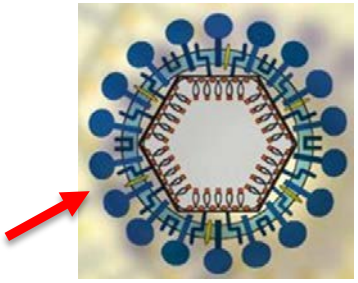
- **Origins**: BATS
- **Use hACE2 Receptor for docking and entry**
  - Use other ACE2 receptor orthologues for entry into different species
- **Grow efficiently in primary human airway epithelial cells, and small airway epithelial cells**

Common Features

Pre-epidemic Group 2B SARS-like CoV

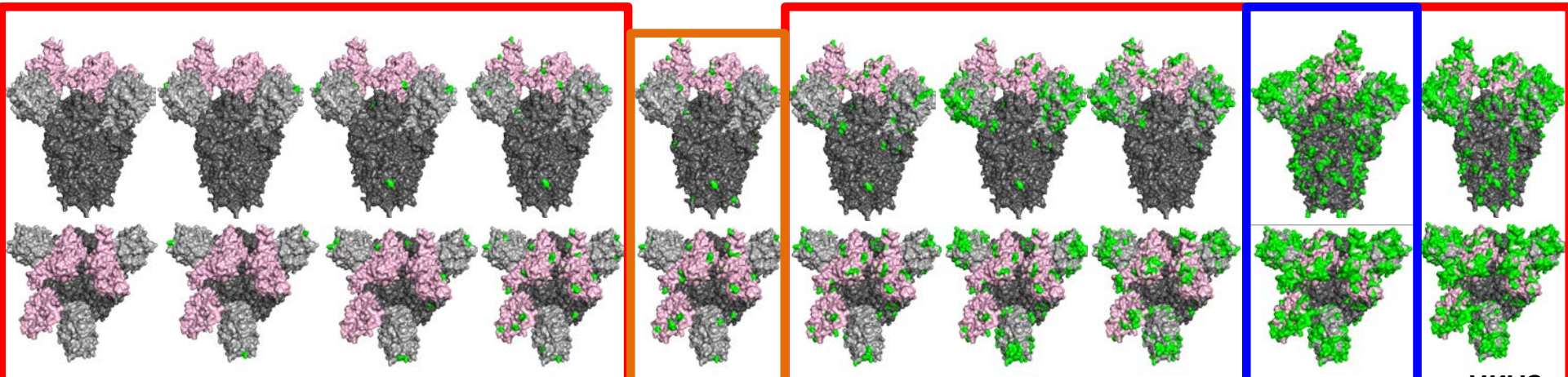
- **Origins**: BATS
- **Use hACE2 Receptor for docking and entry**
  - Use other ACE2 receptor orthologues for entry into different species
- **Grow efficiently in primary human airway epithelial cells, and small airway epithelial cells**
- **Cause Acute Respiratory Disease Syndrome (ARDS) in humans and/or Animals**
  - End stage lung disease with ~30% mortality rates
- **Cause an Age-Related Disease Phenotype**
  - Characterized by Increased Virus Growth and Mortality in immune senescent populations

Immune Therapeutic Countermeasures Fail



2003-2004 SARS-CoV Outbreak Strains

Group 2B SARS-like Bat Coronaviruses



2019-2020 Outbreak

All Are Poised for Human Emergence

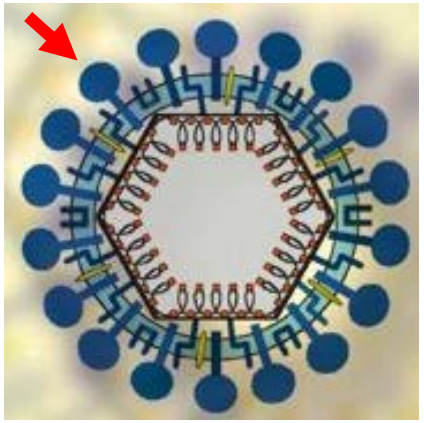
Antigenic Distance is Large so SARS-CoV Immune Therapeutics (hmAB) and Vaccines Fail

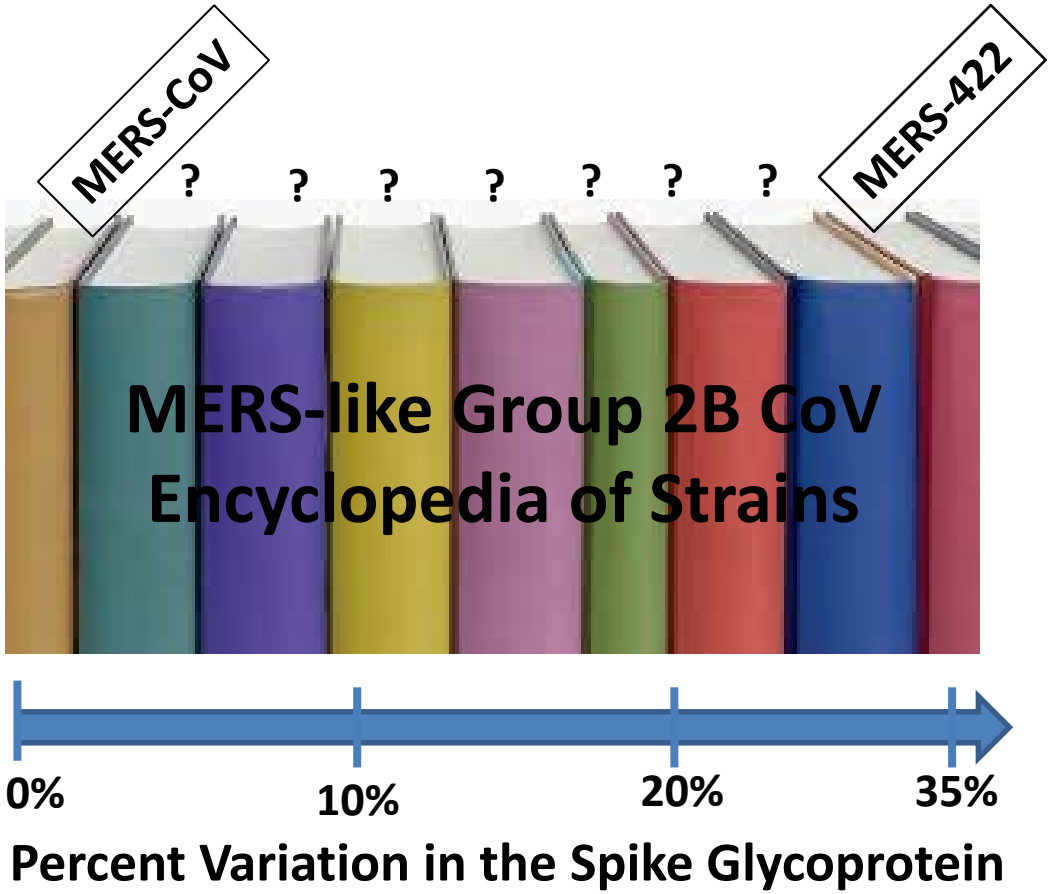
variation

Broadly active drugs are essential to control zoonotic CoV

Known Group 2C MERS-like CoV Poised for Human Emergence

MERS-Related Strains

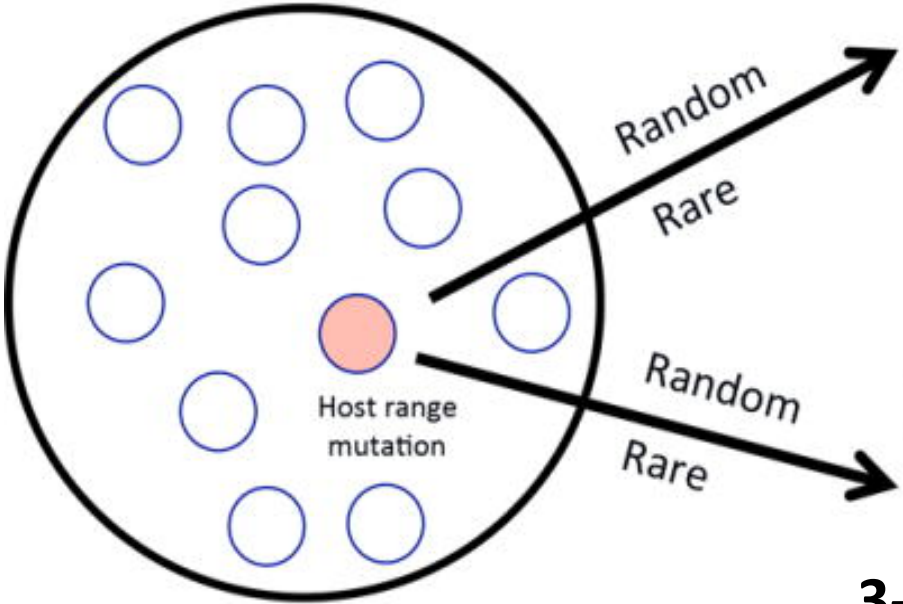




-MERS-like bat CoV (China) 65% Identity with MERS-CoV Spike
-Uses hDPP4 as a receptor for docking and entry
-Replicates efficiently in primary human airway epithelial cells

Zoonotic Virus Emergence Models

Classic Model: Mutation Driven



Zoonotic Virus Pools

a

Secondary host (reservoir) → Human infection

Adaptation

Adaptation

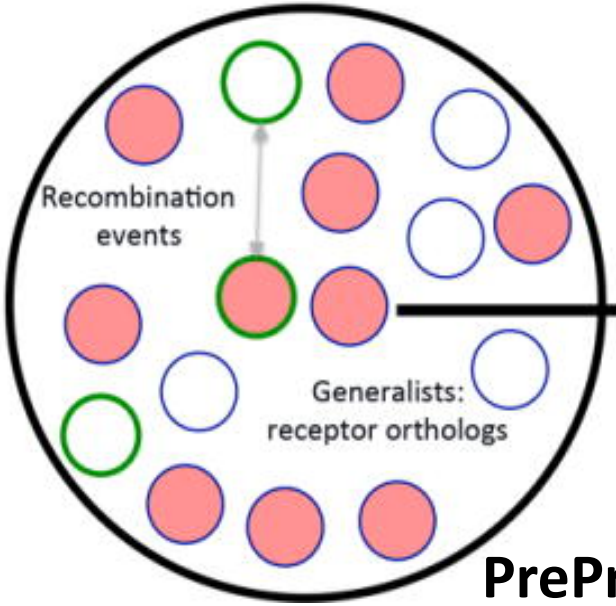
Epidemic strain

b

Adaptation

Direct human infection ↔ Secondary host (reservoir)

3-4 Step Model Requiring Mutations



PreProgrammed Viruses

c

Limited Mutation is Necessary

Direct human infection ↔ Secondary host (reservoir)

Epidemic strain

SARS-CoV Outbreak Drivers

- **Open Animal Markets**


Civets
Animal Reservoir

- **Hospitals: Epicenters for Disease Expansion**

Health Care Workers
Super-spreader Events

- **Transmission occurs 24-36 hrs after Disease Onset**
  - **Community spread limited**
  - **Few asymptomatic cases**

