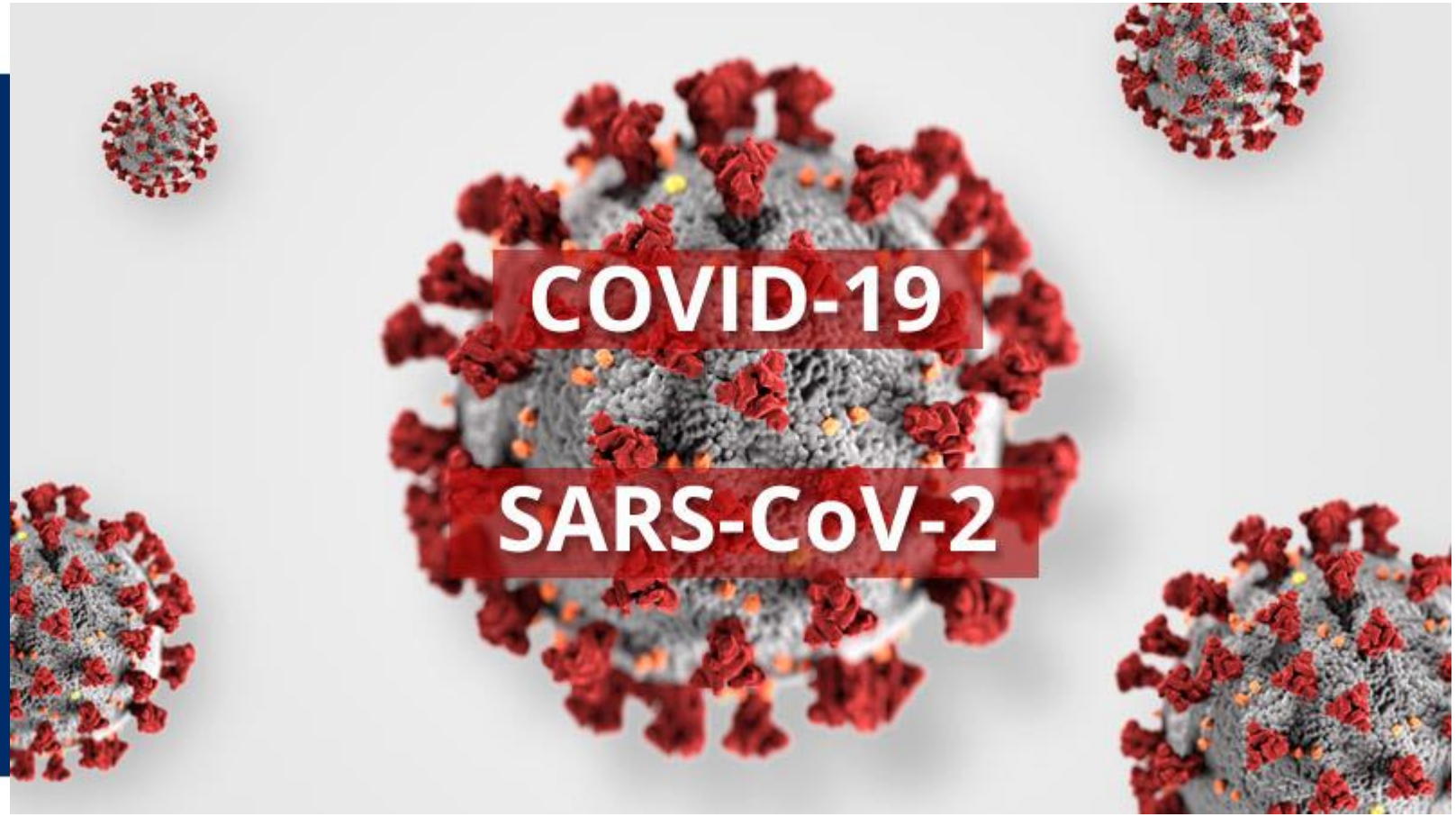
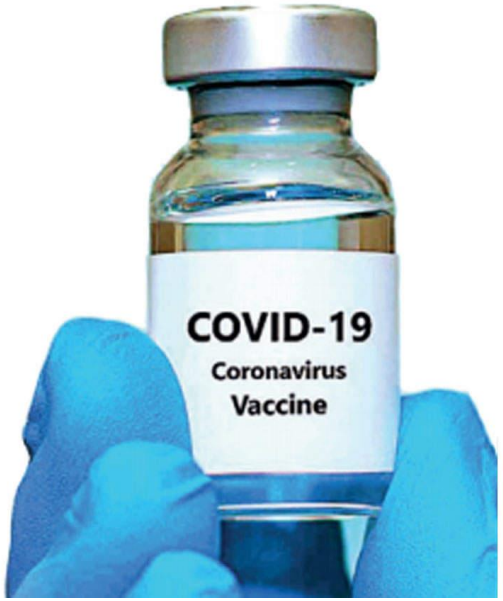
ADAM MICKIEWICZ UNIVERSITY IN POZNAŃ
Faculty of Biology

Mouse Models: COVID-19



Hans Bluyssen, 28.03.2023

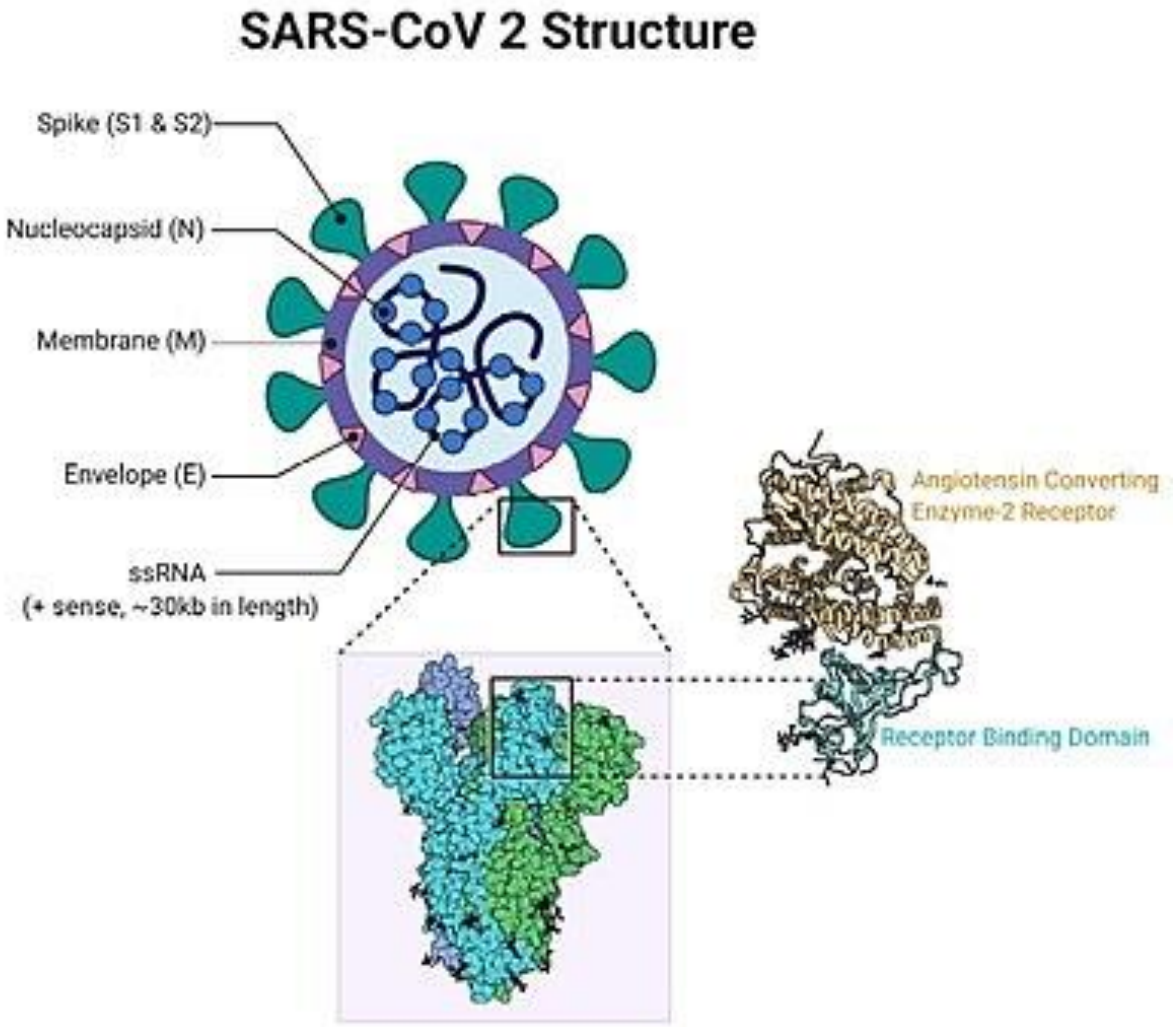


COVID-19 – SARS-CoV-2

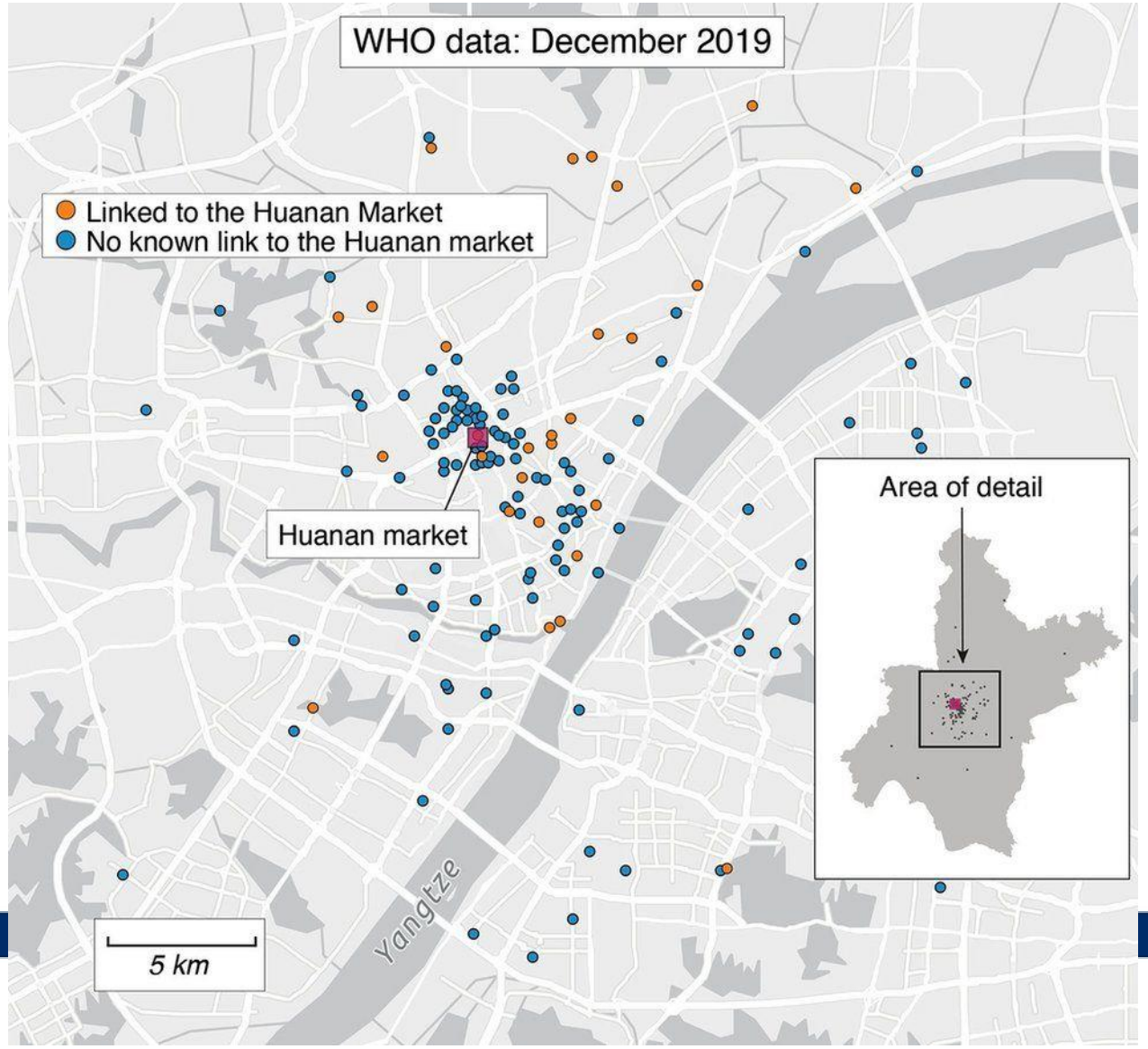
Severe acute respiratory syndrome coronavirus 2 (**SARS-CoV-2**) is the virus that causes coronavirus disease 2019 (COVID-19), the respiratory illness responsible for the COVID-19 pandemic.

The World Health Organization declared the outbreak:
-a Public Health Emergency of International Concern on 30 January 2020
-a pandemic on 11 March 2020.

SARS-CoV-2 is a positive-sense single-stranded RNA virus. As described by the US National Institutes of Health, it is the successor to SARS-CoV-1, the virus that caused the 2002–2004 SARS outbreak.



COVID-19 – Outbreak



World Health Organization

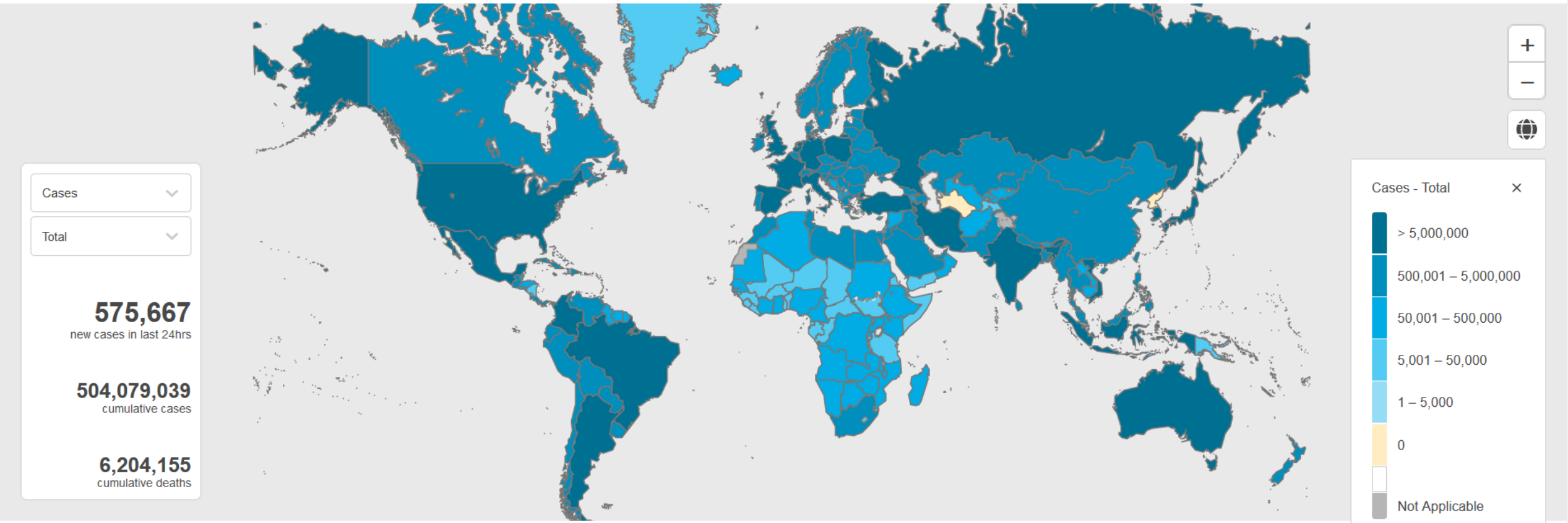
Search by Country, Territory, or Area

Covid-19 Response Fund

Donate

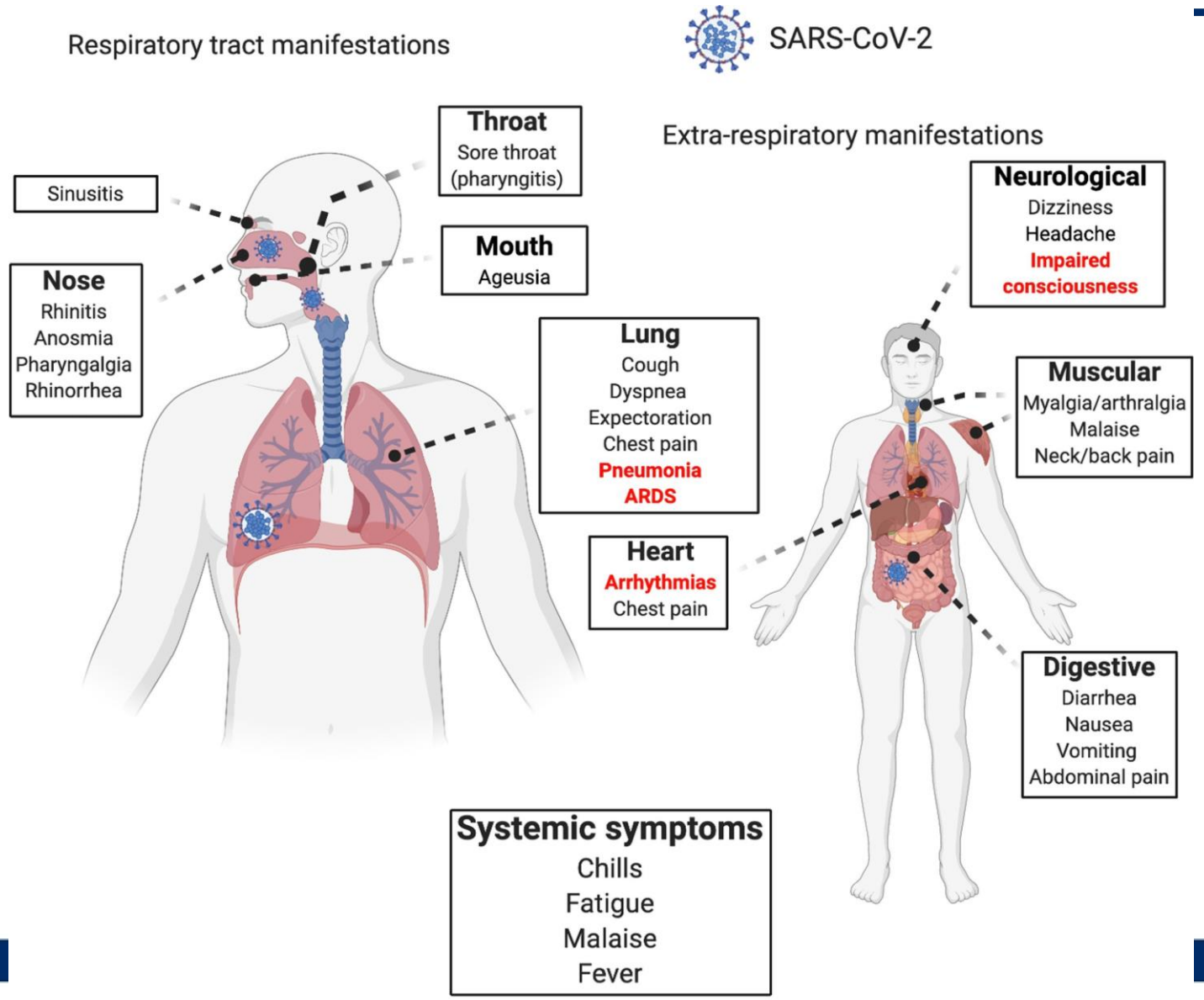
WHO Coronavirus (COVID-19) Dashboard

Overview | Measures | Table View | Data | More Resources



Globally, as of **5:50pm CEST, 20 April 2022**, there have been **504,079,039 confirmed cases** of COVID-19, including **6,204,155 deaths**, reported to WHO. As of **18 April 2022**, a total of **11,324,805,837 vaccine doses** have been administered.