Ro=1.8-2.5 (one person on average infected ~2.0 people)

SARS-CoV Outbreak Drivers

- **Animal Markets-Civets**


civet cats were culled
their sale and
consumption banned

- **Hospitals: Epicenters for Disease Expansion**

Health Care Workers
Super-spreader Events

Barrier
Nursing

- **Transmission occurs 24-36 hrs after Disease Onset**
  - **Community spread limited**
  - **Few asymptomatic cases**

Vulnerable to quarantine
Contact Tracing

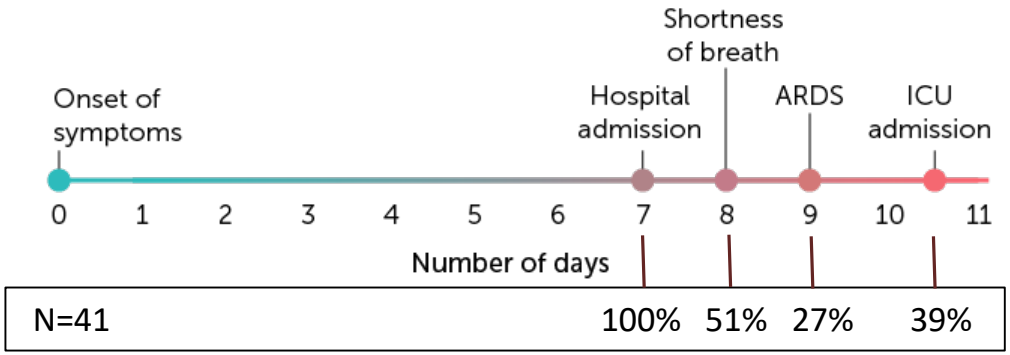
Ro=<1.0 (epidemic goes extinct)

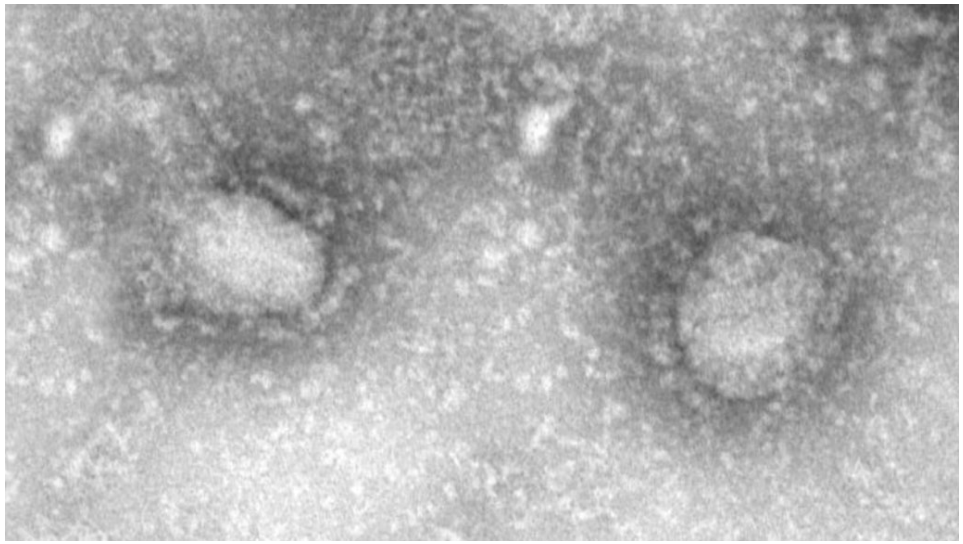
Public Health Response

2019-nHCoV

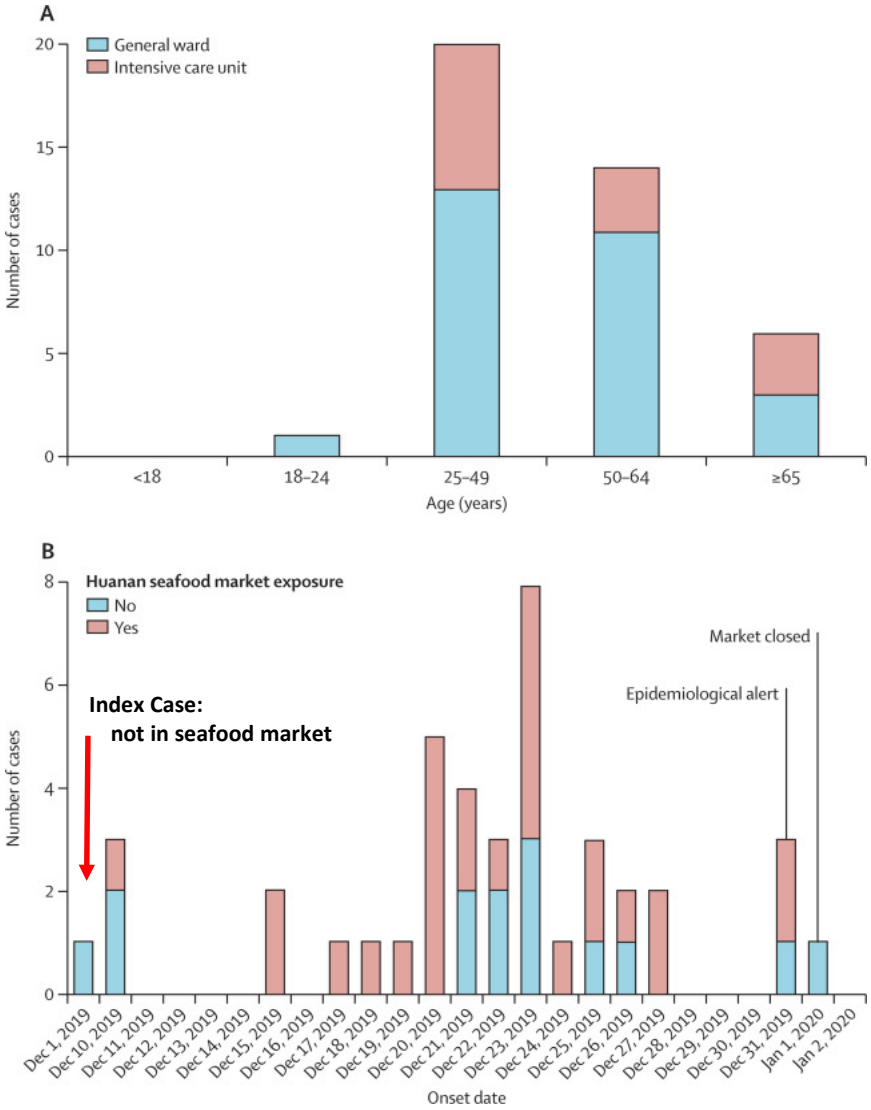
- Emerged Early Dec in Wuhan China (Dec 1)
- Began as Cluster of Cases Associated with Open Markets (Dec 31)
  - No Evidence of Human to Human Transmission
  - Not Very Pathogenic
  - Not SARS-CoV, Likely a Novel Virus
- Wuhan Open Fish Market Closed (Jan 1, 2020)
- Identified as a Coronavirus on Jan 7th, 2020
  - distant relative to the SARS-CoV (kissing cousin)
- Genome Length Sequence Reported (5 isolates) (~9-11th)
- 15 HCW infected, China Confirms Person to Person Spread (~20th)

2019 nHCoV Disease Course





A new coronavirus called 2019 novel coronavirus, or 2019-nCoV, is spreading in China. It is similar to both SARS and MERS.
COURTESY: IVDC, CHINA CDC VIA GISAID



3 of 4 not in seafood market (Open Markets)

Chaolin Huang et al., Lancet Published online January 24, 2020 https://doi.org/10.1016/S0140-6736(20)30183-5

Origins

- **Earlier Open Market Origin**
  - Index case was not identified
  - most recent common ancestor (27 genomes)—pinpoints early Oct as the likely start of the outbreak (Kristian Andersen, an evolutionary biologist at the Scripps Research Institute)
- **People in rural areas, who live or work in near proximity of bat hibernacula**
  - infected and traveled to Wuhan (visitors, etc.)
  - Transmit the disease to local residents, localized spread……..noticed (MD)
  - Serological evidence of rural exposure settings (Virol Sin. 2018 Feb;33(1):104-107.)

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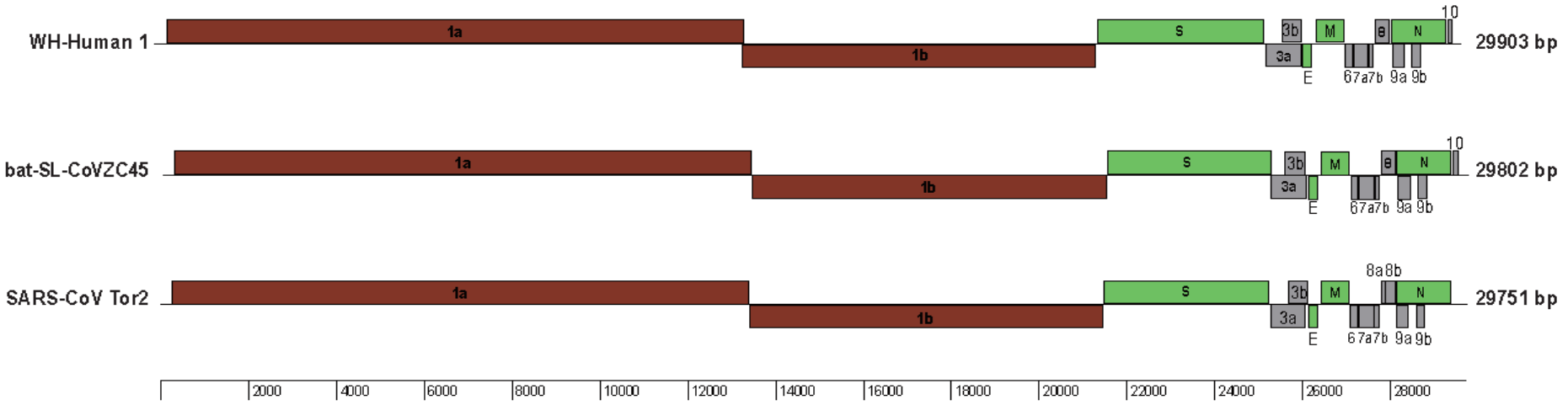
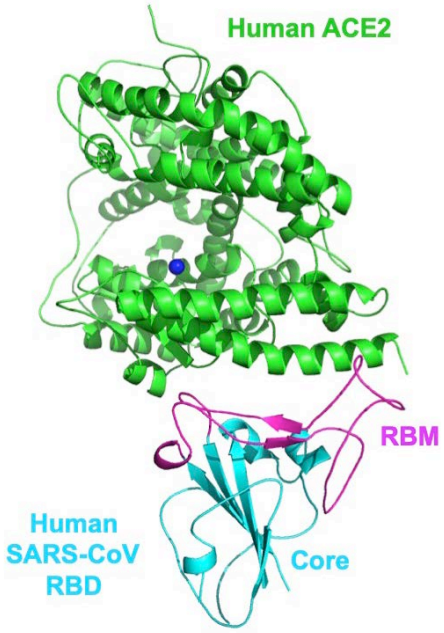
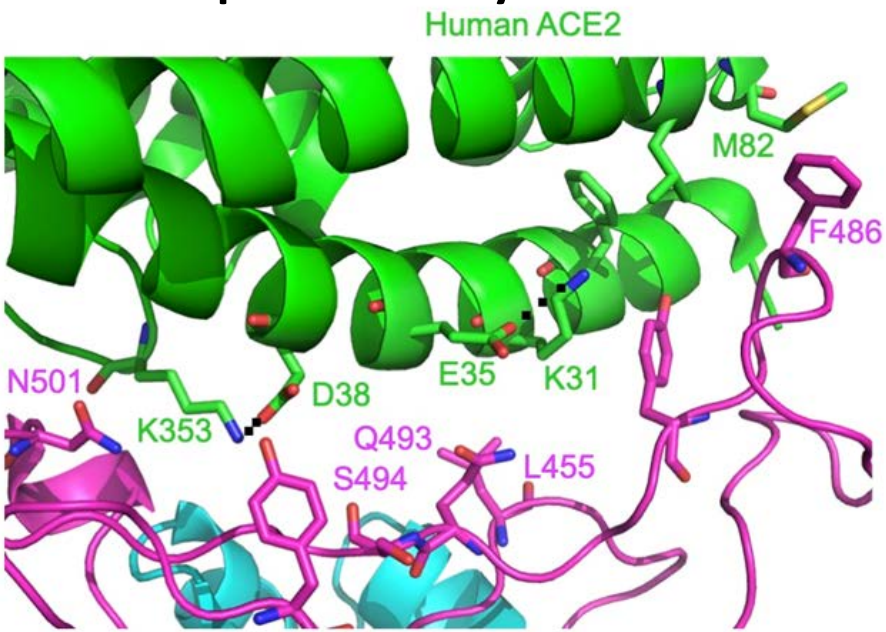
- **Accidental Release**
  - Institute of Virology (Wuhan) Studies SARS-group 2B bat Coronaviruses
  - Sequenced 1,000s of SARS-like group 2B bat coronaviruses
  - Cultured multiple group 2B bat coronaviruses (pre-epidemic strains)
    - Do this work under BSL2 conditions; despite virus use of hACE2 receptor growth in primary human airway epithelial cells
    - J Virol 2016 Jul 15; 90(14): 6573–6582
  - They have reported a bat virus that is similar to 2019-nHCoV, which contains big deletions in RBD, not sure when
  - They had not specifically reported on any virus like 2019-nHCoV (RNAseq data?)

2019-nHCoV Genome Organization



Uses hACE2 Receptor for Entry





Zhou et al., bioRxiv 2020.01.22.914952

2019-nHCoV S Glycoprotein RBD Interface Residues

	WUCV S-RBD ACE2 Interface Residues*													
Virus	402	426	436	440	442	472	473	475	479	484	486	487	488	491
SARS-CoV	T	R	Y	Y	Y	L	N	Y	N	Y	T	T	G	Y
CUHK-W1	T	R	Y	Y	Y	L	N	Y	N	Y	T	T	G	Y
GD03	T	R	Y	Y	Y	P	N	Y	N	Y	T	S	G	Y
HC/SZ/61/03	T	R	Y	Y	Y	P	N	Y	R	Y	T	S	G	Y
WIV16	T	R	Y	Y	S	F	N	Y	N	Y	T	N	G	Y
Rs3367	T	R	Y	Y	S	F	N	Y	N	Y	T	N	G	Y
WIV1	T	R	Y	Y	S	F	N	Y	N	Y	T	N	G	Y
SHC014	T	N	Y	Y	W	P	N	Y	R	F	T	A	G	H
PDF2386	T	N	-	Y	L	L	G	Y	K	T	T	V	G	Y
ZXC45	T	A	-	Y	S	-	-	-	S	N	N	V	P	Y
ZXC21	T	A	-	Y	S	-	-	-	S	N	N	V	P	Y
WUH Original	T	N	Y	Y	L	F	N	Y	Q	Q	T	N	G	Y
WUH 402121	T	N	Y	Y	L	F	N	Y	Q	Q	T	N	G	Y
Rp3	T	A	-	Y	S	-	-	-	S	Y	S	V	P	Y
HKU3	T	A	-	Y	S	-	-	-	S	N	N	V	P	Y
Rm1	T	A	-	Y	S	-	-	-	S	Y	S	I	P	Y
279	T	A	-	Y	S	-	-	-	S	Y	S	I	P	Y
Rf1	T	A	-	Y	S	-	-	-	S	N	N	V	P	Y
273	T	A	-	Y	S	-	-	-	S	N	N	V	P	Y

*Conservations based on BLOSUM62 Matrix

5/14 Conserved Sites

Use
hACE2
bACE2
cACE2
mACE2

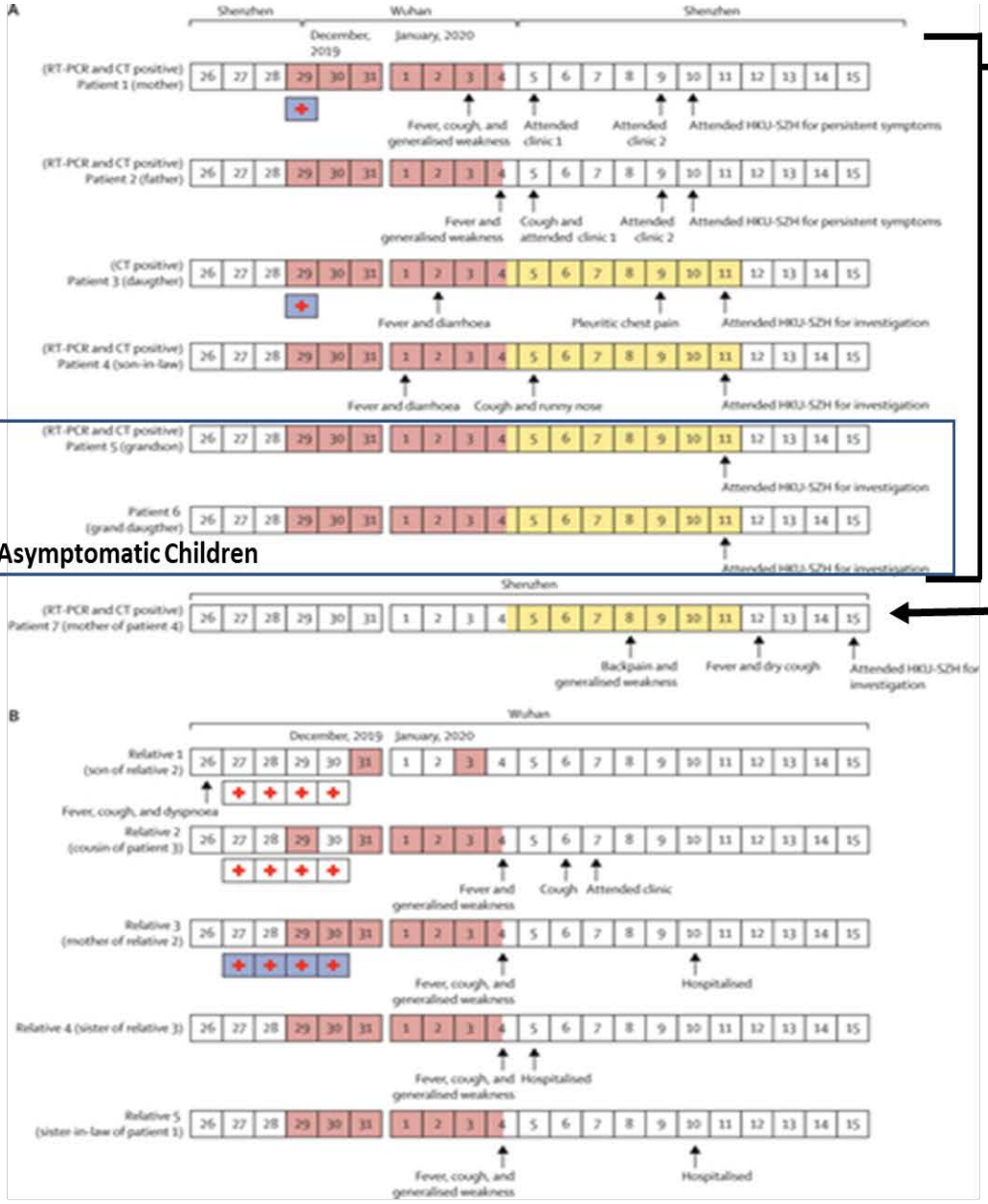
11-12/14 Contact Interface Sites Conserved

Use
hACE2
bACE2
cACE2

No
mACE2

14 Contact Interface Residues that interact with ACE2 Receptor
Variation across the contact interface residues can alter orthologue ACE2 Usage
Change Intermediate Host?

Human to Human Transmission



Six patients (patients 1–6) flew from Shenzhen to Wuhan on Dec 29, 2019, and back home on Jan 4, 2020

no history of contact with animals, visits to markets

Patients 1–6 had met with their relatives (relatives 2–5: one female cousin and three aunts of patient 3) every day during their stay in Wuhan for meals

Patient 1 acquired the infection from a Wuhan hospital while visiting their relative (relative 1)

Patients 1–5 transmitted the virus to patient 7 on returning to Shenzhen.

Attack rate is rather high, up to 83%

close contacts with relatives (1-5)

patients 3–6 stayed with patient 7

patients 1+3 or relatives 1-3 had stayed overnight (white boxes) at or had visited (blue boxes) at hospital visiting patient #1

Jasper Fuk-Woo Chan et al., The Lancet Published online January 24, 2020

UPDATE ON NEWLY DISCOVERED CORONAVIRUS

	SARS CoV	MERS CoV	2019 nCo-V (SARI)
Virion Structure	Enveloped RNA virus	Enveloped RNA virus	Enveloped RNA virus
Outbreak period	2003-2004	2012-present	2019-present
Initial site of isolation	Guangdong province, China	Saudi Arabia	Wuhan, China
No. of countries/cases	29	27	18
No. of cases (mortality)	8,096 (9.6%)	2,494 (~34%)	~5,934 (N=136)*
No. of cases U.S.	8	2 (2014)	5 (WA, IL, CA, AZ)
Reservoir (intermediate host)	Bats (palm civet)	Bats (dromedary camels)	Bats (likely a zoonosis)
Incubation period	2-7 days (range, 2-21)	2-7 (range, 2-14 days)	2-14 days (CDC, based on MERS)
Infectivity, rho	1.8-3.0	0.3-1.3	Unknown, 2.5-3.8*
Super spreaders	Yes	Yes (uncommon)	Yes (1 case infected 14 HCW)
Asymptomatic/mild Spread	No	Rare	Perhaps/Yes
Attack Rate	10.3% to 60%	4 to 20%	?, 80+% (one study)
Transmission (including to HCP)	Droplet/Direct, Airborne/Indirect?	Droplet/Direct, Airborne/Indirect?	Droplet/Direct, Airborne/Indirect?
Treatment (PEP)	Supportive (none)	Supportive (none)	Supportive (none)*
Infection Prevention^	Airborne, contact, face shield	Airborne, contact, face shield	Airborne, contact, face shield

*likely higher than SARS-CoV

Ro>3.0 basically need to reduce reproductive rate by >75% to stop epidemic

Two Day Synopsis of the News Cycle

NBC NEWS Jan 21, 2020

1st case of coronavirus from China confirmed in U.S.