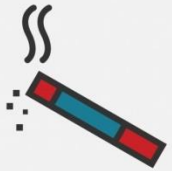
COVID-19 Manifestations



Trends in Immunology

COVID-19 Risk Groups

5 Groups at Risk from COVID-19



Smokers

Severely overweight people

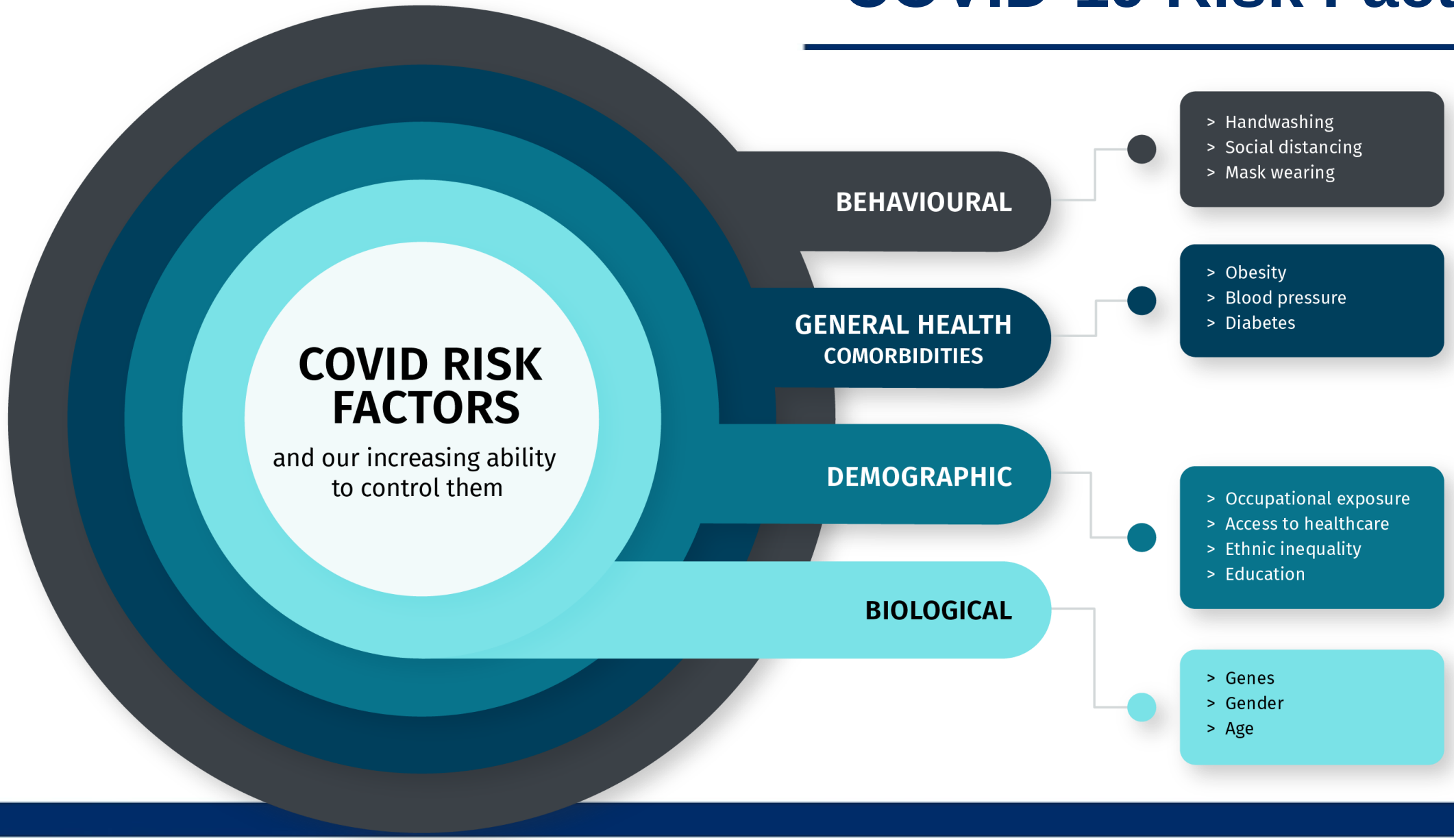
Middle-aged to elderly adults

People with chronic illnesses

Men

MAIN STREET
MEDICAL CLINIC

COVID-19 Risk Factors



COVID-19 Management

10 ways to manage respiratory symptoms at home

If you have fever, cough, or shortness of breath, call your healthcare provider. They may tell you to manage your care from home. Follow these tips:

1. **Stay home** from work, school, and away from other public places. If you must go out, avoid using any kind of public transportation, ridesharing, or taxis.

2. **Monitor your symptoms** carefully. If your symptoms get worse, call your healthcare provider immediately.

3. **Get rest and stay hydrated.**

4. If you have a medical appointment, **call the healthcare provider** ahead of time and tell them that you have or may have COVID-19.

5. For medical emergencies, call 911 and **notify the dispatch personnel** that you have or may have COVID-19.

6. **Cover your cough and sneezes.**

7. **Wash your hands often** with soap and water for at least 20 seconds or clean your hands with an alcohol-based hand sanitizer that contains at least 60% alcohol.

8. As much as possible, **stay** in a specific room and **away from other people** in your home. Also, you should use a separate bathroom, if available. If you need to be around other people in or outside of the home, wear a facemask.

9. **Avoid sharing personal items** with other people in your household, like dishes, towels, and bedding.

10. **Clean all surfaces** that are touched often, like counters, tabletops, and doorknobs. Use household cleaning sprays or wipes according to the label instructions.

CDC

CS 315822-A 03/12/2020

For more information: **www.cdc.gov/COVID19**

COVID-19 Risk Levels

LOW RISK

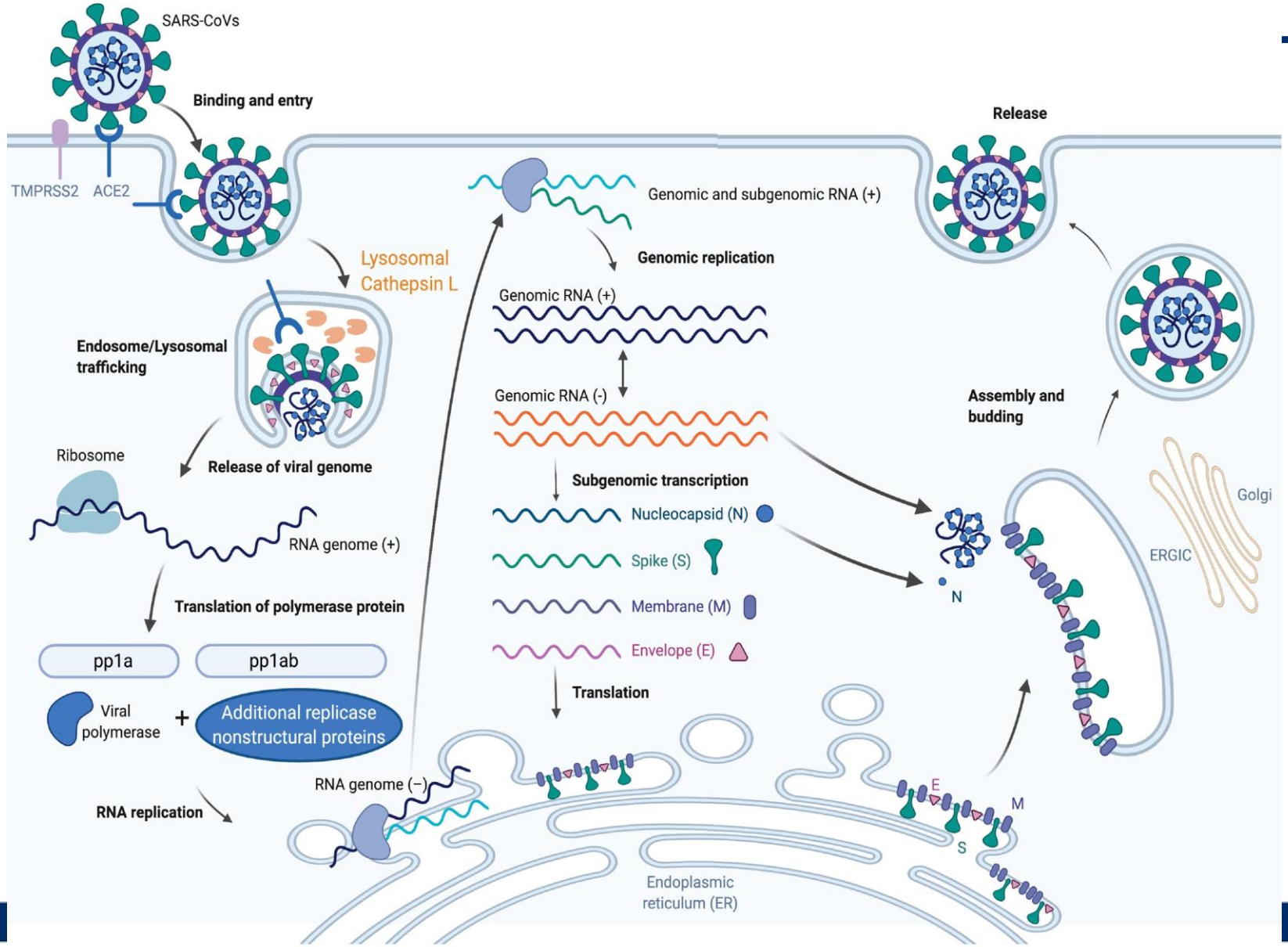
1. Restaurants (take-out) | Tennis
2. Walk, bike, or run with others | Get car gasoline
3. Grocery stores | Camping | Hotels Golfing | Libraries | Museums
4. Dentist office | Doctor waiting room Offices | Walking in busy downtown Restaurants (outdoor)
5. Home dinner parties | Backyard BBQs Airplanes | Malls | Beaches | Bowling
6. Casinos | Restaurants (indoor) Playgrounds | Hair salons | Movie theaters | Pontoon boat ride
7. Basketball | Public pools | Schools
8. Gyms | Amusement parks | Churches Buffets
9. Bars | Big concerts | Sports stadium

HIGH RISK

OU WB

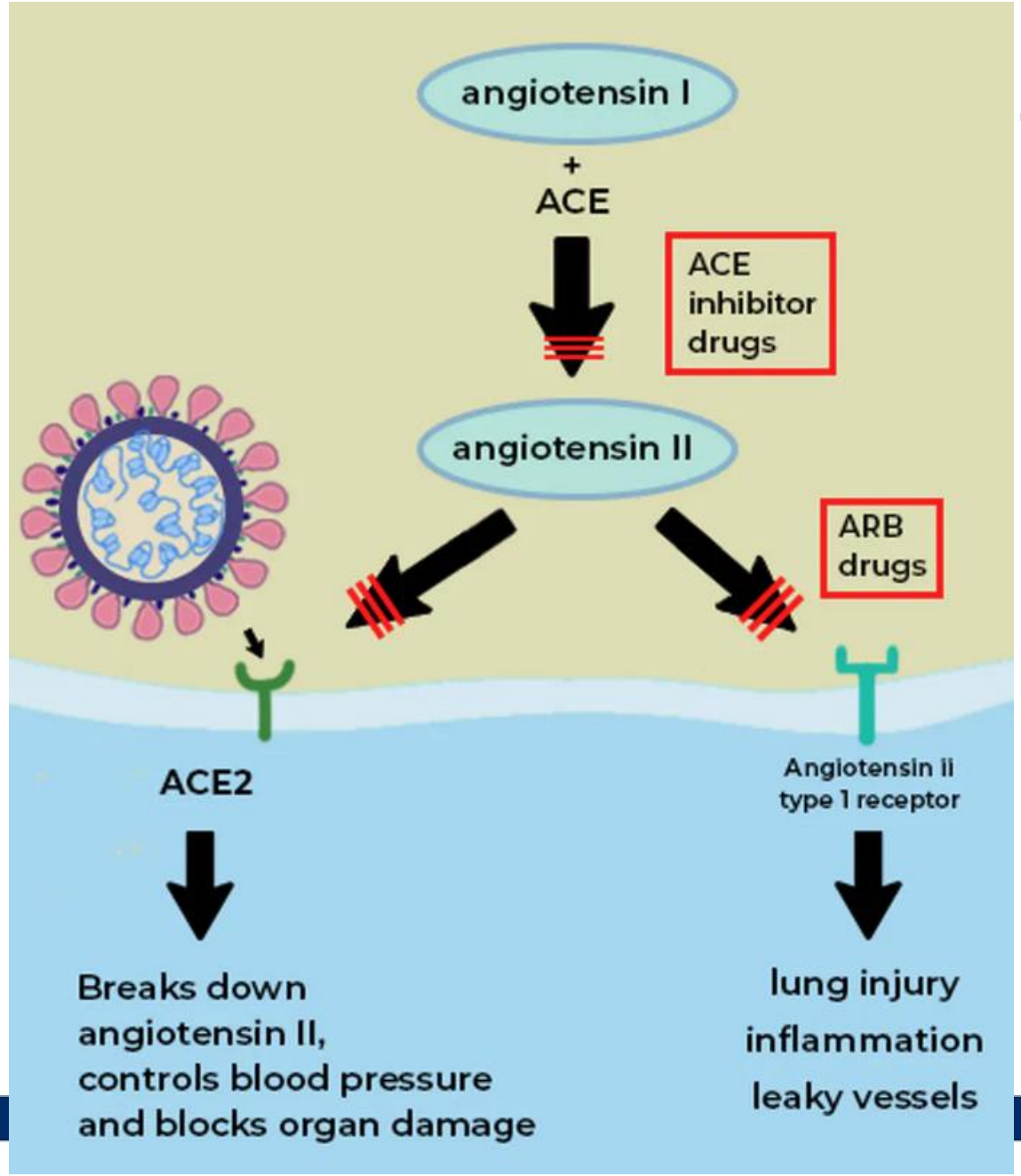
Dr. Matthew Sims, Dr. Dennis Cunningham, Dr. Mimi Emig, Dr. Nasir Husain. Based on risk factors including inside/outside, nearness to others, exposure time, compliance likelihood, and personal risk.

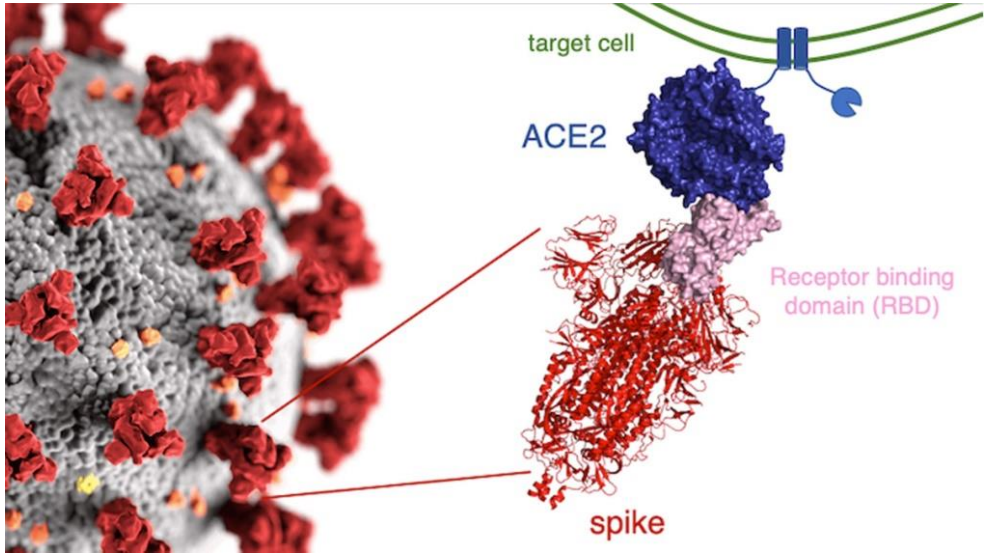
SARS-CoV-2 Life Cycle



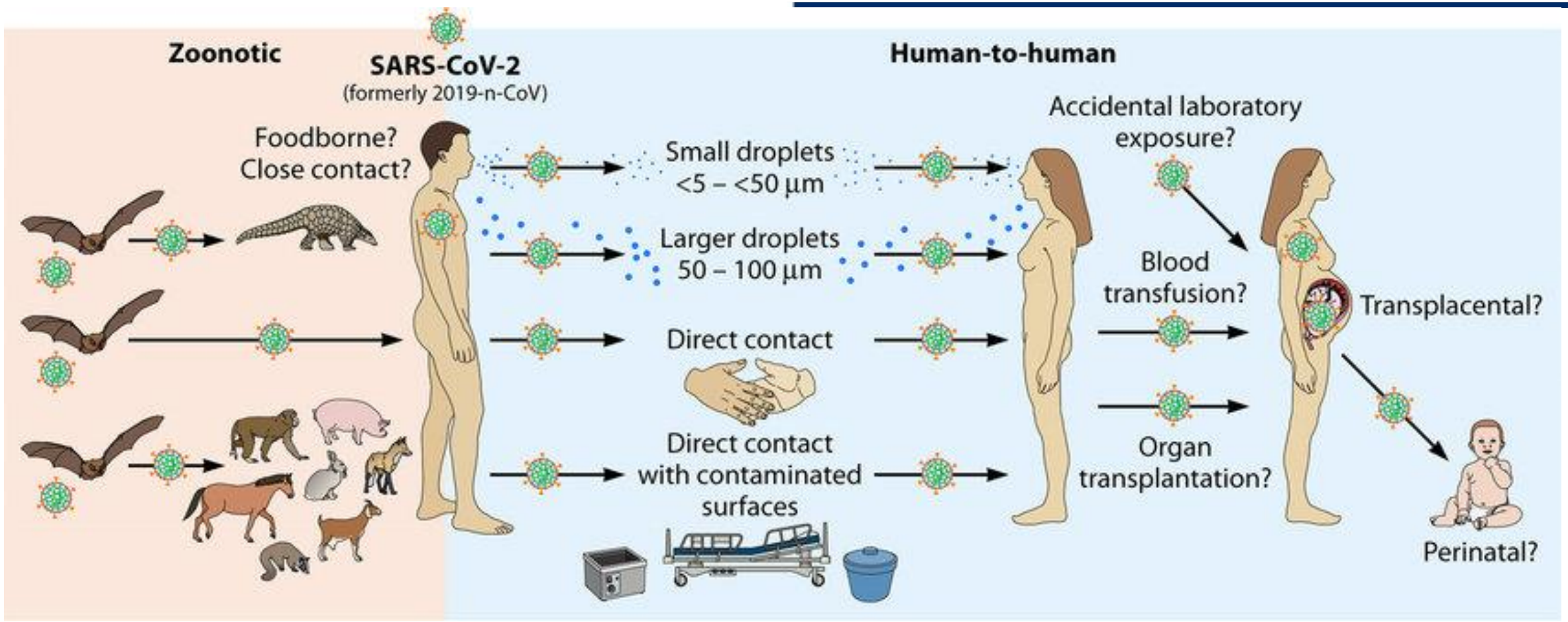
Trends in Immunology

SARS-CoV-2 & ACE2



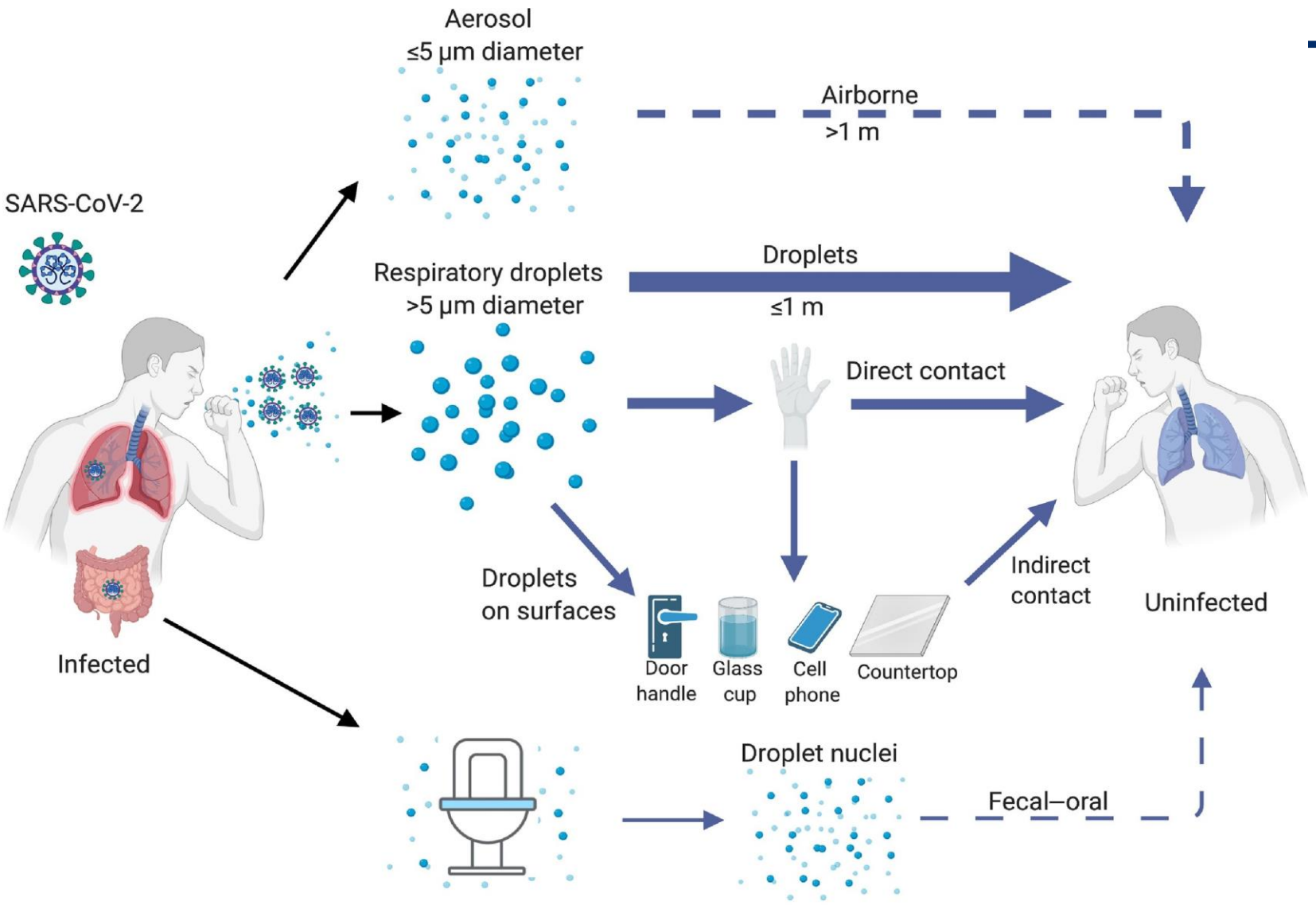


SARS-CoV-2 Transmission

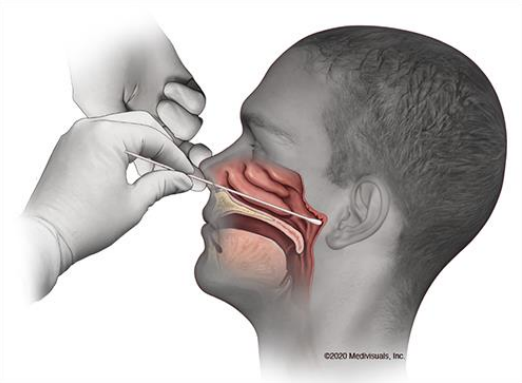


A **zoonosis** (plural **zoonoses**, or **zoonotic diseases**) is an infectious disease caused by a pathogen (an infectious agent, such as a bacterium, virus, parasite or prion) that has jumped from an animal (usually a vertebrate) to a human.
Typically, the first infected human transmits the infectious agent to at least one other human, who, in turn, infects others.

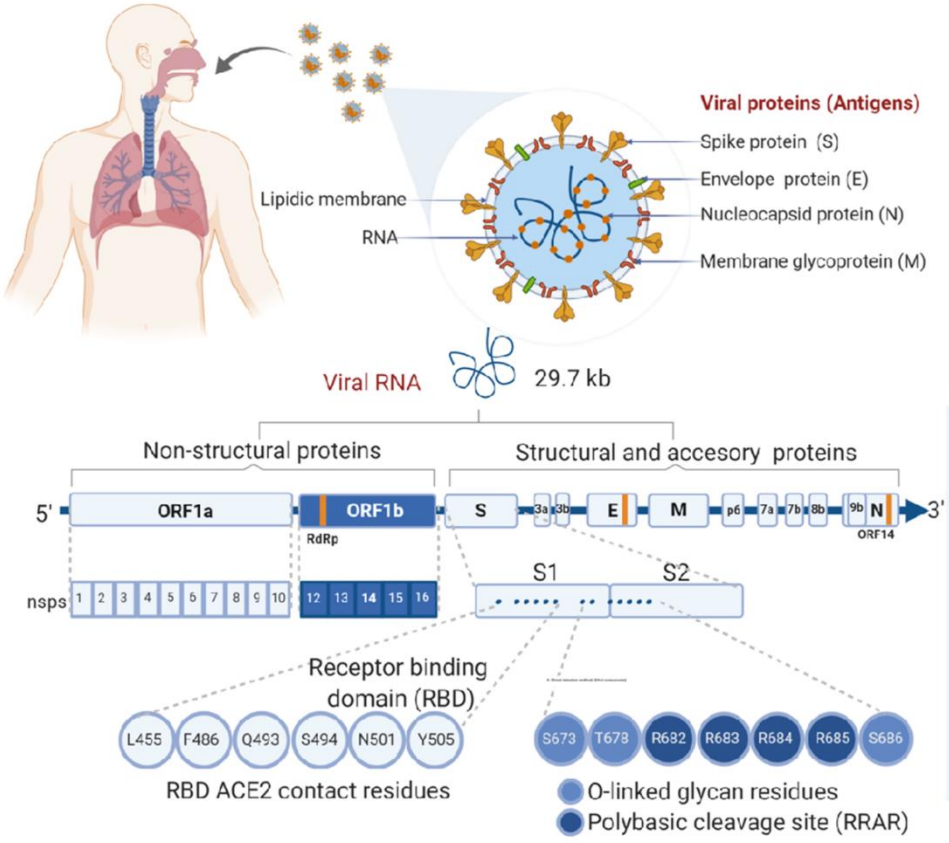
SARS-CoV-2 Transmission

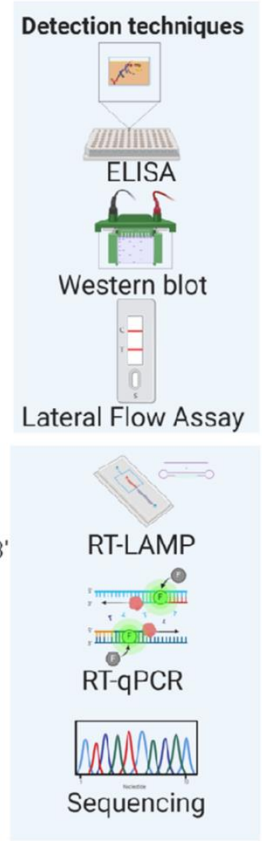


Detection Methods

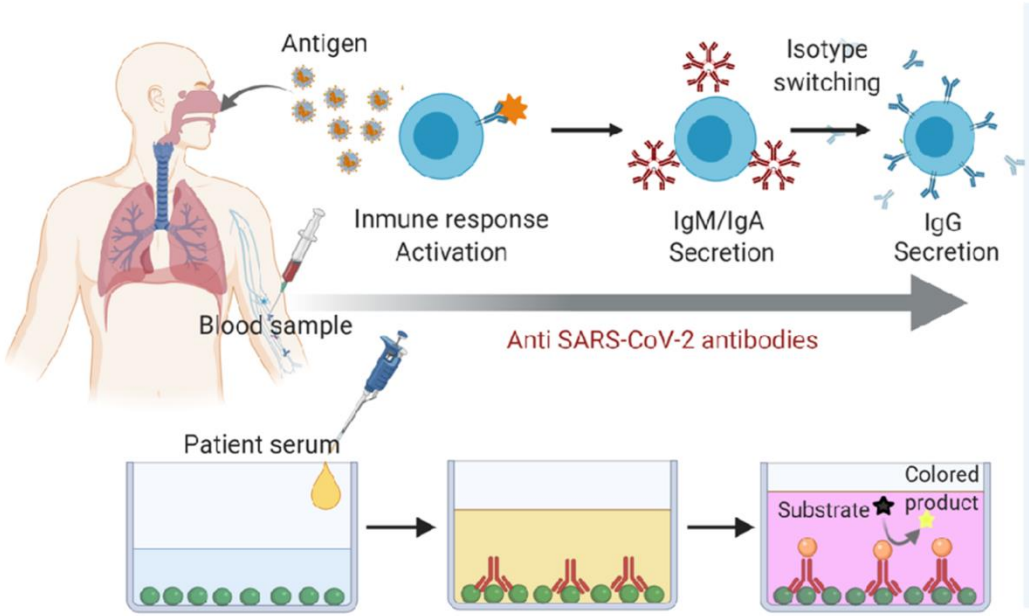


A. Direct detection methods (Viral components)

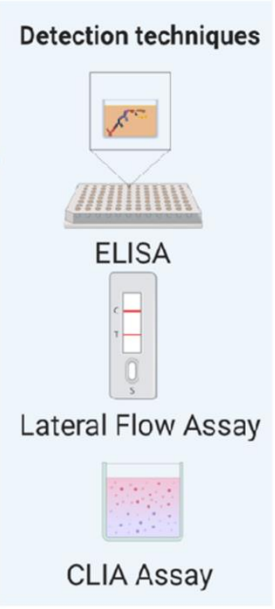




B. Indirect detection methods (Host immune response)



Mechanism of antibody detection



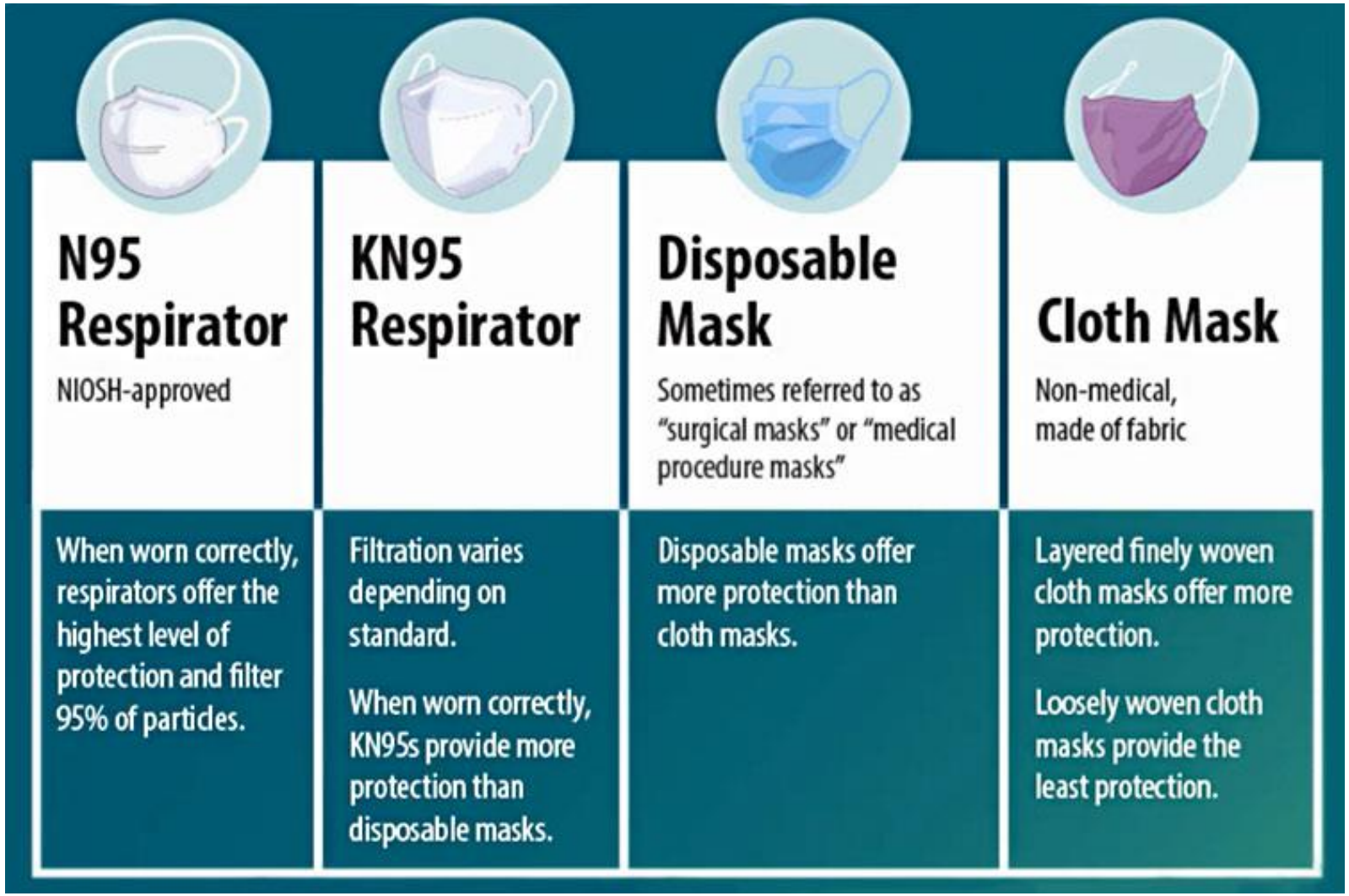
Antibody tests

World Health Organization
Western Pacific Region

- Detects antibodies against the virus generated by prior infection or vaccination
- Not useful for telling if you have the disease now
- Positive test result doesn't mean you can't catch the virus again
- Are usually a finger prick/blood test
- Only currently recommended by WHO for research purposes