JAN 22, 2020

The CDC announced Tuesday that five US airports

--New York's John F. Kennedy International Airport
--San Francisco International Airport
--Los Angeles International Airport
--Hartsfield-Jackson Atlanta International Airport
--Chicago O'Hare International Airport

— would begin screening passengers for the virus.

Coronavirus reaches US, death toll climbs: Jan 22, 2020

The virus, which has infected more than 570 people and caused 17 deaths, arrived in Washington state this week. Here are details about the mysterious new disease.

Business Insider (Jan 22, 2020)

Wuhan, China, is about to be quarantined. The city has 3 million more residents than New York City.

-shut down the city's public transportation, including buses, trains, ferries, and the airport.

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WHO says virus is not a global health emergency: Jan 23, 2020

The World Health Organization said Thursday the viral illness in China is not yet a global health emergency.

Wuhan to build designated hospital to treat coronavirus patients, aims to complete in six days

seven hospitals are being "fully utilized" (3,000 beds)

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BBC News: Jan 23, 2020 (Morning)

Wuhan and Huanggang (7 million) on lockdown.....and then Ezho (1 million).....(10 cities)

299,600 train passengers departed from Wuhan (22nd)

Jan 23 (evening) CBS NEWS

177/830 cases of coronavirus reported in China involve severe infections (21%), as death toll rises to 25 (3%), virus has affected 29 provinces in China

a full-blown community epidemic (>50% never in market)

Two Day Synopsis of the News Cycle

cnet Coronavirus reaches US, death toll climbs:

NBC NEWS

1st case of co

LOS ANGEL

SCIENCE, China

Cases, WHO d

emergency

The CDC anr

--New York's J

--San Francisc

--Los Angeles

--Hartsfield-Ja

--Chicago O'H

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WHO says vi

emergency:

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illness in Chi

Wuhan to bu

coronavirus p

seven hospitals are being "fully utilized" (3,000 beds)

Jan 22, 2020

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3 million more

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China involve

to 25 (3%),

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Chinas Health Minister: Ma Xiaowei

"people can spread it before they become symptomatic"

"the Wuhan virus has an incubation period of couple days to two weeks " US Official

China quarantines 56 million people/20 cities

Hong Kong closes schools, public functions, places where people congregate

Imagine the Impact on the National Economy!

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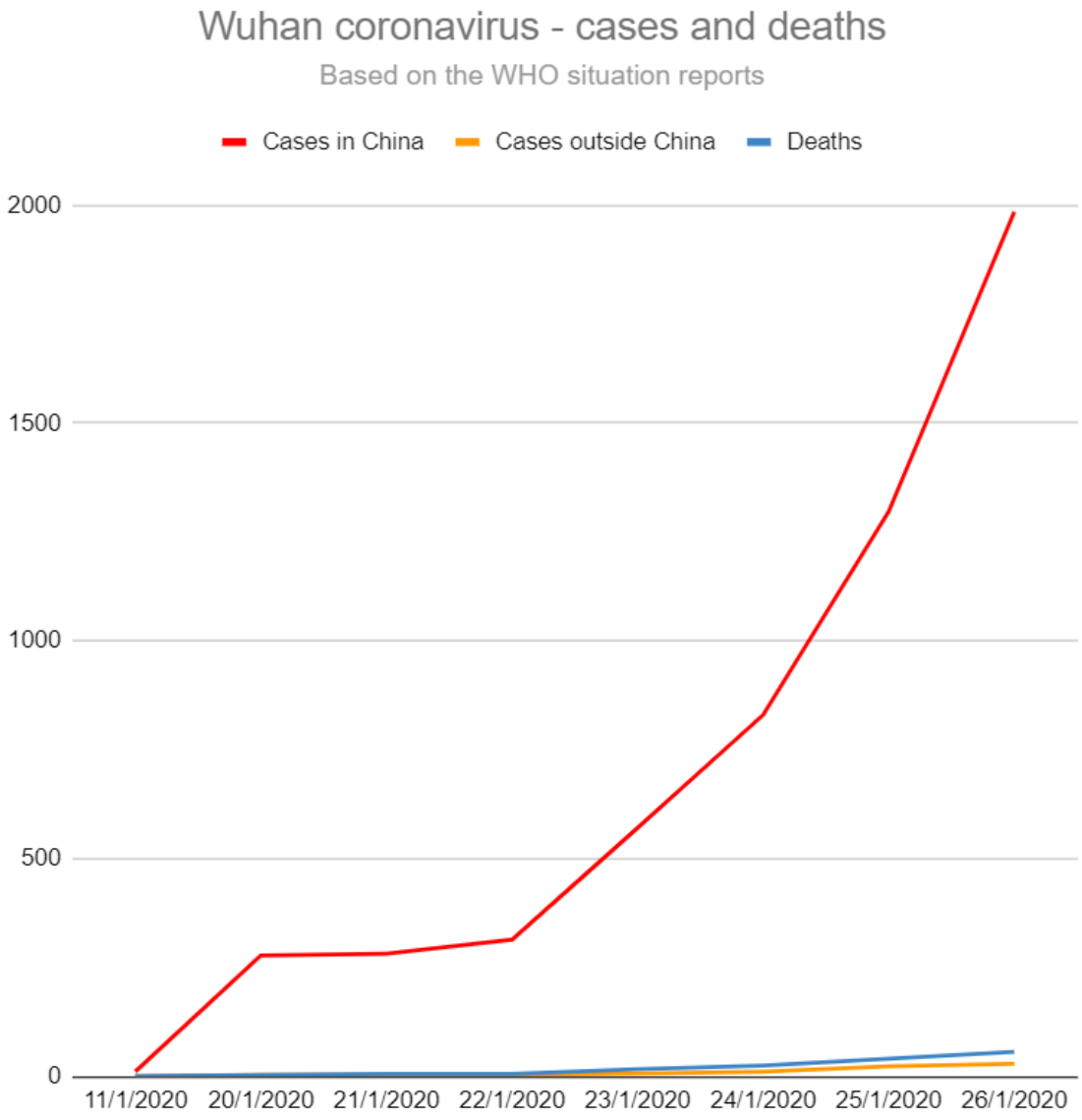
Imagine the Impact on the National Economy!

You Don't Do this Unless Your Very Worried/Situation Dire

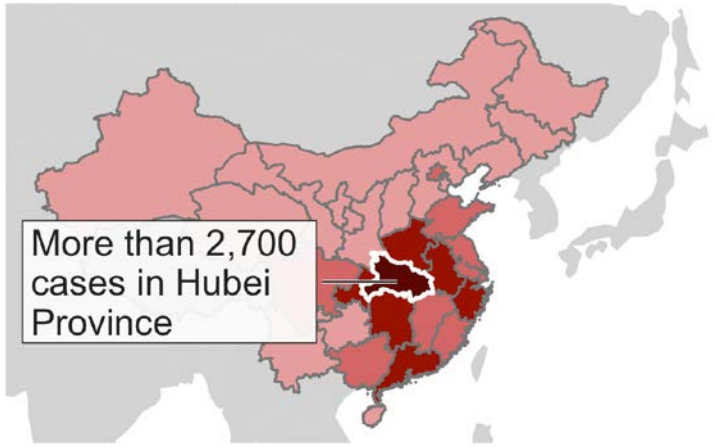
1/26/2020

New coronavirus has killed 80 people and infected at least 2,774 more in China
5 Cases Reported in the US (Az, Ill, Ca, Wash)



1/28/2020:

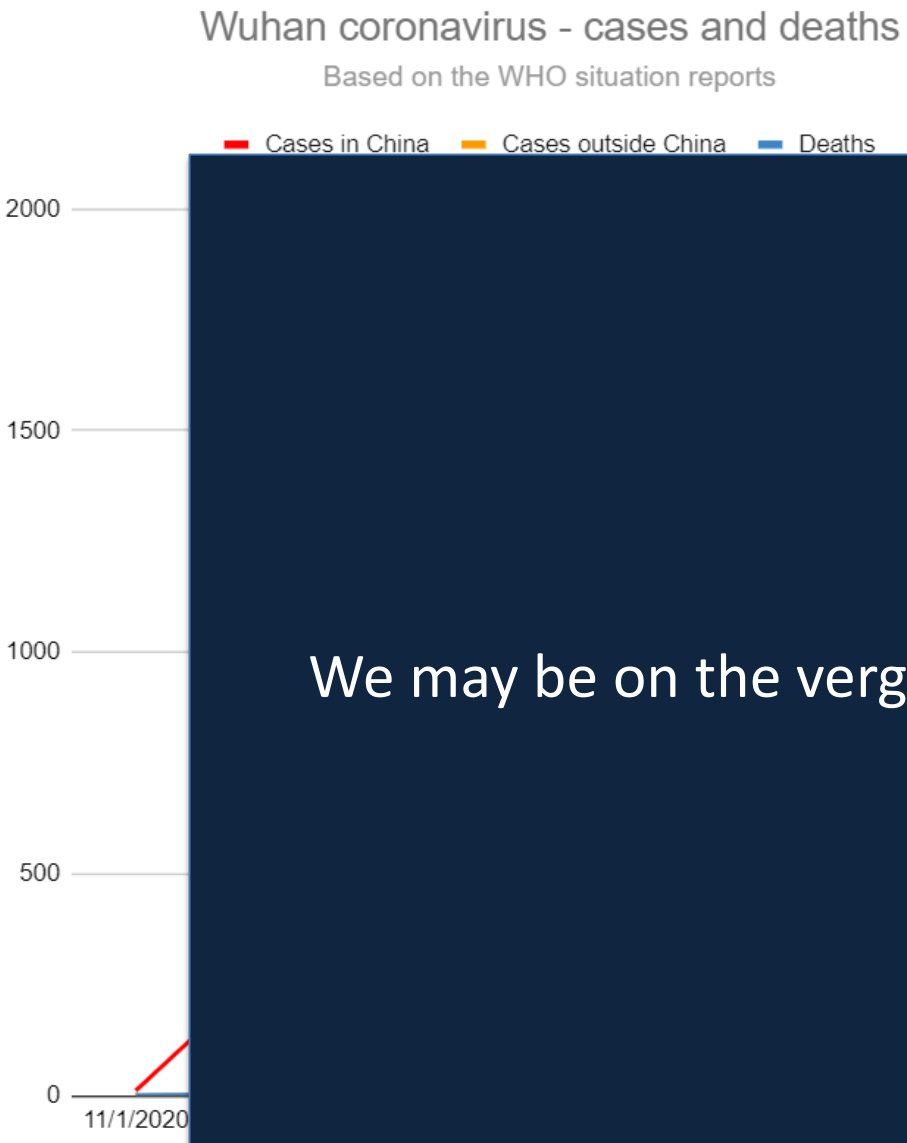
5985 cases confirmed in China,
136 deaths (~3% mortality)