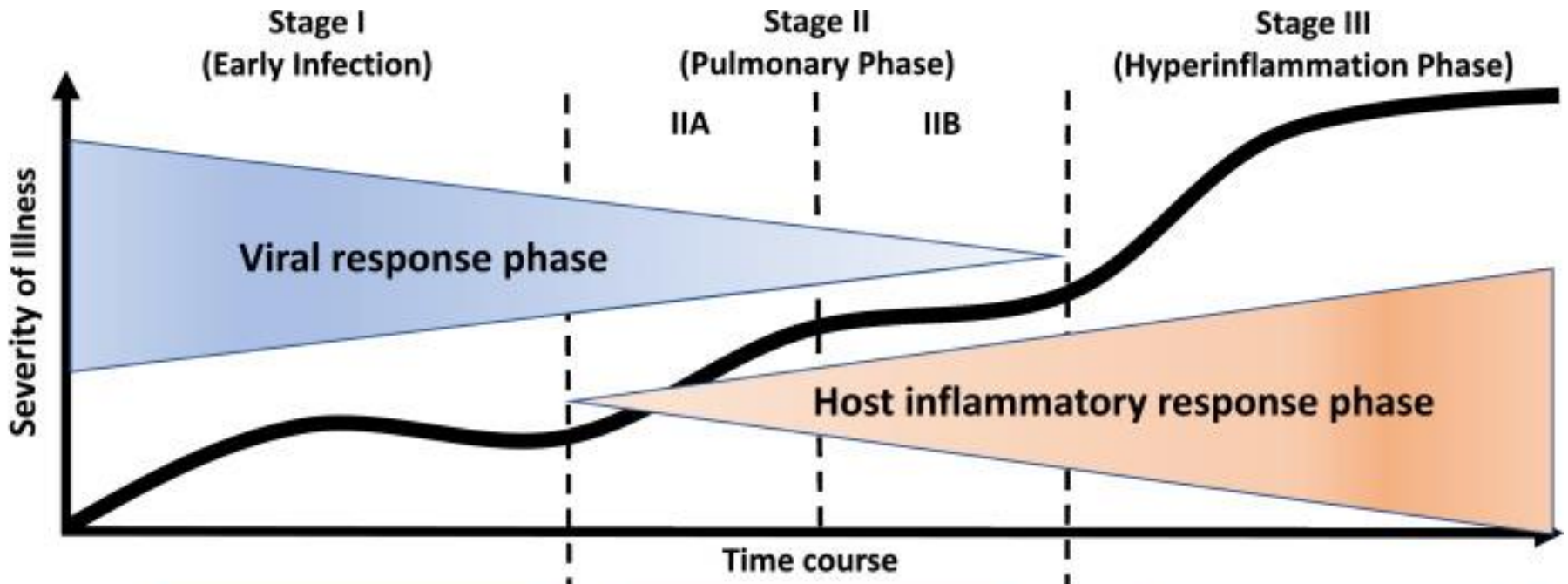
Updated 5 April 2022

Covid-19: Protective masks



https://theconversation.com/evidence-shows-that-yes-masks-prevent-covid-19-and-surgical-masks-are-the-way-to-go-167963

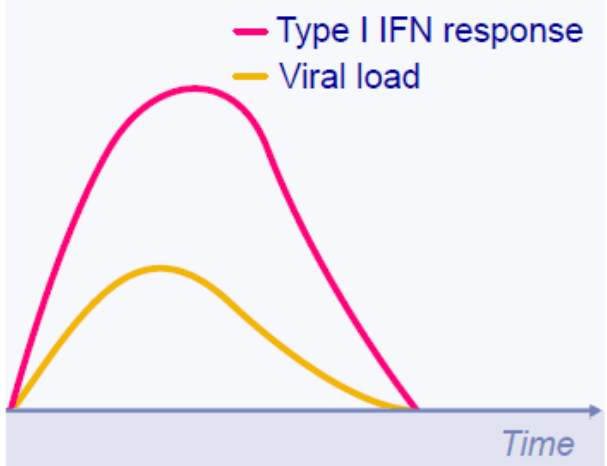
Covid-19: Clinical Symptoms



Clinical Symptoms	Mild constitutional symptoms Fever >99.6˚F Dry Cough	Shortness of Breath without (IIA) and with Hypoxia (IIB) (PaO2/FiO2≤300mmHg)	ARDS SIRS/Shock Cardiac Failure
Clinical Signs	Lymphopenia	Abnormal chest imaging Transaminitis Low-normal procalcitonin	Elevated inflammatory markers (CRP, LDH, IL-6, D-dimer, ferritin) Troponin, NT-proBNP elevation

Covid-19: IFN-I & Clinical Symptoms

Early robust type I IFN

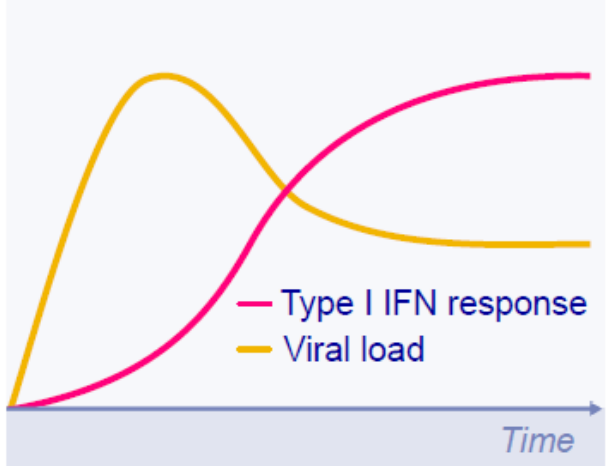


- Early type I IFN response
- Rapid viral clearance

Mild disease

Young
Low viral exposure

Delayed type I IFN

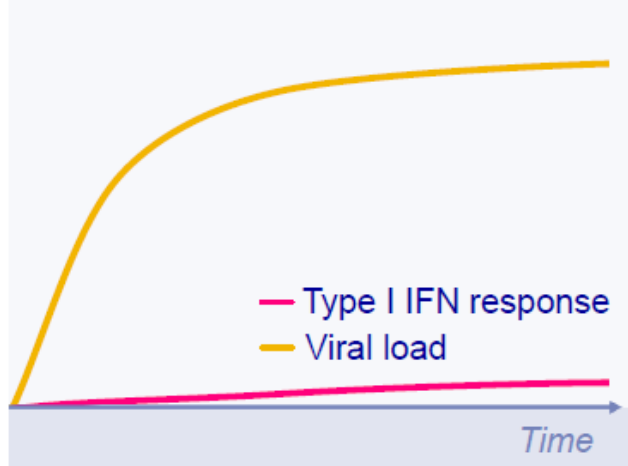


- Delayed type I IFN response
- Viral persistence, inflammation

Severe disease

Older adults
High viral exposure

Type I IFN deficiency

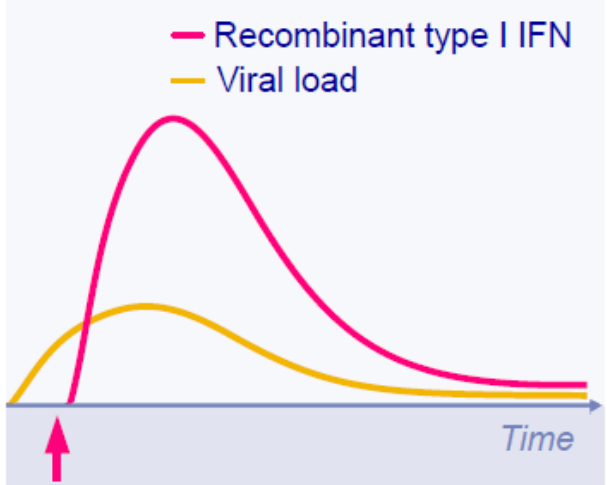


- Low or no type I IFN response
- No viral control, inflammation

Severe disease

Genetic mutations
in type I IFN pathways
Neutralizing Abs to type I IFNs

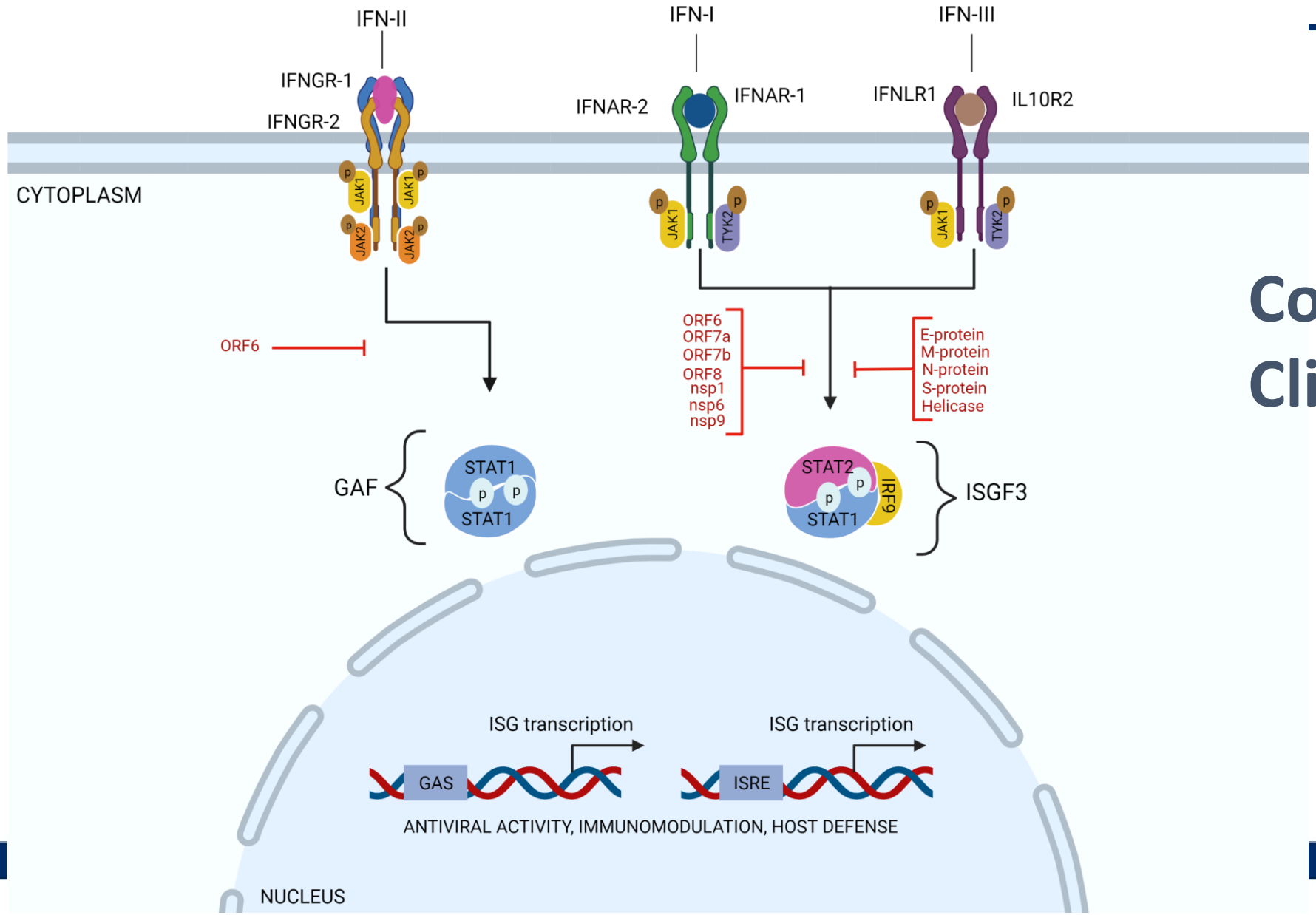
Type I IFN therapy



- Injection of recombinant type I IFN
- Viral clearance

Milder disease

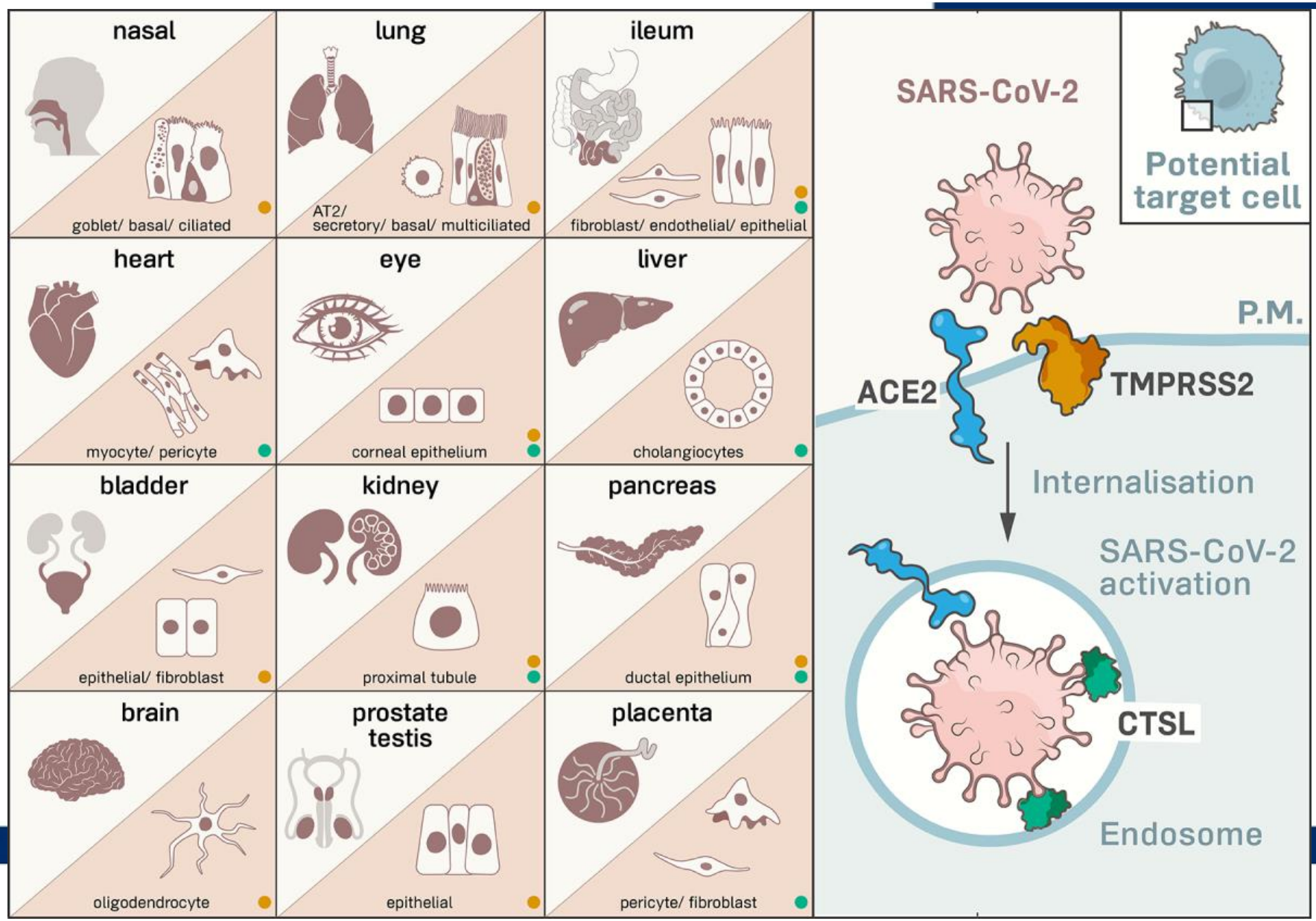
Early treatment
with recombinant type I IFN