China Frantically Shuts Down Stock Market to Prevent Coronavirus Selloff

US has upgraded its travel advice to China to level 3 – its highest level

2019 nHCoV successfully recovered by researchers in Melbourne, Australia (1/28/2020)

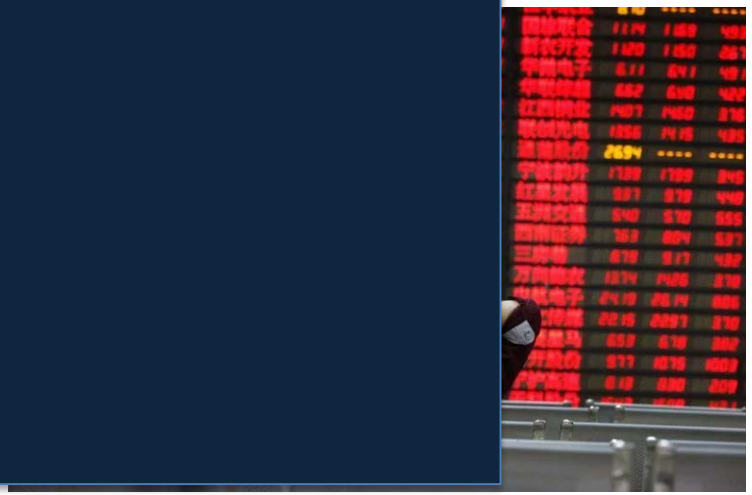


1/28/2020:

5985 cases confirmed in China,

tality)

We may be on the verge of a global pandemic



US has upgraded its travel advice to China to level 3 – its highest level

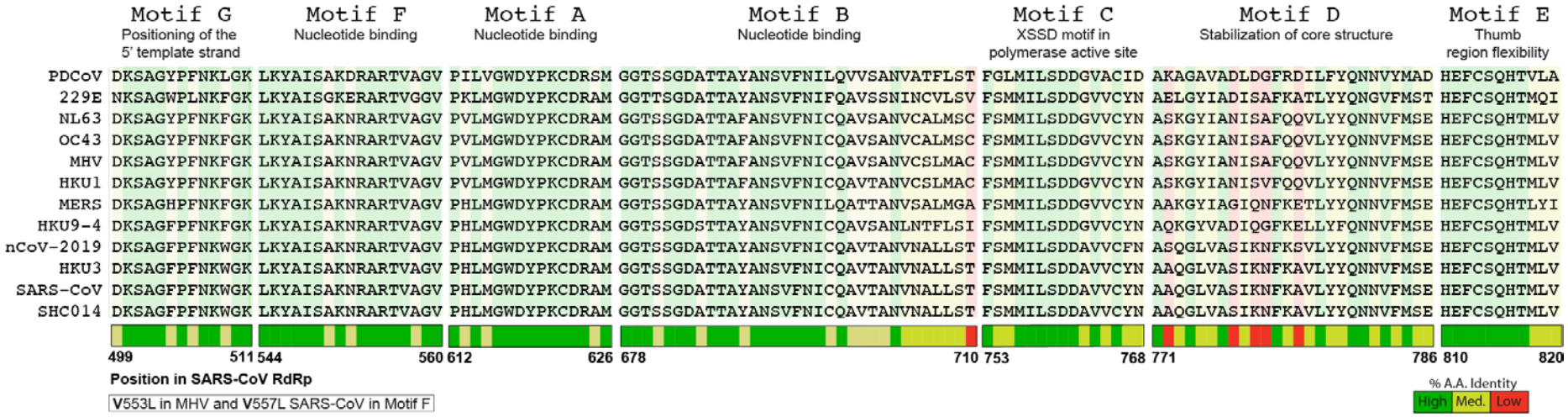
China Frantically Shuts Down Stock Market to Prevent Coronavirus Selloff

2019 nHCoV successfully recovered by researchers in Melbourne, Australia (1/28/2020)

Therapeutic Interventions

- **No approved drugs, immune therapeutics and vaccines against any group 2b coronavirus**
- **Experimental Drugs (nsp12-RdRp target)**
  - **Remdesivir**-ribonucleoside inhibitor
  - **EIDD-1931**-(b-D-N^4-hydroxycytidine)-ribonucleoside inhibitor
  - **Combination lopinavir, ritonavir, and interferon beta against MERS-CoV**
  - **Therapeutic antibodies** (MERS-CoV)

Conservation of key RdRp motif residues

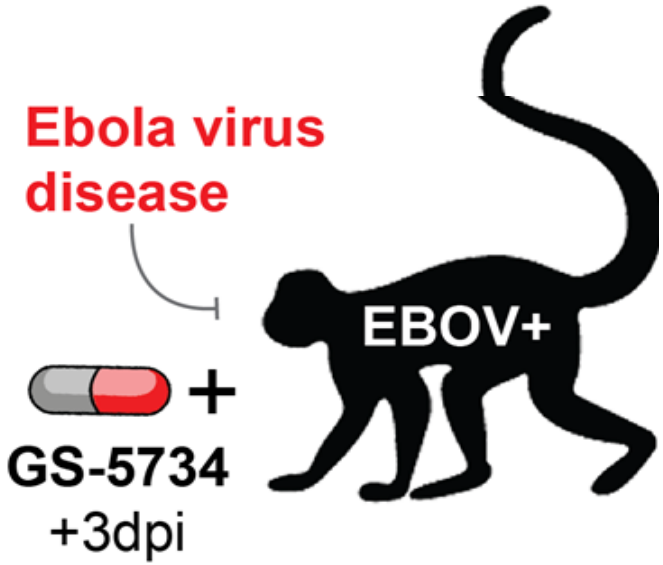


Sheahan et al., Nature Communications 11, 222 (2020)

Sheahan et al., Sci Transl Med. 2017 Jun 28;9(396).

GS-5734 is a broad-spectrum antiviral

efficacy against EBOV in vivo



Protects

EBOV DRC Clinical Trials

Mortality in Untreated: ~70%

Overall mortality was 50% (84/169) in all patients treated with Zmapp

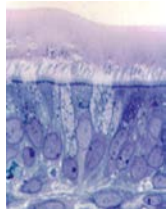
Mortality rate in remdesivir treated patients was 51%

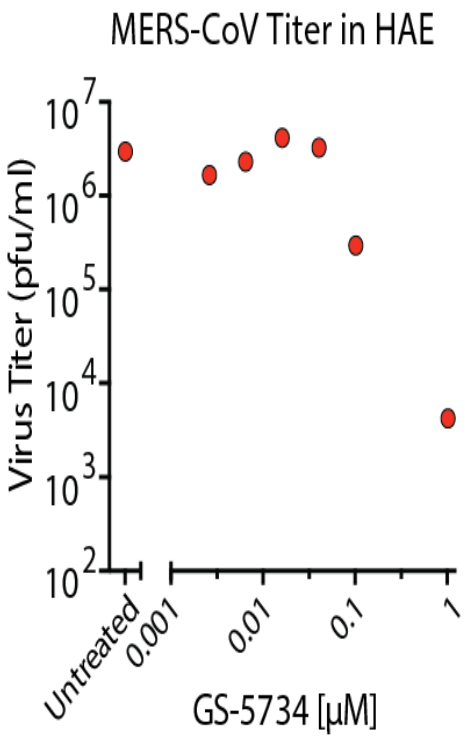
35% (61/174) of patients in the mAb114 treatment group

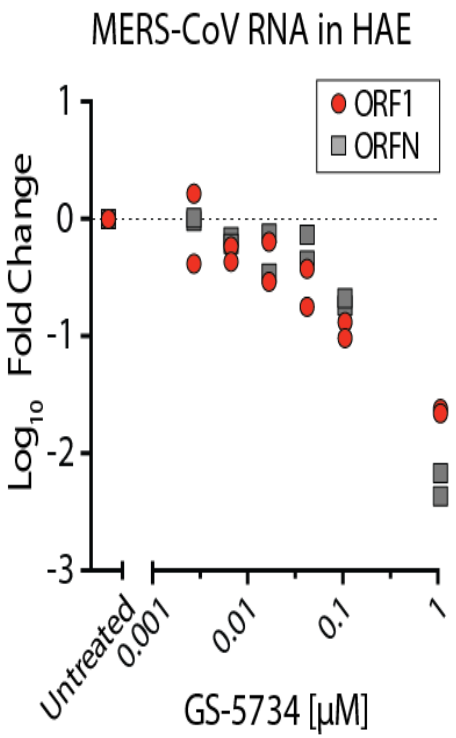
34% (52/155) of patients in the REGN-EB3 group died by 28 days

Nucleoside Analogues have poor activity against CoV?