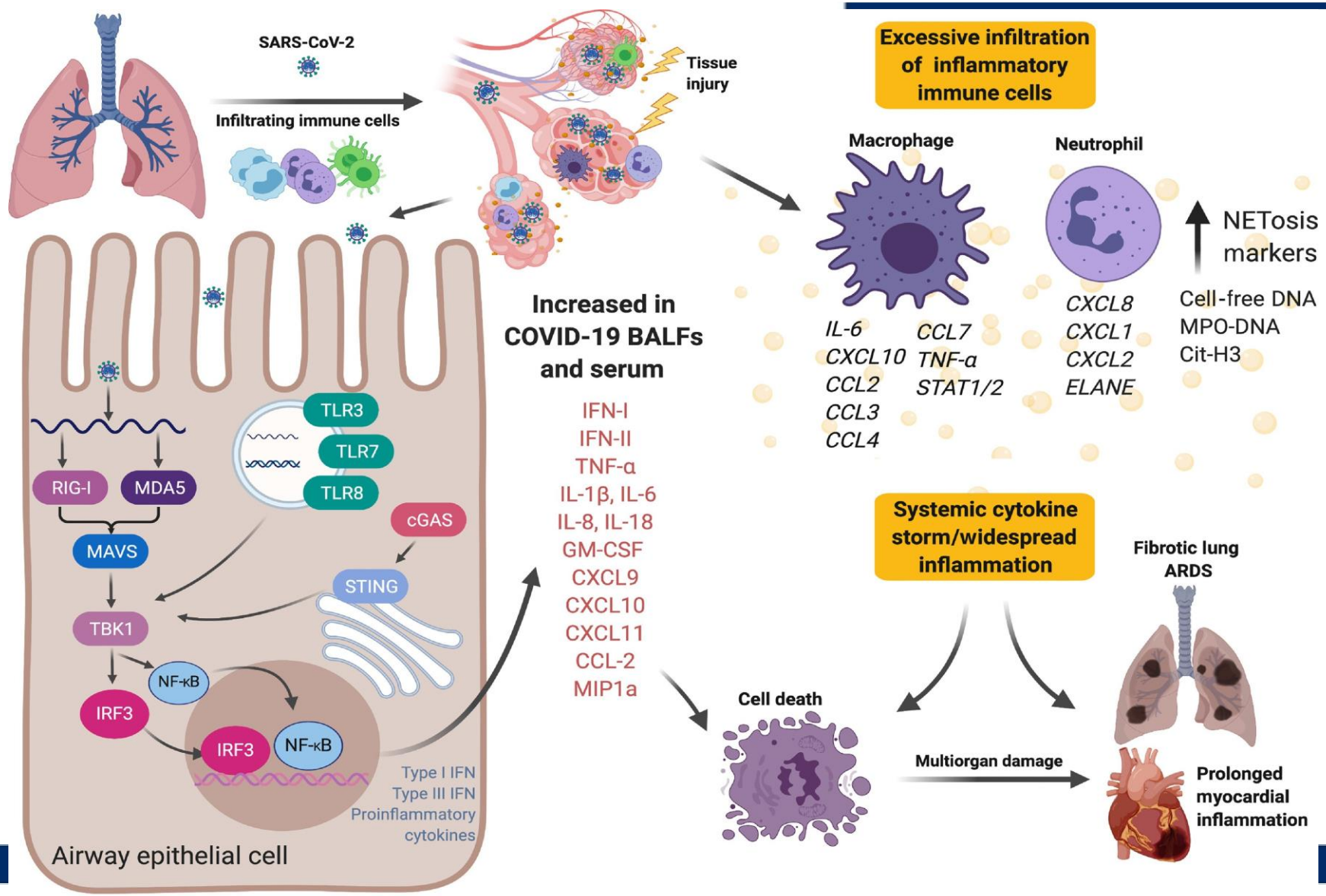
Covid-19: IFN-I & Clinical Symptoms

Mahdi Eskandarian Boroujeni, et al.
Frontiers in Immunology, 2022

SARS CoV-2: Potential target tissues

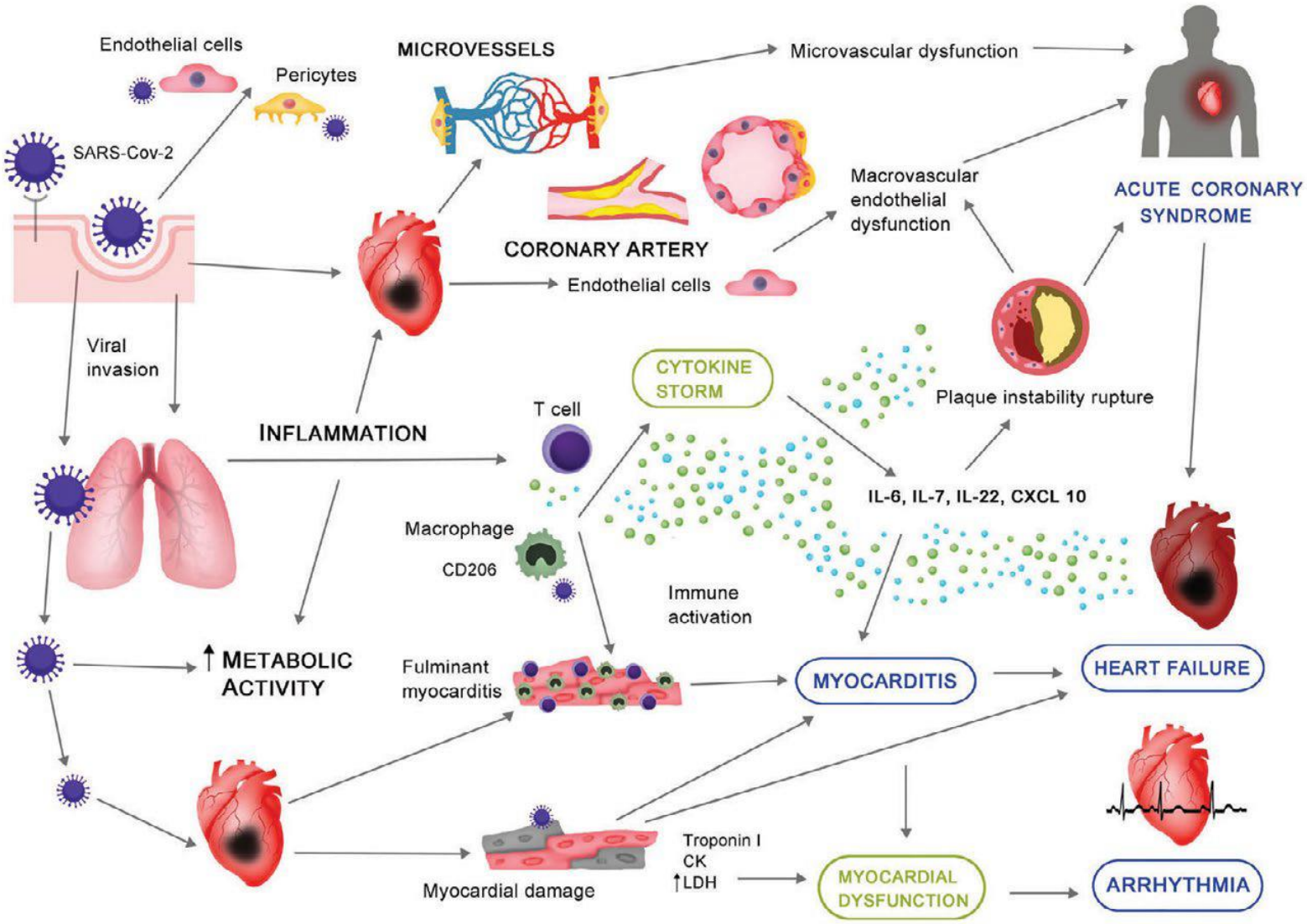


SARS CoV-2: Excessive Lung Inflammation

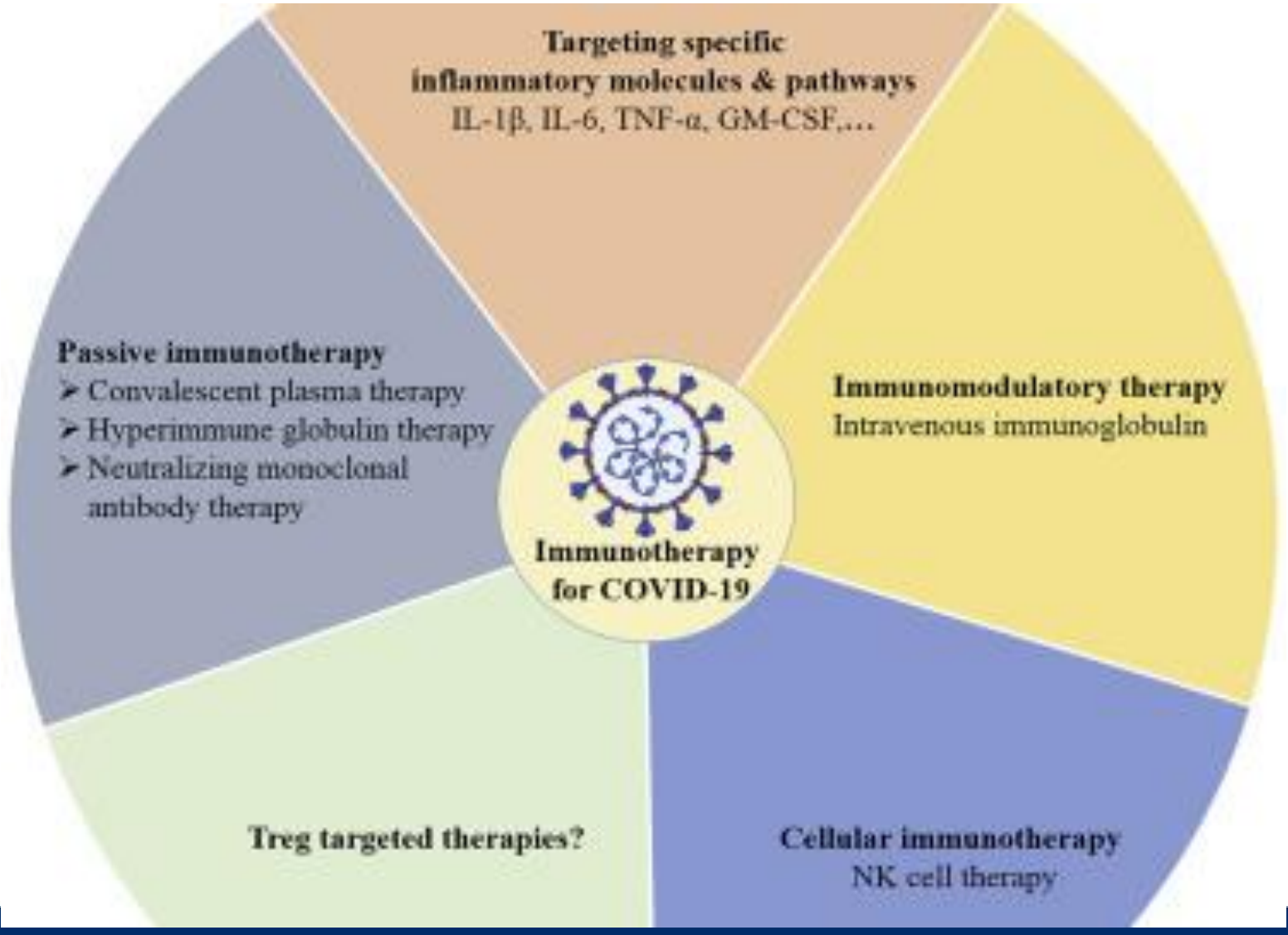


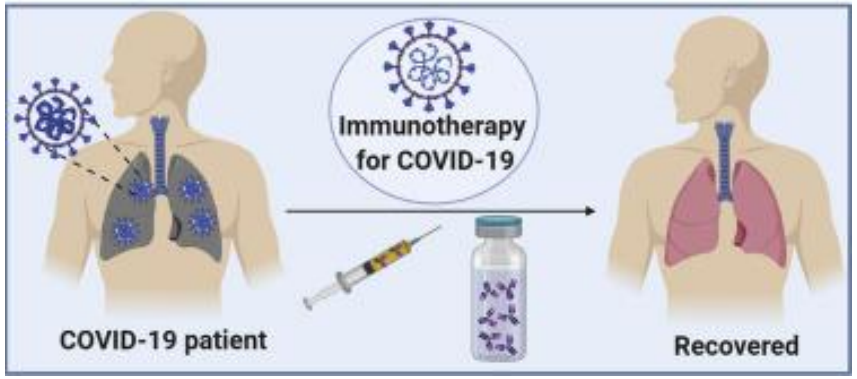
Trends in Immunology

SARS CoV-2: Cardiovascular Complications



Covid-19: Immune Therapy

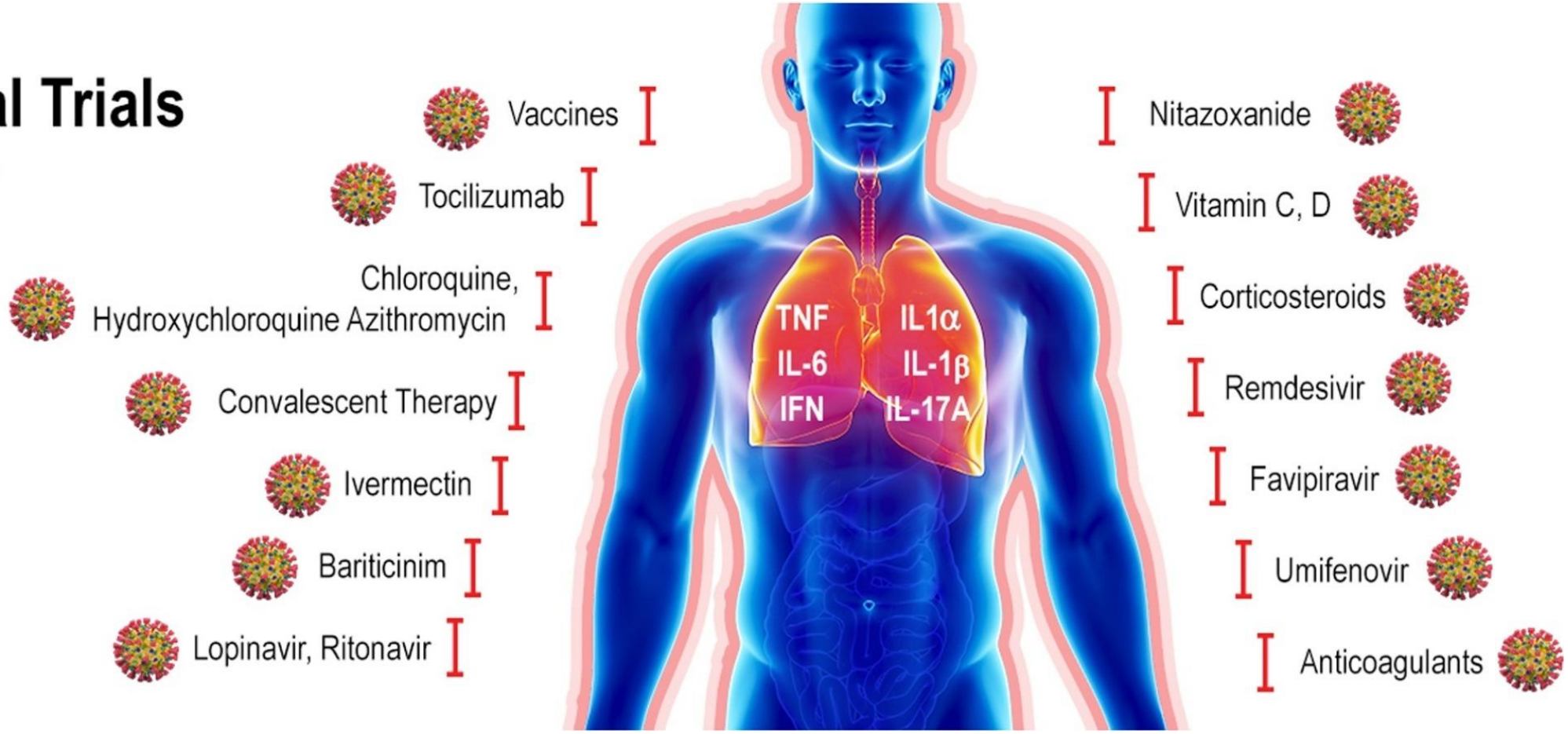




COVID-19: Treatment

Clinical Trials

COVID-19



COVID-19 Real-Time Learning Network

Brought to you by CDC and IDSA

Therapeutics Under Early Investigation

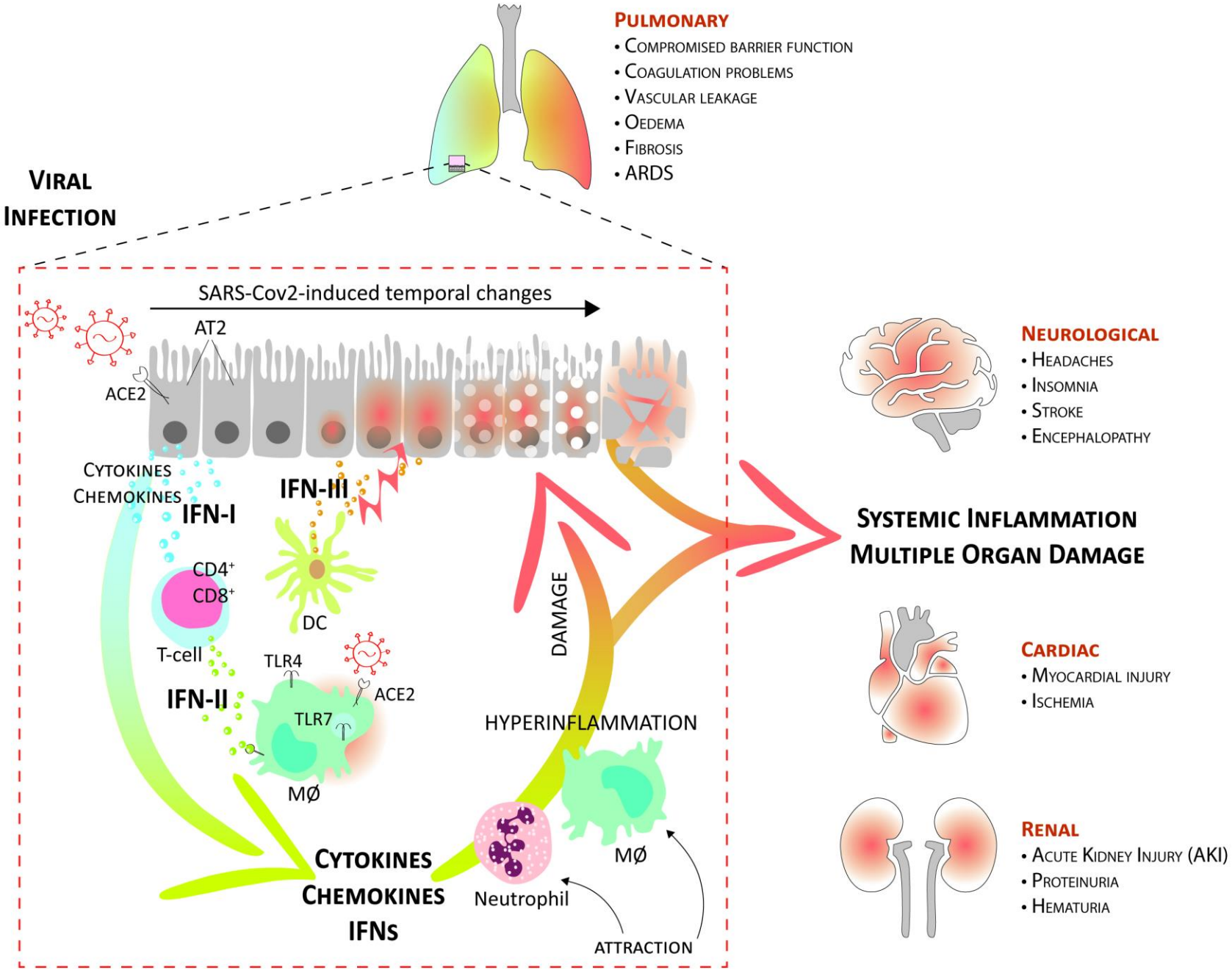
Last updated: February 24, 2021

There are many therapeutics under early investigation for treatment of COVID-19 for which there is currently insufficient clinical data to recommend either for or against. This overview is not a comprehensive summary, but a list of therapeutics with strong biological plausibility that are available in the United States and are or will be studied by clinical trial.