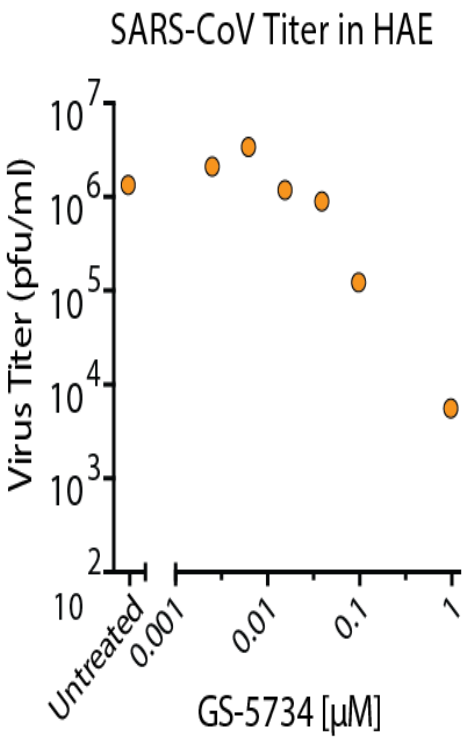
Antiviral effect in primary human cells

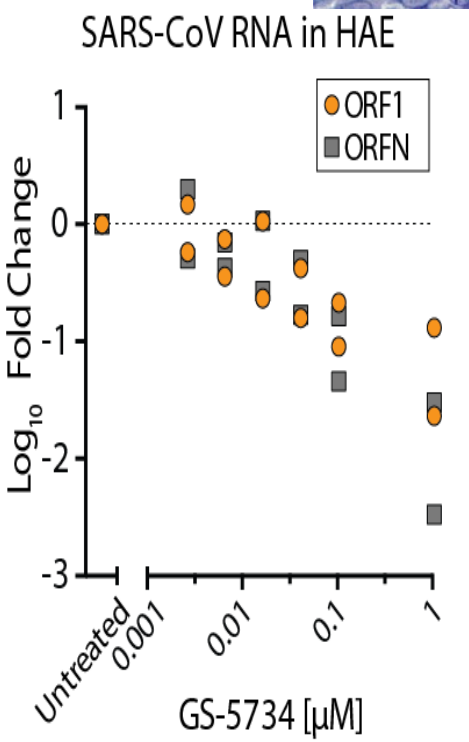






IC_{50} = 0.74μM



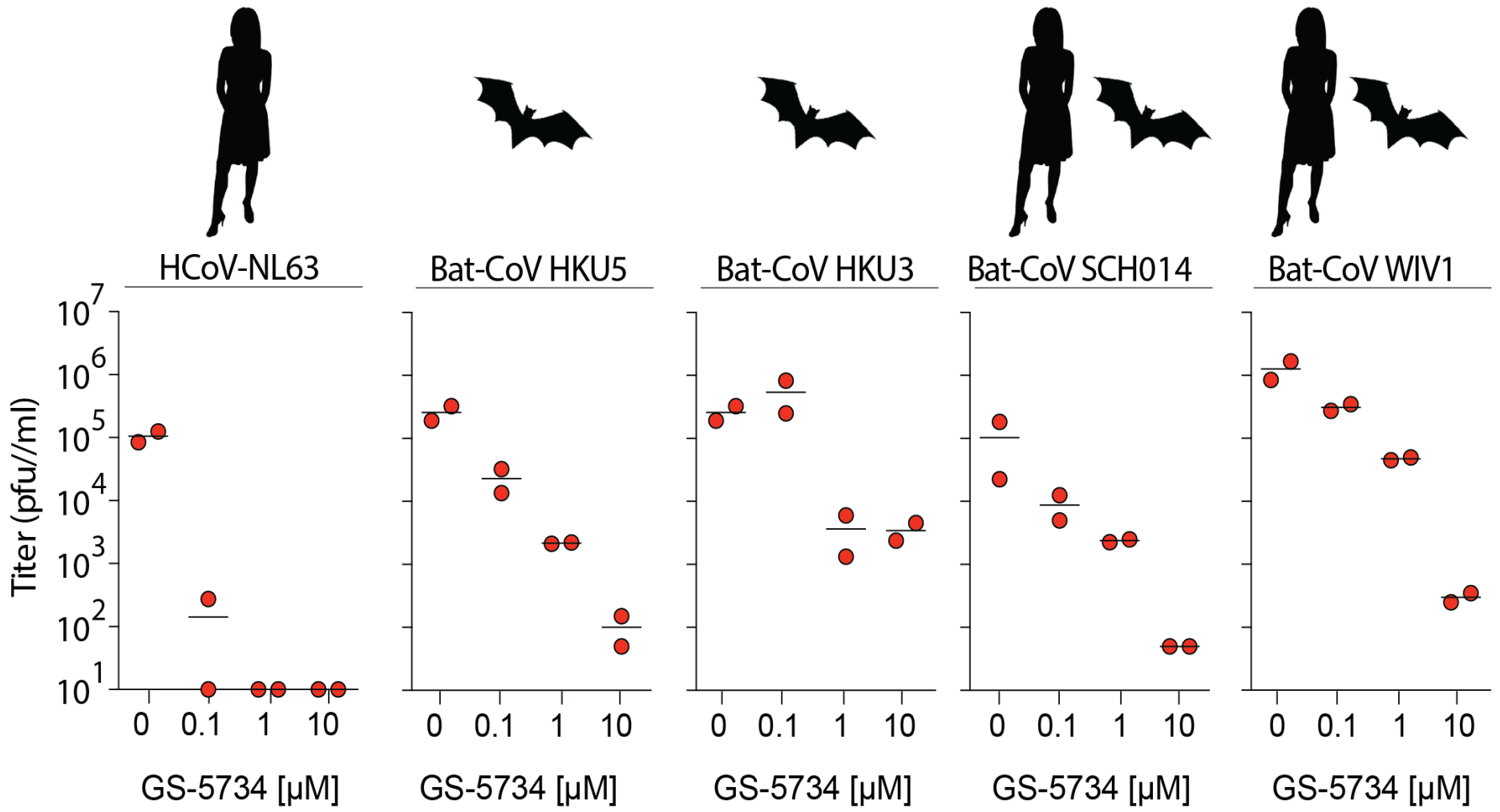


IC_{50} = 0.69μM

GS5734 Also Inhibits MERS-CoV replication in primary lung fibroblasts and vascular endothelial cells at similar levels

Sheahan et. al 2017 Science Translational Medicine 2017 Jun 28;9(396)

Efficacy of GS-5734 against diverse CoV

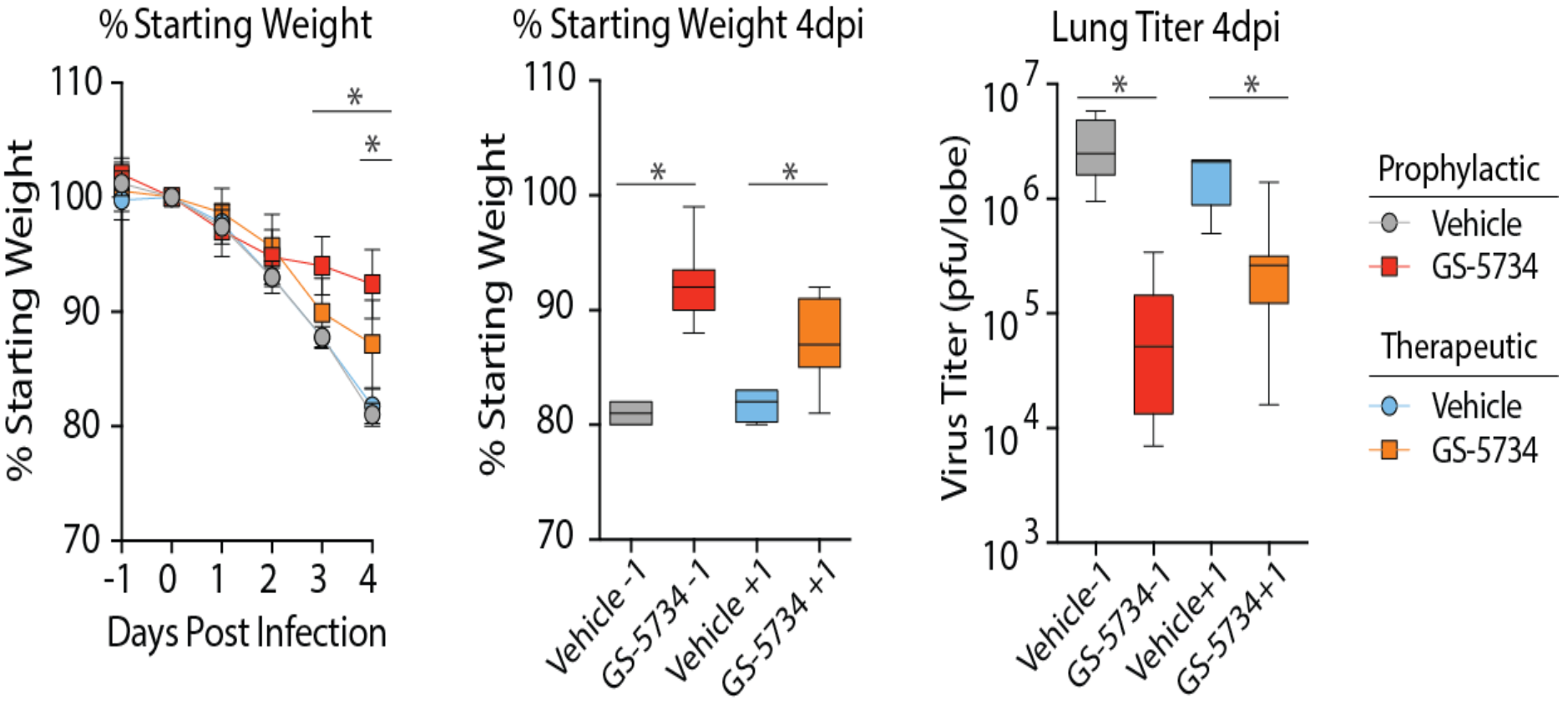


Contemporary Human

Prepandemic SARS and MERS-like BtCoV

Sheahan et. al 2017 Science Translational Medicine 2017

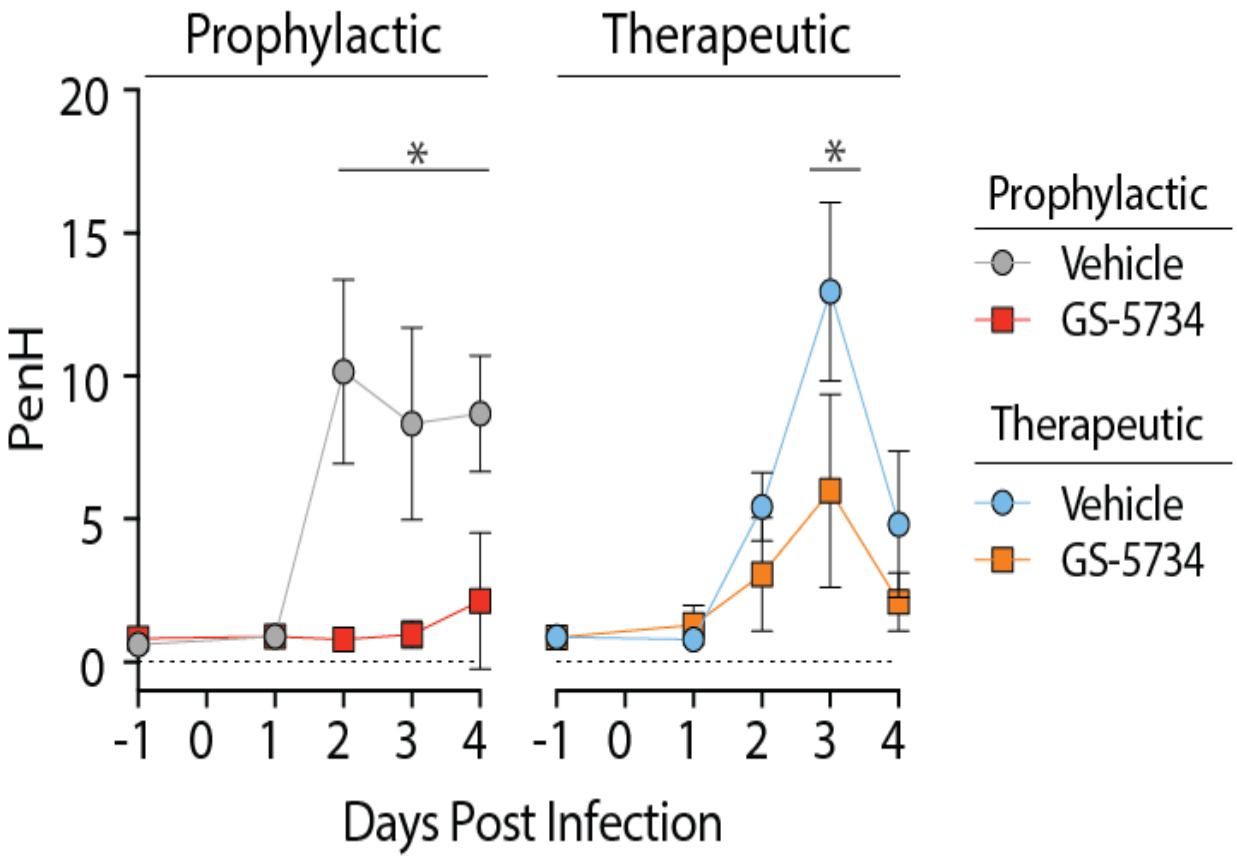
GS-5734 diminishes SARS-CoV Disease

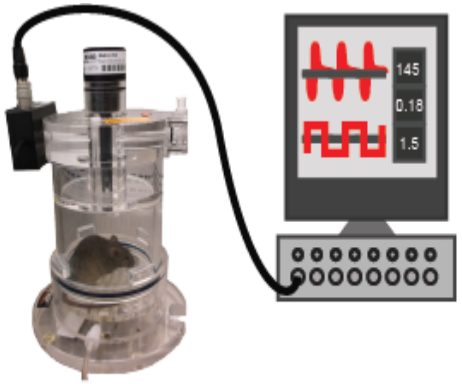


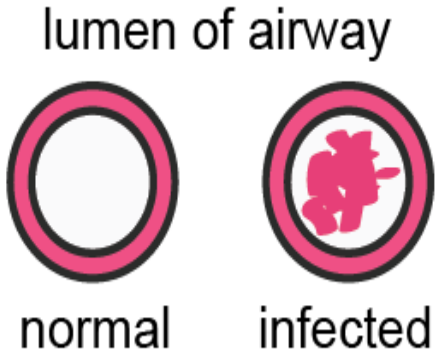
Effective against SARS-like HKU3 in Aged animals

Sheahan et. al 2017 Science Translational Medicine 2017

GS-5734 improves pulmonary function

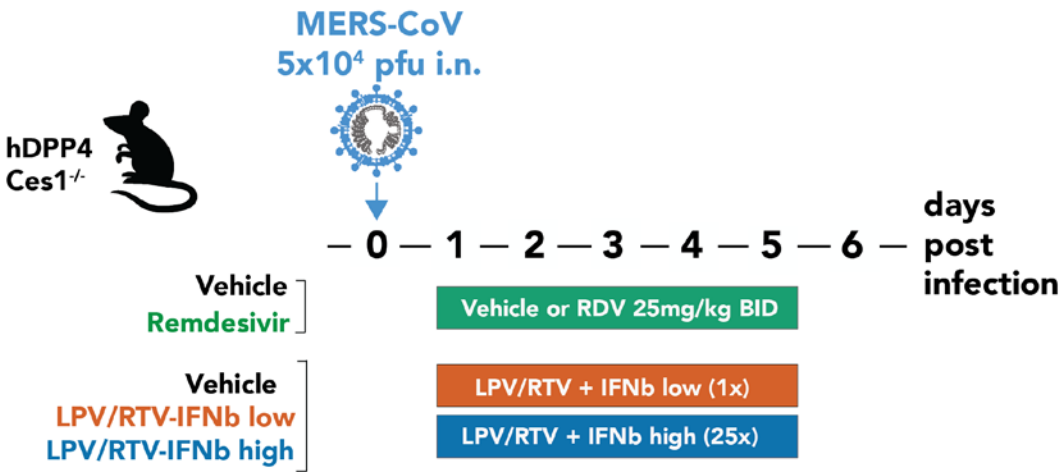






Sheahan et. al 2017 Science Translational Medicine 2017

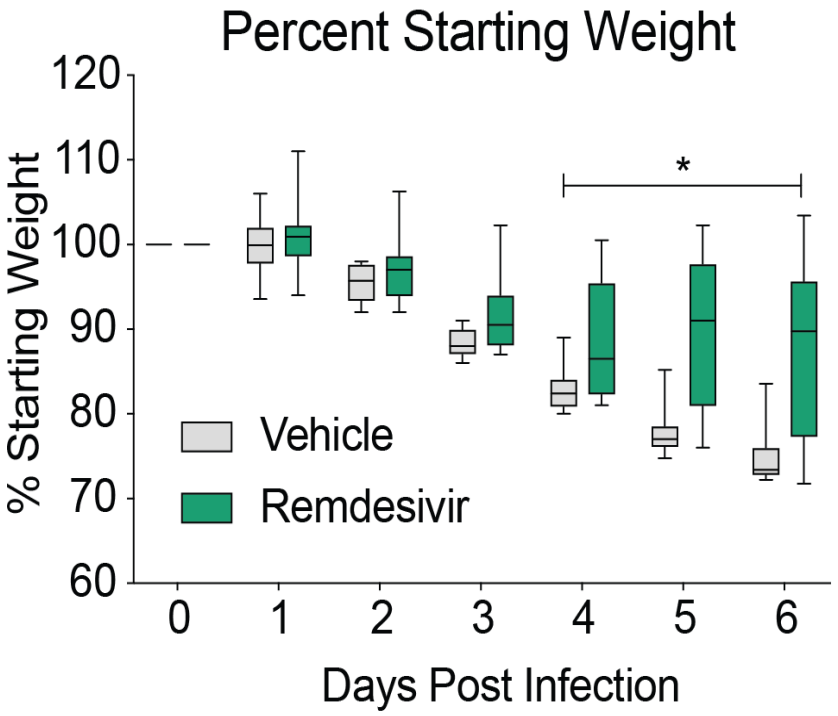
Will therapeutic Rx improve outcomes?