Class/Drug	Mechanism of Action	Notable Publications*
Anakinra	• Interleukin (IL)-1 receptor antagonist; blocks activity of the proinflammatory cytokines IL-1α and IL-1β.	Cavalli, June 2020 Huet, May 2020
Baricitinib	• Janus kinase (JAK) 1 and 2 inhibitor; inhibits JAK1-2 mediated cytokine release. • Disrupts endocytosis regulators and cyclin G-associated kinase; may reduce inflammation and interfere with intracellular virus assembly.	Cantini, April 2020
Colchicine	• Exhibits broad anti-inflammatory and immunomodulatory properties. • Disrupts microtubule formation and reduces chemotaxis, phagocytosis and migration of neutrophils.	Tardif, January 2021 Della-Torre, August 2020 Lopes, August 2020 Gendelman, July 2020 Deftereos, June 2020
Interferons	• Modulate the immune response in specific—not all—viral infections. • Bind to interferon-α and -β receptors on the cell membrane, resulting in various transcription factor phosphorylation. Subsequent activation of interferon-stimulated genes leads to immunomodulatory effects and interference with viral replication.	Monk, November 2020 Wang, July 2020 Davoudi-Monfared, May 2020 Zhou, May 2020 Hung, May 2020
Intravenous immunoglobulin	• Derived from pooled plasma; contains antibodies typically present in adult human blood. • May provide passive immune protection from viral infections via modulation of inflammation.	Sakoulas, November 2020 Gharebaghi, October 2020 Xie, August 2020 Sakoulas, July 2020 Shao, April 2020
Ruxolitinib	• Janus kinase (JAK) 1 and 2 inhibitor; inhibits JAK1-2 mediated cytokine release. • Disrupts endocytosis regulators and cyclin G-associated kinase; may reduce inflammation and interfere with intracellular virus assembly.	
Statins	• Statins have anti-inflammatory and immunomodulatory properties that may allow for lung protection in the setting of infection.	Zhang, August 2020 Kow, August 2020 De Spiegeleer, July 2020
Calcifediol/Vitamin D	• Prohormone of the active form of vitamin D3, calcitriol (1,25-dihydroxyvitamin D3).	Murai, February 2021 Patchen, February 2021 Castillo, October 2020

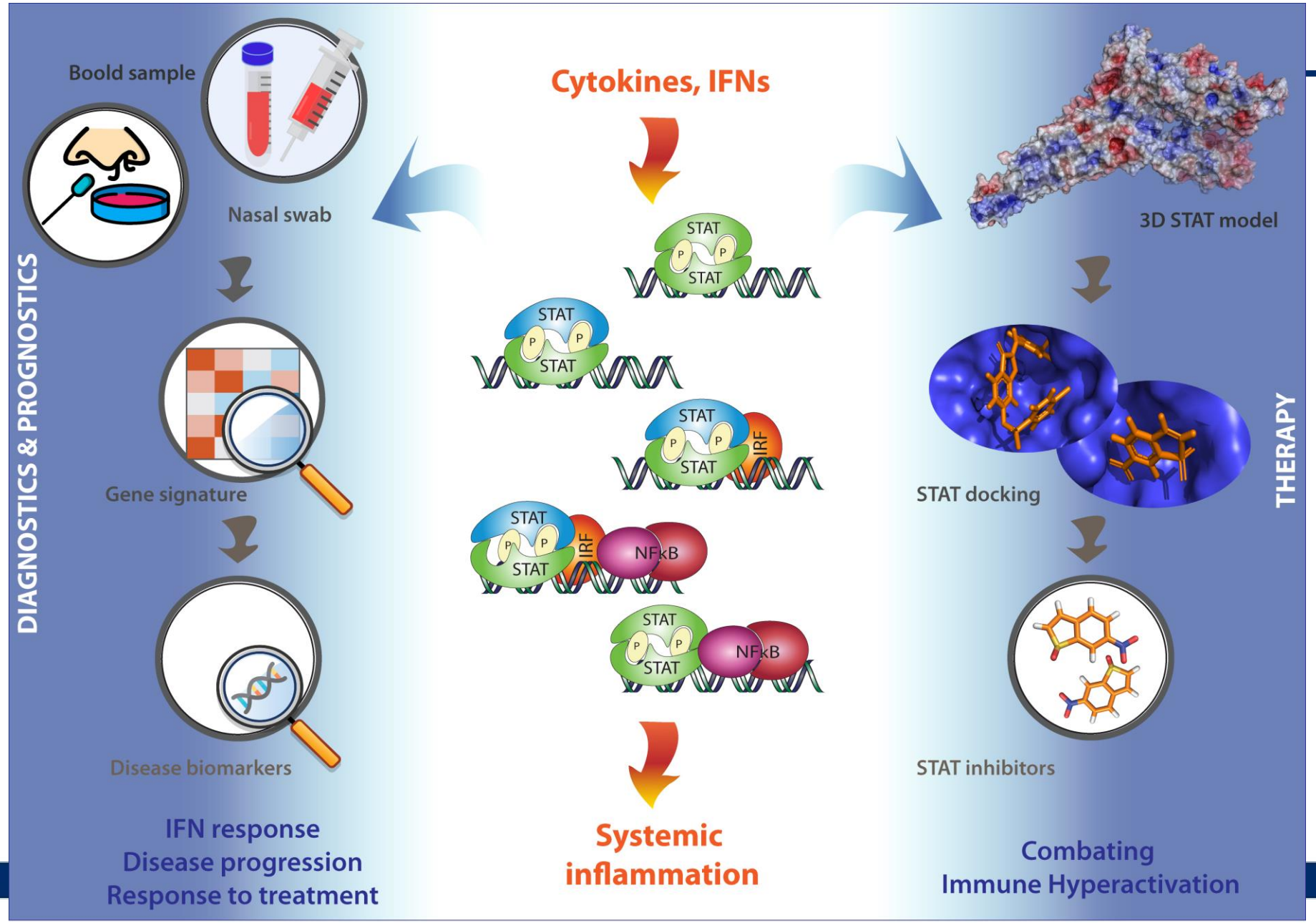
COVID-19: Treatment

COVID-19: Treatment



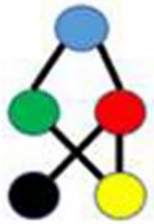
Mahdi Eskandarian Boroujeni, et al.
Frontiers in Immunology, 2022

COVID-19: Treatment



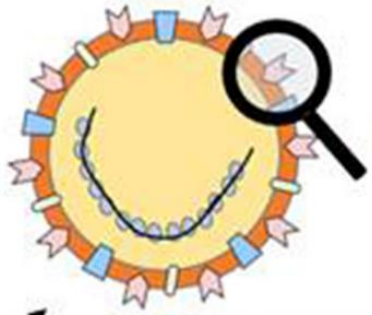
Mahdi Eskandarian Boroujeni, et al. Frontiers in Immunology, 2022

Drug Discovery



Literature analysis and AI/ML-driven platforms

(Machine learning)

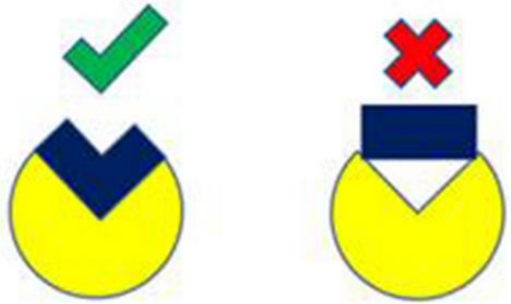


Epitope Identification for peptide inhibitors

Drug Discovery for SARS-CoV-2

Repurposed for SARS-CoV-2

Drug/inhibitors against MERS CoV/SARS-CoV



Molecular Docking

Translational Model Systems

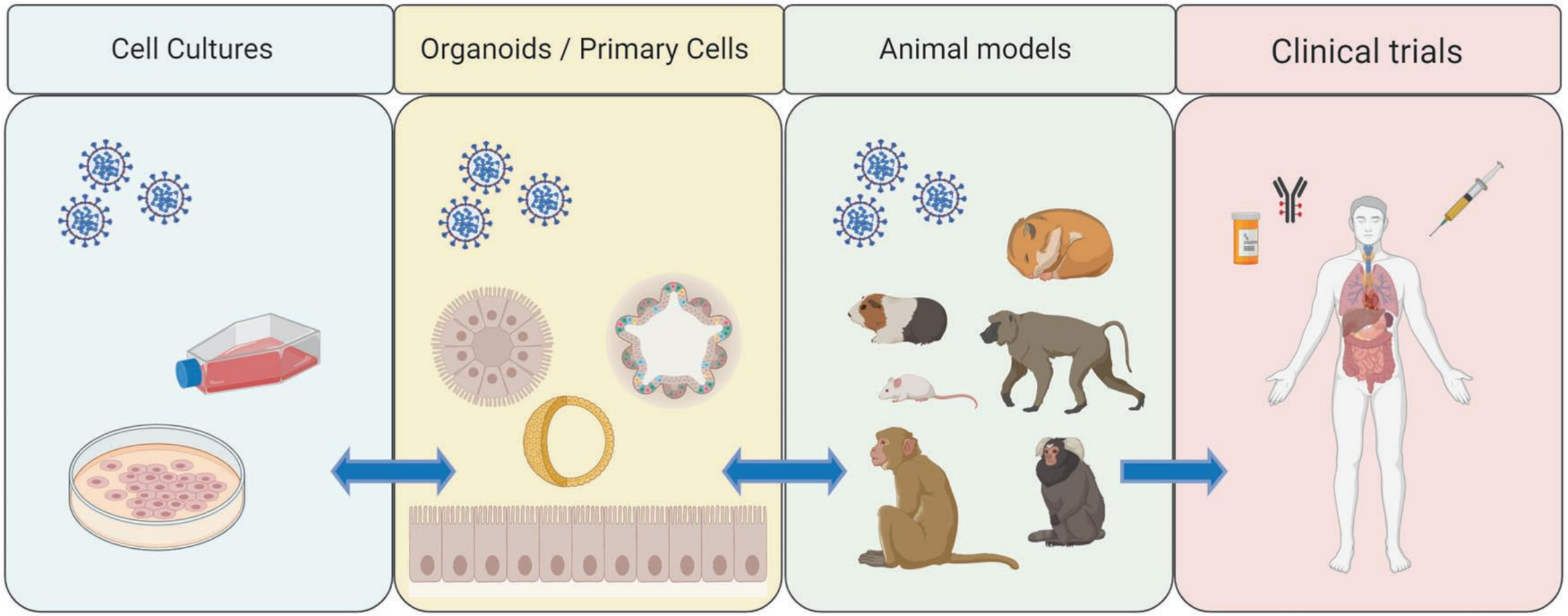


Fig. 4 Overview of the different translational model systems used to interrogate disease mechanisms of SARS-CoV-2.

Cell lines & Organoids

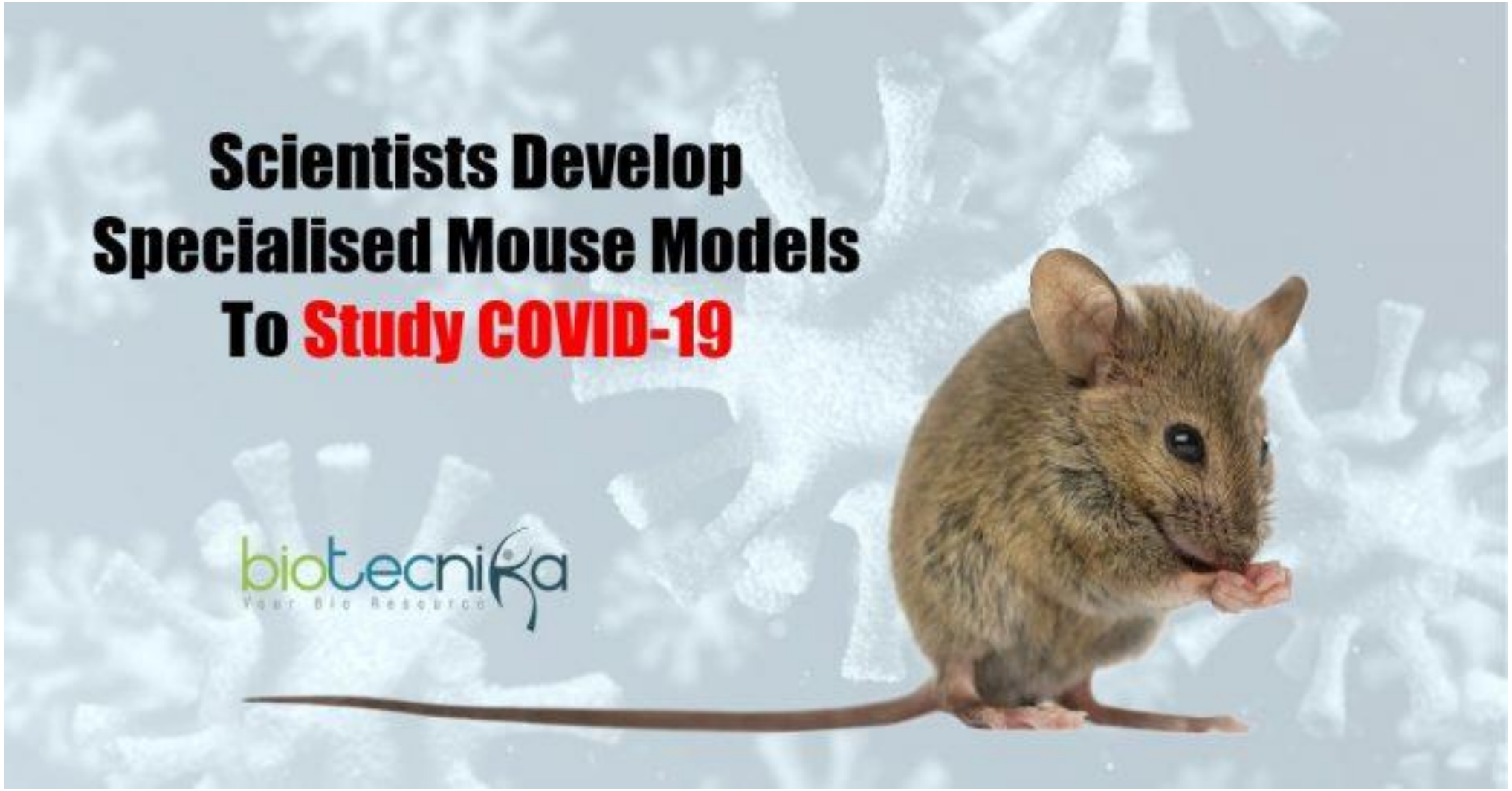
Table 1. Cell Lines and Organoids and Animal Models Currently Being Used in COVID-19 Research

Cell lines and organoids				
Type		Origin	Key points	Refs
Human airway epithelial cells		Commercially available from various vendors (Lonza, PromoCell, etc.)	Human airway epithelial cells can isolate SARS-CoV-2 and mimic infected human lung cells. After SARS-CoV-2 infection, cytopathic effects were observed.	[5]
Vero E6 cells	Wild type cells	Isolated from kidney epithelial cells of an African green monkey	Vero E6 cells are the most widely used clone used to replicate and isolate the SARS-CoV-2.	[11]
	TMPRSS2-overexpressing cells		Viral RNA copies in the culture supernatants of these cells were >100 times higher than those of wild type Vero E6 cells.	[12]
Caco-2 cells		Isolated from human colon adenocarcinoma	SARS-CoV-2 could replicate in Caco-2 cells (data not shown).	[6]
Calu-3 cells		Isolated from non-small cell lung cancer	Compared with mock control, SARS-CoV-2 S pseudovirions showed an over 500-fold increase in luciferase activities in Calu3 cells.	[7]
HEK293T cells		Isolated from human embryonic kidney (HEK) cells grown in tissue culture	Cells showed only modest viral replication.	[8]
Huh7 cells		Isolated from hepatocyte-derived cellular carcinoma cells	Cells showed about a tenfold increase in luciferase activity when transduced by SARS-CoV-2 S pseudovirions.	[7]
Human bronchial organoids		Generated from commercially available human bronchial epithelial cells	After SARS-CoV-2 infection, not only the intracellular viral genome, but also progeny virus, cytotoxicity, pyknotic cells, and moderate increases of the type I interferon signal can be observed.	[17]
Human lung organoids		Generated from human embryonic stem cells	The lung organoids, particularly alveolar type II cells, are permissive to SARS-CoV-2 infection.	[18]
Human kidney organoids		Generated from human embryonic stem cells	Human kidney organoids produce infectious progeny virus.	[19]
Human liver ductal organoids		Generated from primary bile ducts isolated from human liver biopsies	Human liver ductal organoids are permissive to SARS-CoV-2 infection, and SARS-CoV-2 infection impairs the bile acid transporting functions of cholangiocytes.	[20]
Human intestinal organoids		Generated from primary gut epithelial stem cells	Human intestinal organoids were readily infected by SARS-CoV-2, as demonstrated by confocal and electron microscopy. Significant titers of infectious viral particles were detected.	[22,23]
Human blood vessel organoids		Generated from human induced pluripotent stem cells	SARS-CoV-2 can directly infect human blood vessel organoids.	[19]

Animal Models

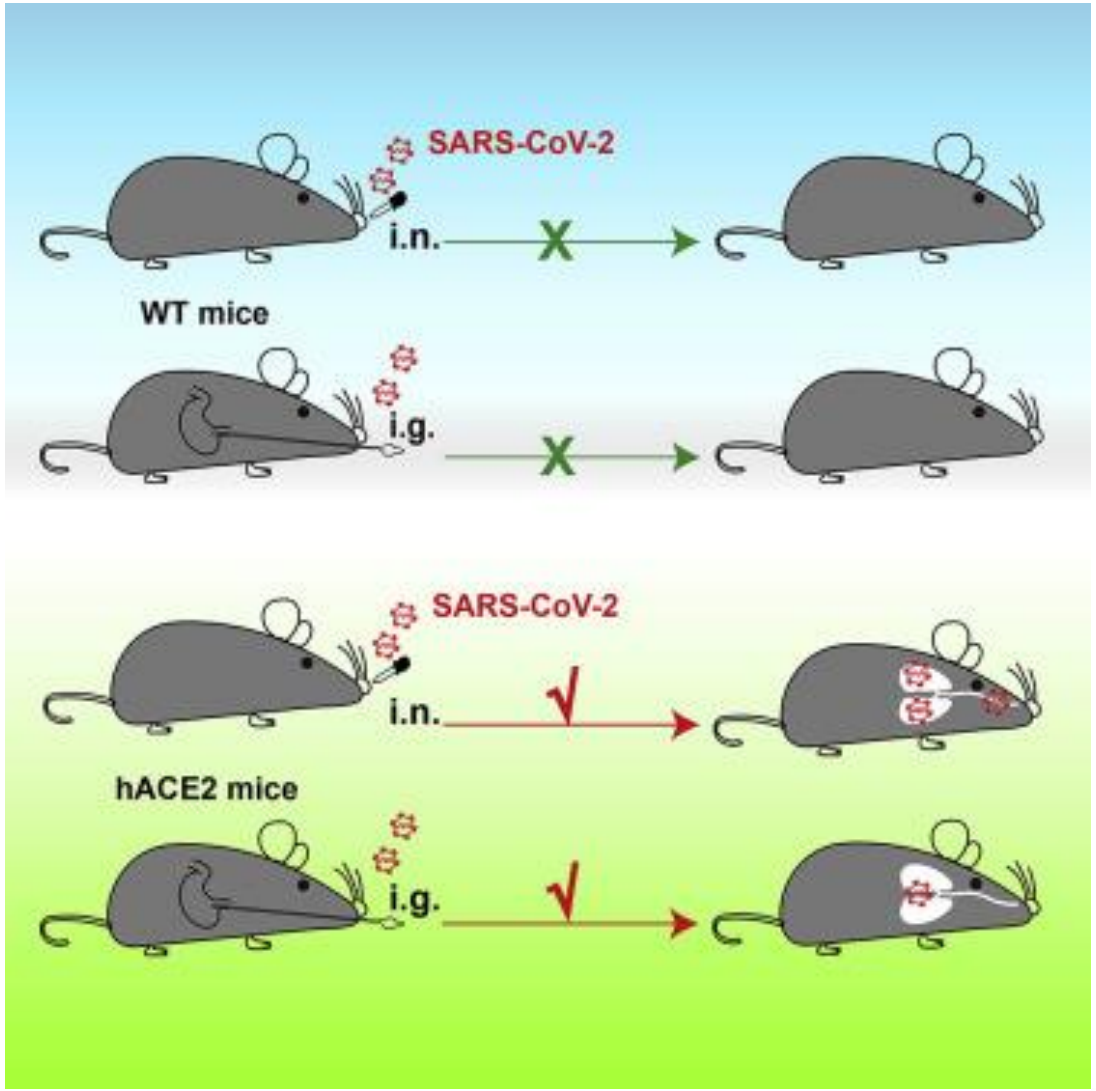
Animal models			
Animal species		Key points	Refs
Mice	Wild type mice	SARS-CoV-2 cannot invade cells through mouse Ace2.	[11]
	Human ACE2 transgenic mice	After SARS-CoV-2 infection, the mice show weight loss, virus replication in the lungs, and interstitial pneumonia.	[25]
Syrian hamster		After SARS-CoV-2 infection, the hamsters show rapid breathing, weight loss, and diffuse alveolar damage with extensive apoptosis.	[26]
Ferrets		After SARS-CoV-2 infection, acute bronchiolitis was observed in the lungs.	[27]
Cats		After SARS-CoV-2 infection, intra-alveolar edema and congestion in the interalveolar septa were observed. Abnormal arrangement of the epithelium with loss of cilia and lymphocytic infiltration into the lamina propria were also observed.	[28]
Cynomolgus macaques		SARS-CoV-2 can infect both type I and type II pneumocytes. After SARS-CoV-2 infection, pulmonary consolidation, pneumonia, and edema fluid in alveolar lumina were observed.	[29]
Rhesus macaques		Infected macaques had high viral loads in the upper and lower respiratory tract, humoral and cellular immune responses, and pathologic evidence of viral pneumonia. The therapeutic effects of adenovirus-vectored vaccine, DNA vaccine candidates expressing S protein, and remdesivir treatment could be evaluated.	[30–33]

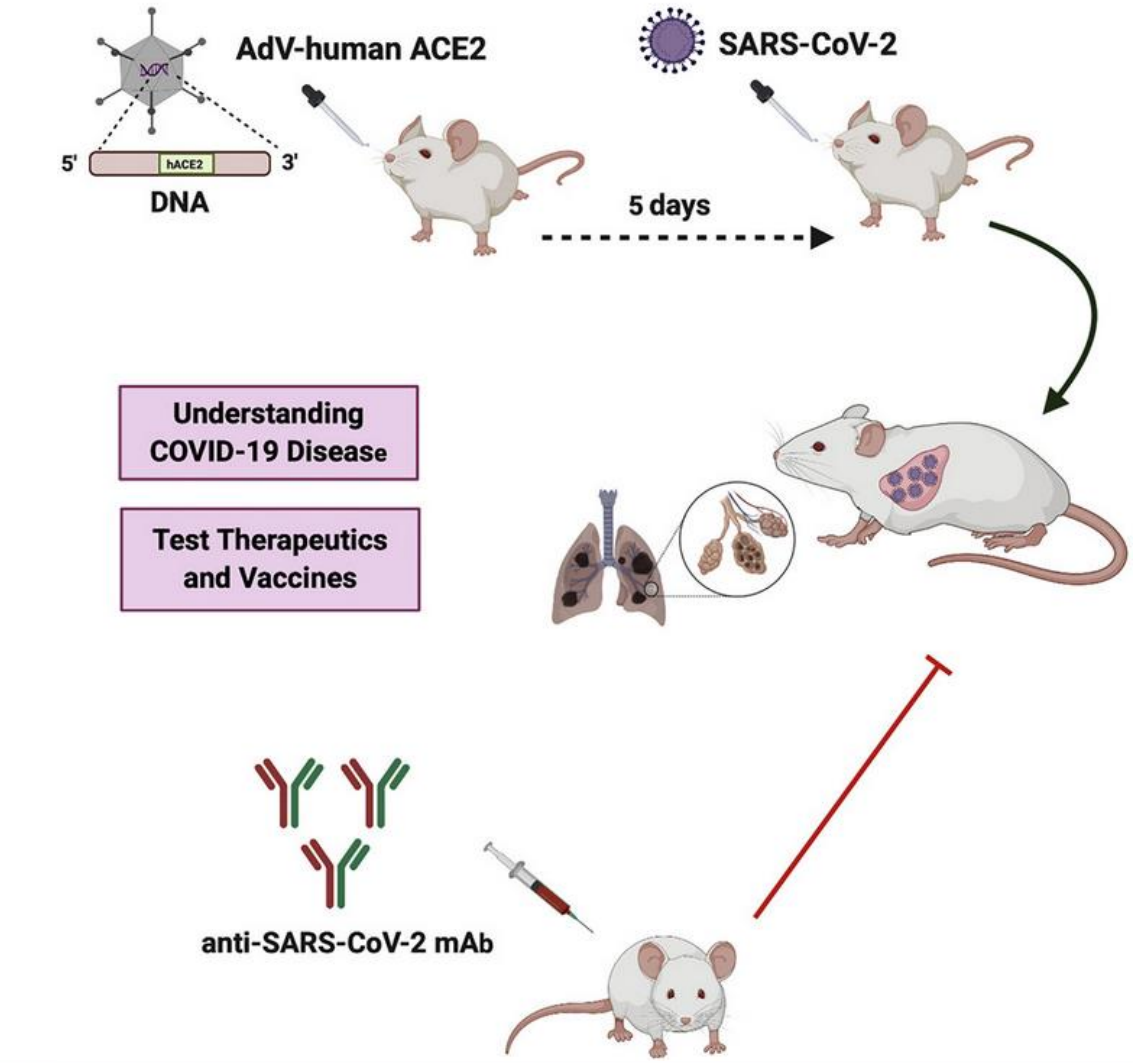
COVID-19: Mouse Models



hACE2 Expressing Mouse

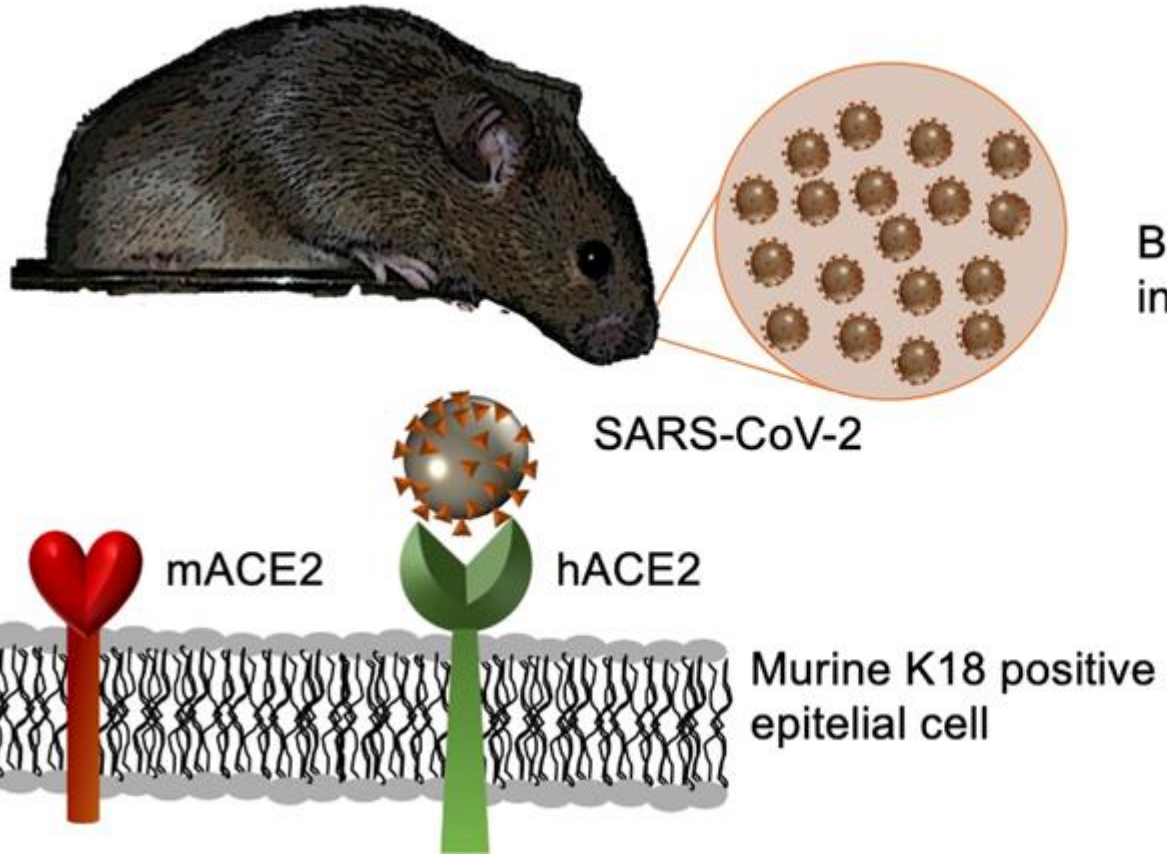
Intra Nasal vs Intra Gastric

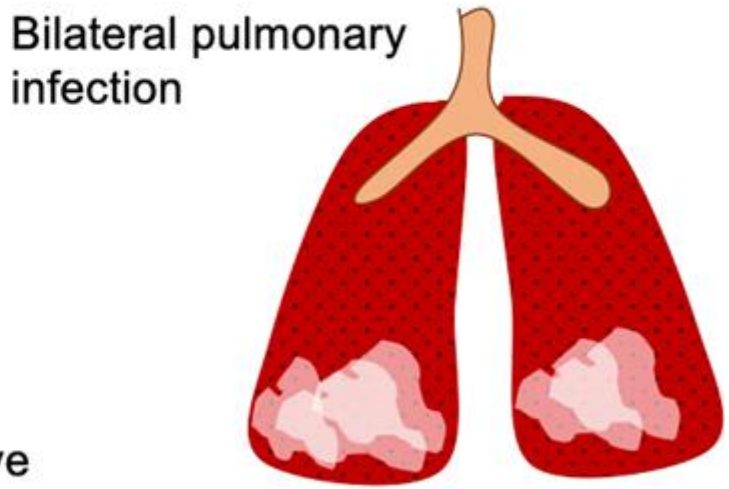




SARS-CoV-2 infection in K18-ACE2 transgenic mice replicates human pulmonary disease in COVID-19

hACE2 Transgenic Mouse





Overexpression of ACE2 in the lung epithelium facilitates SARS-CoV-2 infection in mice

hACE2 Transgenic Mouse Lines

Differences between hACE2 transgenic mouse lines

Corresponding Author(s)	Transgene	Expressions Pattern	Tg Lines	Susceptibility to SARS-CoV					
				Morbidity	Mortality (%)	Mean Survival (days post-infection)	Site of Viral Replication	Lung Pathology	Brain Pathology
Paul B. McCray, Jr. and Stanley Perlman University of Iowa, IA	Human ACE2 CDS driven by Keratin 18 (K18) promoter	Epithelial-specific expression in airways (excluding alveolar), liver, kidney, GI tract. Also expression in the brain, heart	Line 1	++	100	3-5	Lung and brain	++	+++
			Line 2	++	100	3-5	Lung and brain	++	+++
			Line 3	+	100	5-7	Lung and brain	++	+++
Chien-Te K. Tseng University of Texas Medical Branch, TX	Human ACE2 CDS driven by CAG promoter	Ubiquitous	AC70	+	100	6.2	Lung and brain	++	***
			AC50	+	100	6.9	n.r.	n.r.	n.r.
			AC12	+	100	4.5	n.r.	n.r.	n.r.
			AC22	+	0	n/a	Lung>>brain	+++	+
			AC63*	+	0	n/a	Lung only	+++	-
Hong-kui Deng and Chuan Qin Peking Union Medical College and Peking University, China	Human ACE2 CDS driven by mouse Ace2 promoter	Lung, kidney, intestine	Single line	+	0	n/a	Lung and brain	++	++

n.r. not reported. *poor breeding performance

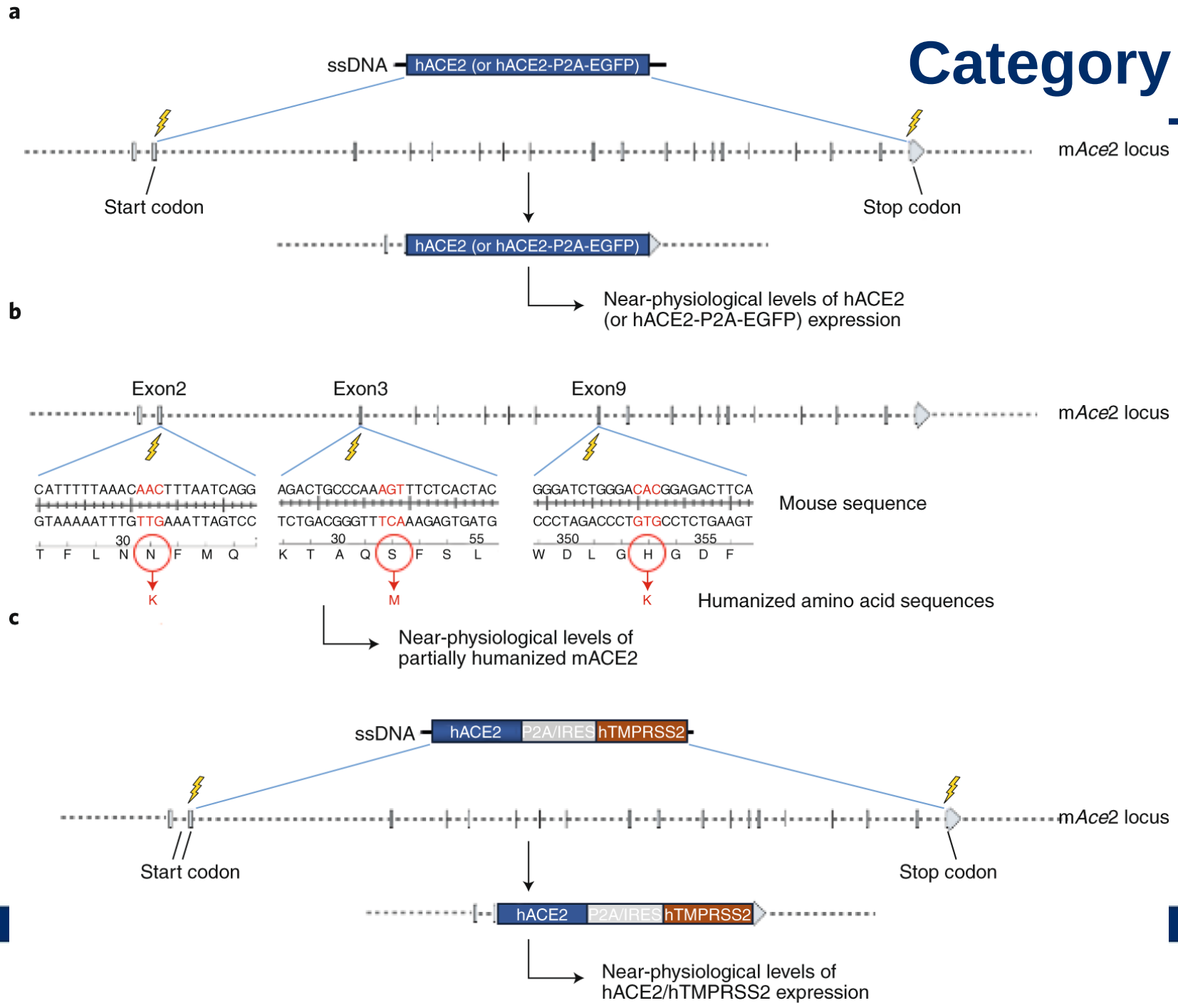
Table 1 | GEMM designs suitable for COVID-19 and SARS-CoV-2 research