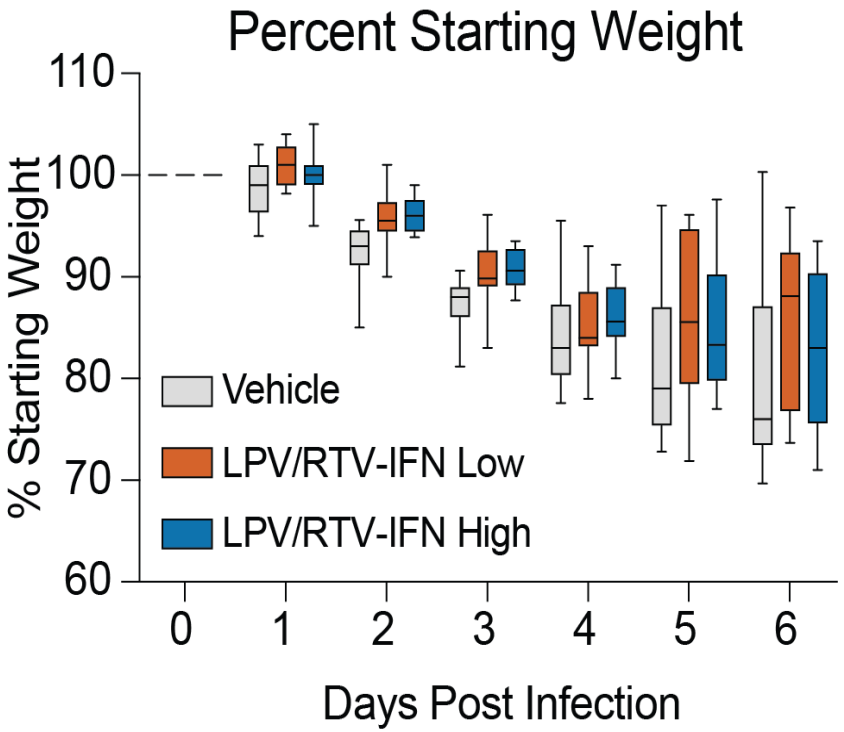


Metrics of Efficacy

Body Weight Loss
Pulmonary Function
Virus Lung Titer
Lung Pathology

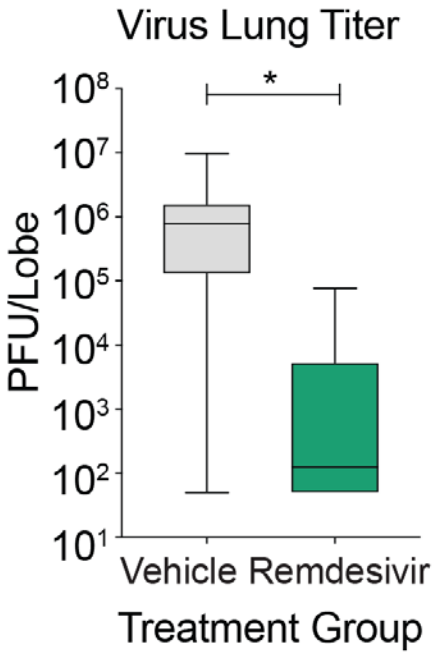
Therapeutic RDV reduces weight loss

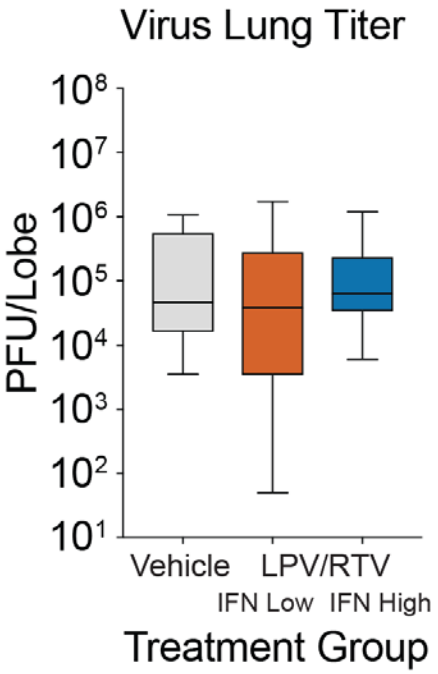




Sheahan et. al Nature Communications 2020

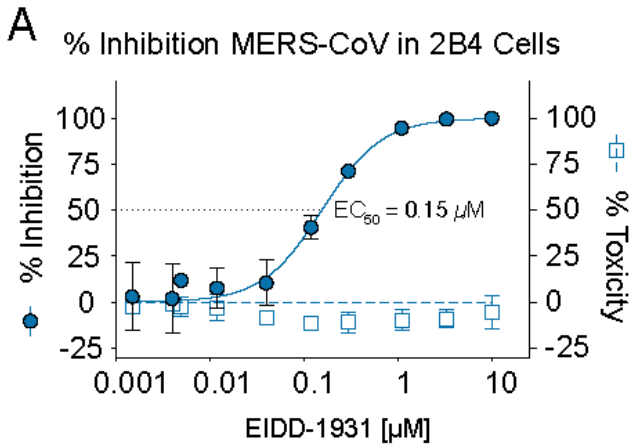
Therapeutic RDV reduces viral load



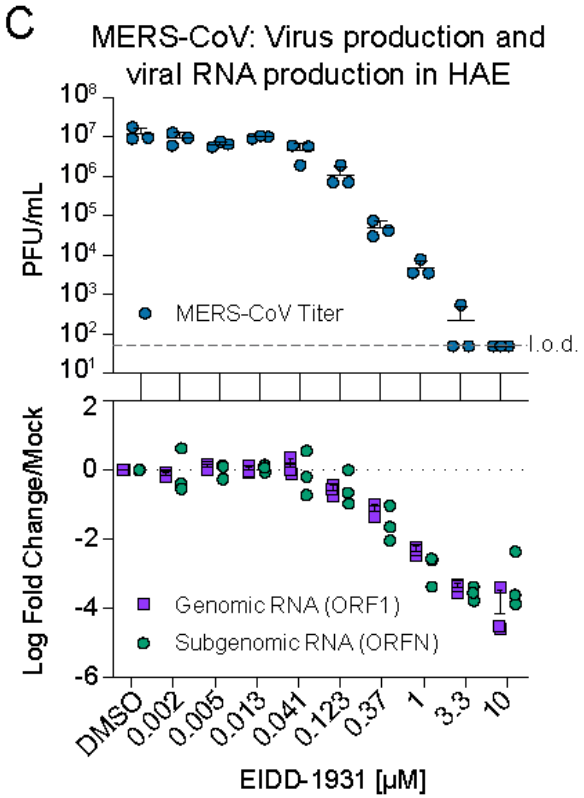


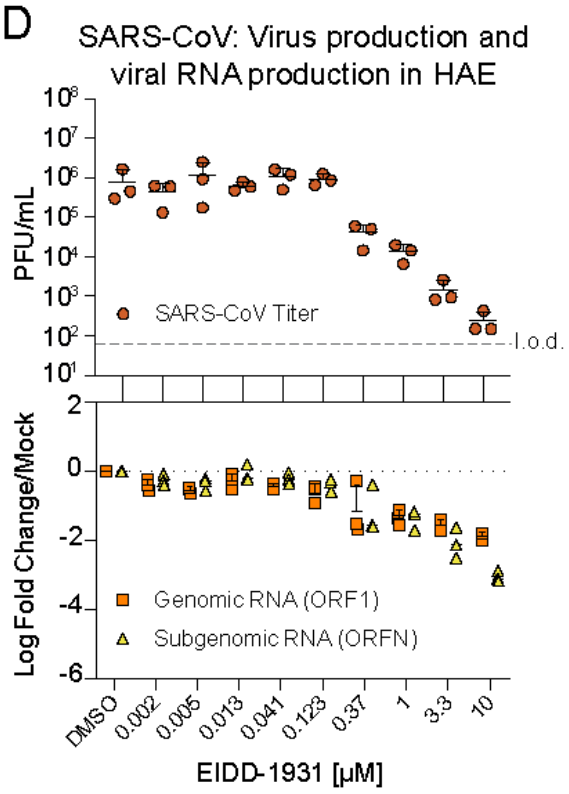
Sheahan et. al Nature Communications 2020

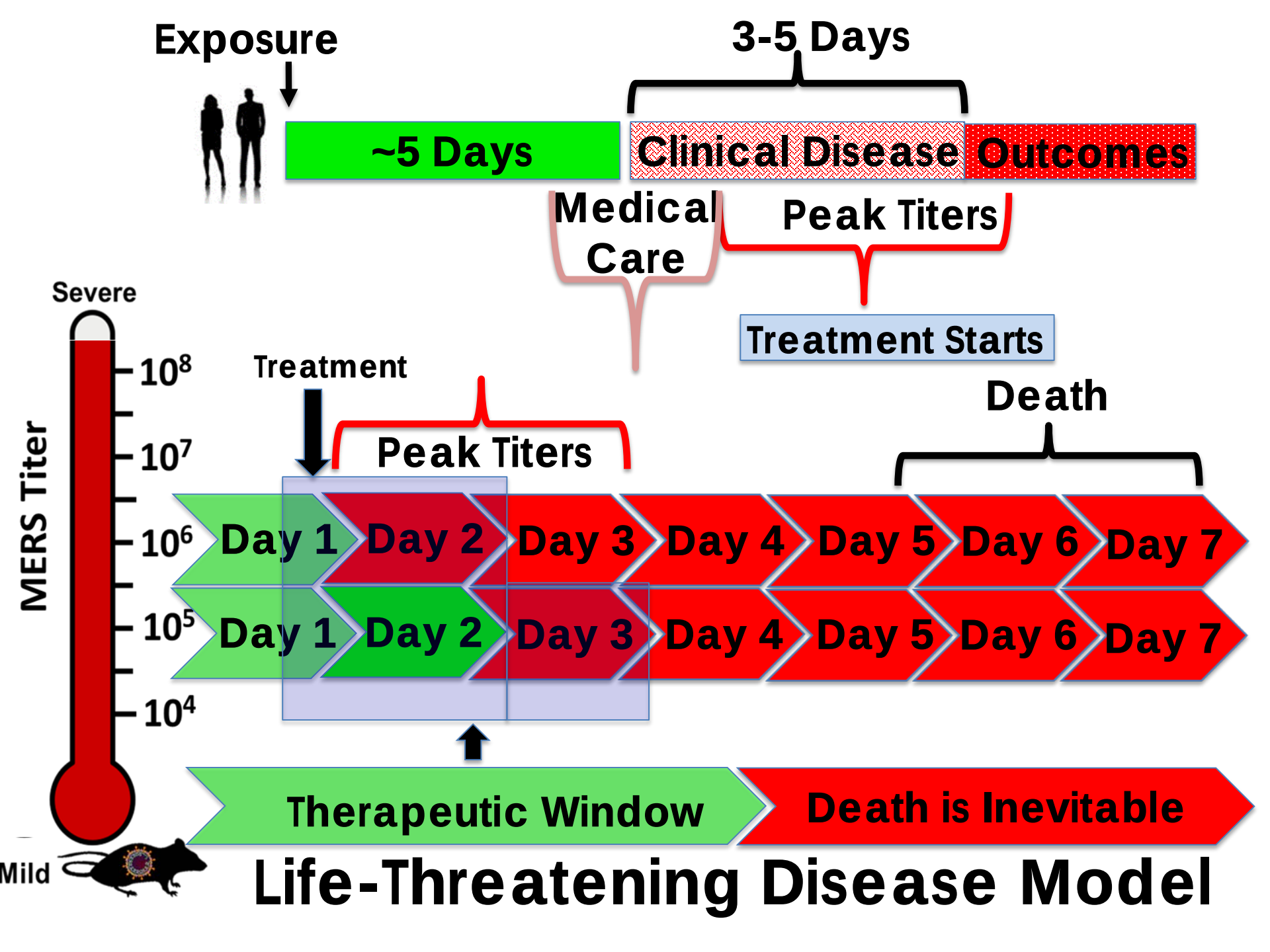
EIDD-1931


A
% Inhibition MERS-CoV in 2B4 Cells
% Inhibition
% Toxicity
EC50 = 0.15 μM
100
75
50
25
0
-25
0.001
0.01
0.1
1
10
EIDD-1931 [μM]

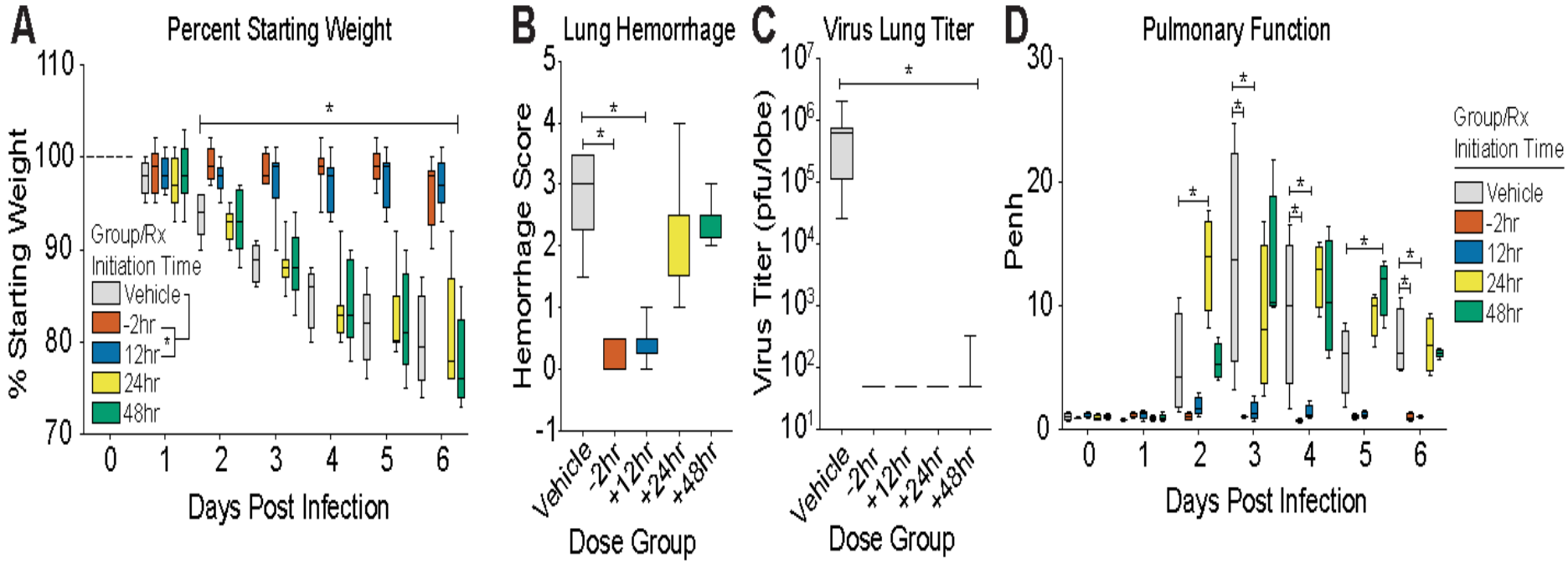

B
Cell death factor expression in HAE
EIDD-1931 [μM]
100
33
11
3.7
1.1
0.37
0.12
0.047
Stauro-sporine
18S
Tank
Fas
Tradd
Bad
Bcl2
Mcl1
Bcl2L11
Bax
Log2 Fold Change/GAPDH
2
1
0
-1
* P < 0.05


C
MERS-CoV: Virus production and viral RNA production in HAE
PFU/mL
MERS-CoV Titer
l.o.d.
Log Fold Change/Mock
Genomic RNA (ORF1)
Subgenomic RNA (ORFN)
DMSO
0.002
0.005
0.013
0.041
0.123
0.37
1
3.3
10
EIDD-1931 [μM]


D
SARS-CoV: Virus production and viral RNA production in HAE
PFU/mL
SARS-CoV Titer
l.o.d.
Log Fold Change/Mock
Genomic RNA (ORF1)
Subgenomic RNA (ORFN)
DMSO
0.002
0.005
0.013
0.041
0.123
0.37
1
3.3
10
EIDD-1931 [μM]


Exposure
3-5 Days
~5 Days
Clinical Disease
Outcomes
Medical Care
Peak Titers
Treatment Starts
Severe
MERS Titer
10^8
10^7
10^6
10^5
10^4
Mild
Treatment
Peak Titers
Death
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Day 1
Day 2
Day 3
Day 4
Day 5
Day 6
Day 7
Therapeutic Window
Death is Inevitable
Life-Threatening Disease Model

EIDD-1931 In Vivo



Effective in vivo against MERS-CoV and SARS-CoV

Baric Laboratory: 2019 nHCoV

- 2019-nHCoV replicates and causes lethal disease by day 7 in C57Bl/6 hACE2 mice
  - Z. Shi-Institute of Virology, Wuhan China
  - Test variety of vaccines NIH VRC/CEPI, protective immunity in vivo
  - Test therapeutic hmABs and drugs
- Chimeric SARS-like bat CoV SHC014 encoding the 2019-nHCoV S glycoprotein spike
  - Building mouse adapted versions-mutations in RBD than enhance mACE2 interaction
- 2019-nHCoV Reverse genetic Platform and recombinant viruses
  - Building mouse adapted versions-mutations in RBD than enhance mACE2 interaction