Model no.	Name	Locus/promoter	Gene to express	Expression	Additional features
Category 1: knocking-in expression cassettes or point mutations into the endogenous mouse *Ace2* locus					
1	B6.mAce2^{KO}-hACE2^{KI}	mAce2/ mAce2	hACE2	Constitutive	mAce2 gene is inactivated.
2	B6.mAce2^{KO}-hACE2-P2A-EGFP^{KI}	mAce2/ mAce2	hACE2-P2A-EGFP	Constitutive	mAce2 gene is inactivated; includes a reporter
3	N5G.mAce2^{KO}-hACE2^{KI}	mAce2/ mAce2	hACE2	Constitutive	mAce2 gene is inactivated; immunocompromised mouse strain background, useful for studies involving interaction of human immune system
4	N5G.mAce2^{KO}-hACE2-P2A-EGFP^{KI}	mAce2/ mAce2	hACE2-P2A-EGFP	Constitutive	mAce2 gene is inactivated; includes a reporter; immunocompromised mouse strain background, useful for studies involving interaction of human immune system
5	BALB/c.mAce2^{KO}-hACE2^{KI}	mAce2/ mAce2	hACE2	Constitutive	mAce2 gene is inactivated; mouse strain background commonly used for SARS and MERS virus research
6	BALB/c.mAce2^{KO}-hACE2-P2A-EGFP^{KI}	mAce2/ mAce2	hACE2-P2A-EGFP	Constitutive	mAce2 gene is inactivated; includes a reporter; mouse strain background commonly used for SARS and MERS virus research
7	B6.mAce2$^{KI-S19K,82V,353K}$	mAce2/ mAce2	Partially humanized mAce2	Constitutive	Enables mACE2 to bind to the SARS-CoV-2 spike protein
8	N5G.mAce2$^{KI-S19K,82V,353K}$	mAce2/ mAce2	Partially humanized mAce2	Constitutive	Enables mACE2 to bind to the SARS-CoV-2 spike protein; immunocompromised mouse strain background, useful for studies involving interaction of human immune system
9	BALB/c.mAce2$^{KI-S19K,82V,353K}$	mAce2/ mAce2	Partially humanized mAce2	Constitutive	Enables mACE2 to bind to the SARS-CoV-2 spike protein; mouse strain background commonly used for SARS and MERS virus research
10	B6.mAce2^{KO}-hACE2-P2A-hTMPRSS2^{KI}	mAce2/ mAce2	hACE2, hTMPRSS2	Constitutive	mAce2 gene is inactivated; hTMPRSS2 fused to hACE2 via a self-cleavable P2A peptide
11	N5G.mAce2^{KO}-hACE2-P2A-hTMPRSS2^{KI}	mAce2/ mAce2	hACE2, hTMPRSS2	Constitutive	mAce2 gene is inactivated; immunocompromised mouse strain background, useful for studies involving interaction of human immune system; hTMPRSS2 fused to hACE2 via a self-cleavable P2A peptide
12	BALB/c.mAce2^{KO}-hACE2-P2A-hTMPRSS2^{KI}	mAce2/ mAce2	hACE2, hTMPRSS2	Constitutive	mAce2 gene is inactivated; mouse strain background commonly used for SARS and MERS virus research; hTMPRSS2 fused to hACE2 via a self-cleavable P2A peptide
13	B6.mAce2^{KO}-hACE2-IRES-hTMPRSS2^{KI}	mAce2/ mAce2	hACE2, hTMPRSS2	Constitutive	mAce2 gene is inactivated; hTMPRSS2 expressed as a separate polypeptide via an IRES
14	N5G.mAce2^{KO}-hACE2-IRES-hTMPRSS2^{KI}	mAce2/ mAce2	hACE2, hTMPRSS2	Constitutive	mAce2 gene is inactivated; immunocompromised mouse strain background, useful for studies involving interaction of human immune system; hTMPRSS2 expressed as a separate polypeptide via an IRES
15	BALB/c.mAce2^{KO}-hACE2-IRES-hTMPRSS2^{KI}	mAce2/ mAce2	hACE2, hTMPRSS2	Constitutive	mAce2 gene is inactivated; mouse strain background commonly used for SARS and MERS virus research; hTMPRSS2 expressed as a separate polypeptide via an IRES
Category 2: knocking-in CRE-activatable or tetracycline-inducible expression cassettes into safe-harbor loci by re-engineering existing reporter or inducer mouse lines					
16	ROSA26$^{(ACTB-Lox-hACE2-P2A-tdT-Lox-EGFP)}$	ROSA26/ pCAG	hACE2	Constitutive	Constitutive expression of hACE2 with reporter capability
17	ROSA26$^{(ACTB-Lox-hACE2-IRES-tdT-Lox-EGFP)}$	ROSA26/ pCAG	hACE2	Constitutive	Constitutive expression of hACE2 with reporter capability
18	ROSA26$^{(ACTB-Lox-tdT-Lox-hACE2-P2A-EGFP)}$	ROSA26/ pCAG	hACE2	Tissue specific	CRE-activatable expression of hACE2 with reporter capability
19	ROSA26$^{(ACTB-Lox-tdT-Lox-hACE2-IRES-EGFP)}$	ROSA26/ pCAG	hACE2	Tissue specific	CRE-activatable expression of hACE2 with reporter capability
20	A/63-TIGRE-TRE-hACE2-P2A-tdT	TIGRE/ TRE	hACE2	Tetracycln inducible	Tetracycline-inducible expression of hACE2 with reporter capability
21	A/63-TIGRE-TRE-hACE2-IRES-tdT	TIGRE/ TRE	hACE2	Tetracycln inducible	Tetracycline-inducible expression of hACE2 with reporter capability
Category 3: knocking-in CRE-activatable cassettes into the mouse *Ace2* locus					
22	B6.mAce2^{tKO}-hACE2^{tKI}	mAce2/ mAce2	hACE2	Tissue-specific expression of hACE2 at physiological levels	The mAce2 gene is conditionally inactivated, allowing expression of hACE2.
23	N5G.mAce2^{tKO}-hACE2^{tKI}	mAce2/ mAce2	hACE2	Tissue-specific expression of hACE2 at physiological levels	The mAce2 gene is conditionally inactivated, allowing expression of hACE2; immunocompromised mouse strain background, useful for studies involving interaction of human immune system

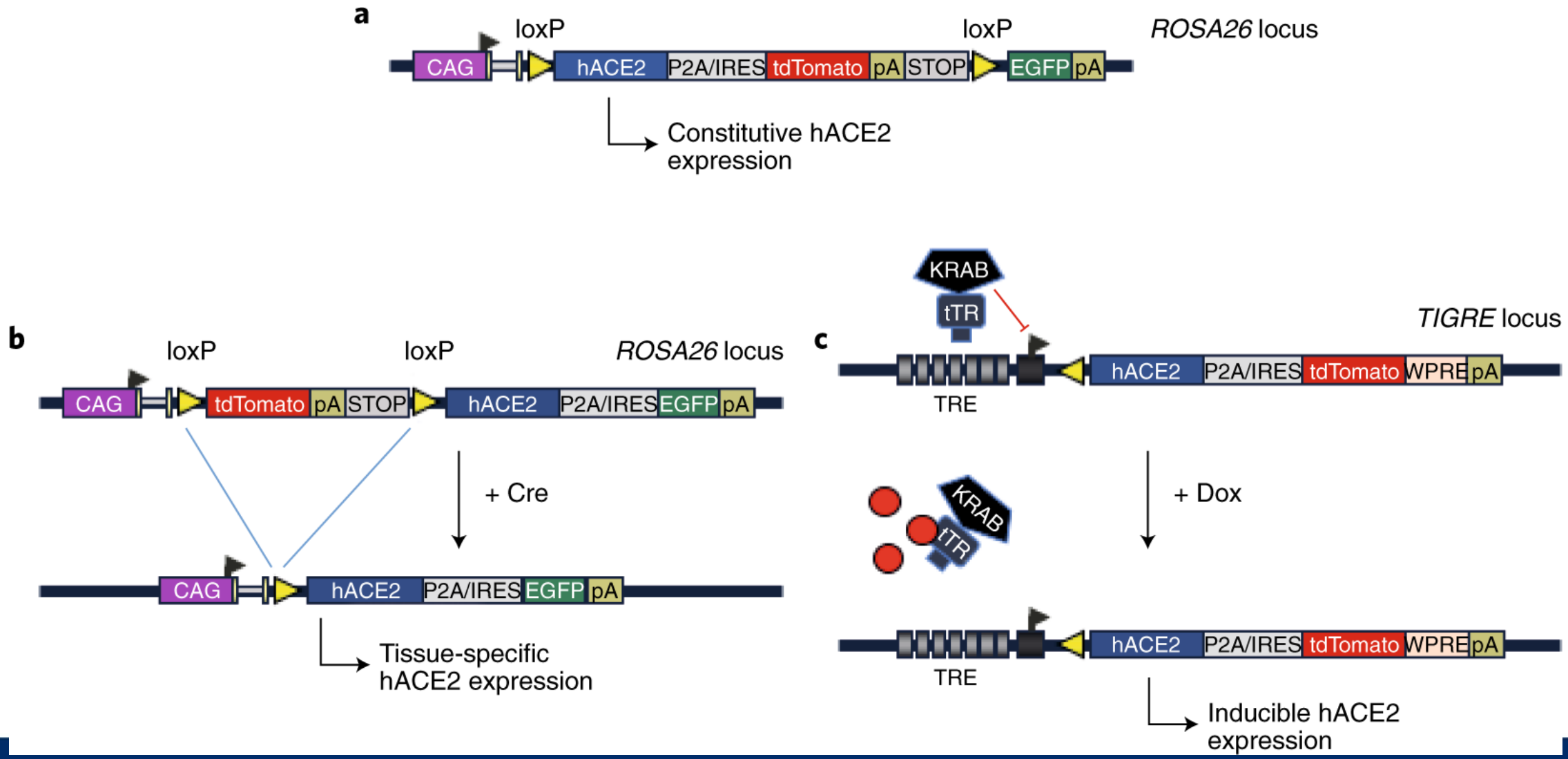
Table continued

hACE2 Transgenic Mouse Lines

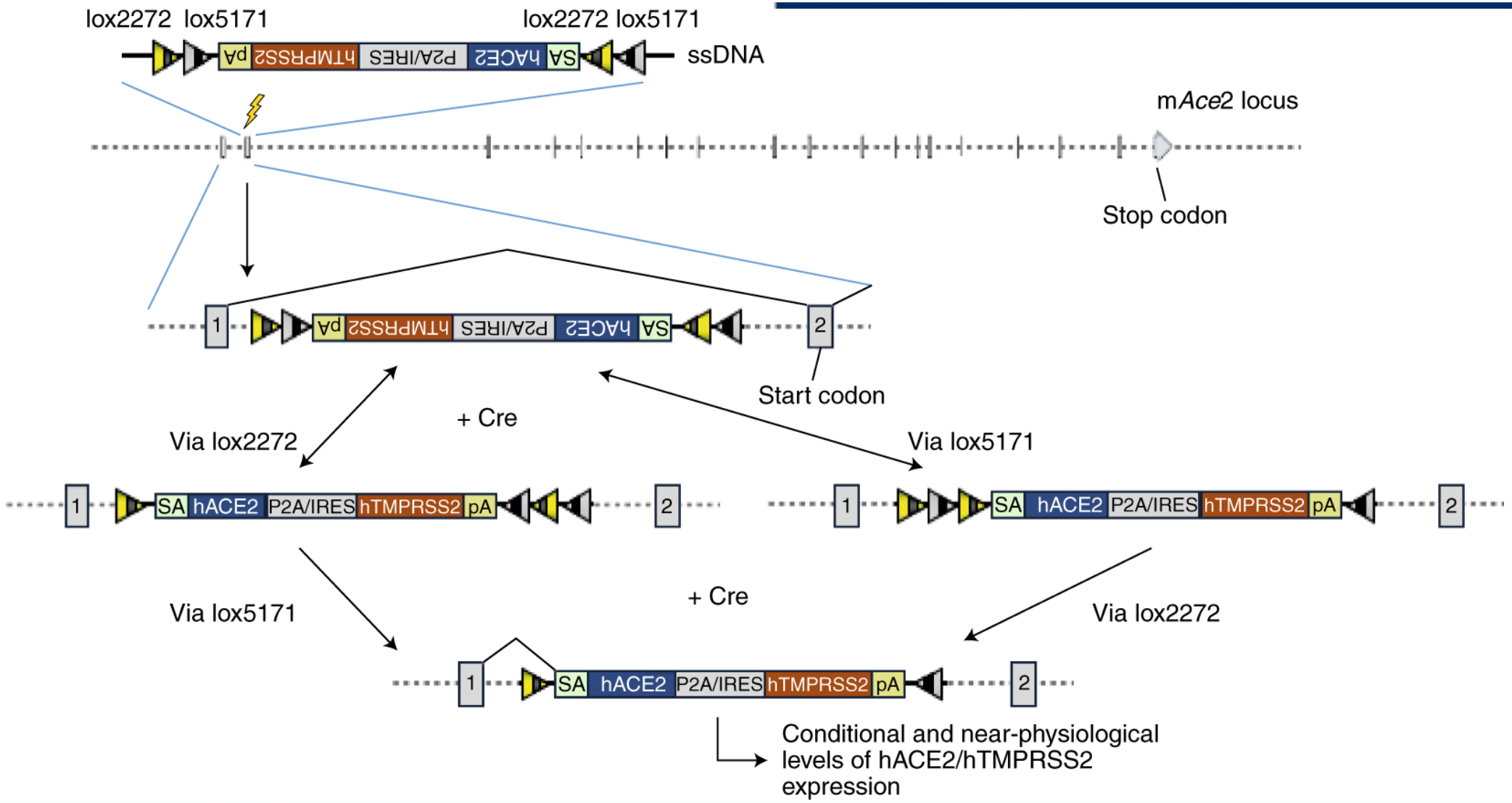
Category 1 Design: Knock-In



Category 2 Design: Cre-Lox



Category 3 Design



Survival after Infection

	K18-hACE2 [66, 67]	AC70, AC22, and AC63 [59, 68]	HFH4-ACE2 [69]	Mouse ACE2 promoter-driven hACE2 Tg mice [70]
Promoter	Human K18 promoter	CAG promoter	Human HFH4 promoter	Mouse ACE2 promoter
Parental mice of zygotes	(C57BL/6J × SJL/J) F2	(C57BL/6J × C3H/HeJ) F1	(C3H × C57BL/6) F1	ICR
Viral strains	Urbani	Urbani	Urbani	PUMC01
TCID50[a]of SARS-CoV	1.6×10^{4}[b]	AC70: 10^{3} AC22: 10^{6} AC63: 10^{6}	7×10^{4}[c]	10^{5}
Mortality (%)	Line 1: 100 Line 2: 100 Line 3: 100	AC70: 100 AC22: 0 AC63: 0	100	0
Survival days (p.i.)	Line 1: 2–5 Line 2: 3–4 Line 3: 5–7	AC70: 4–8 AC22: n.a.[d] AC63: n.a.	5–6	n.a.

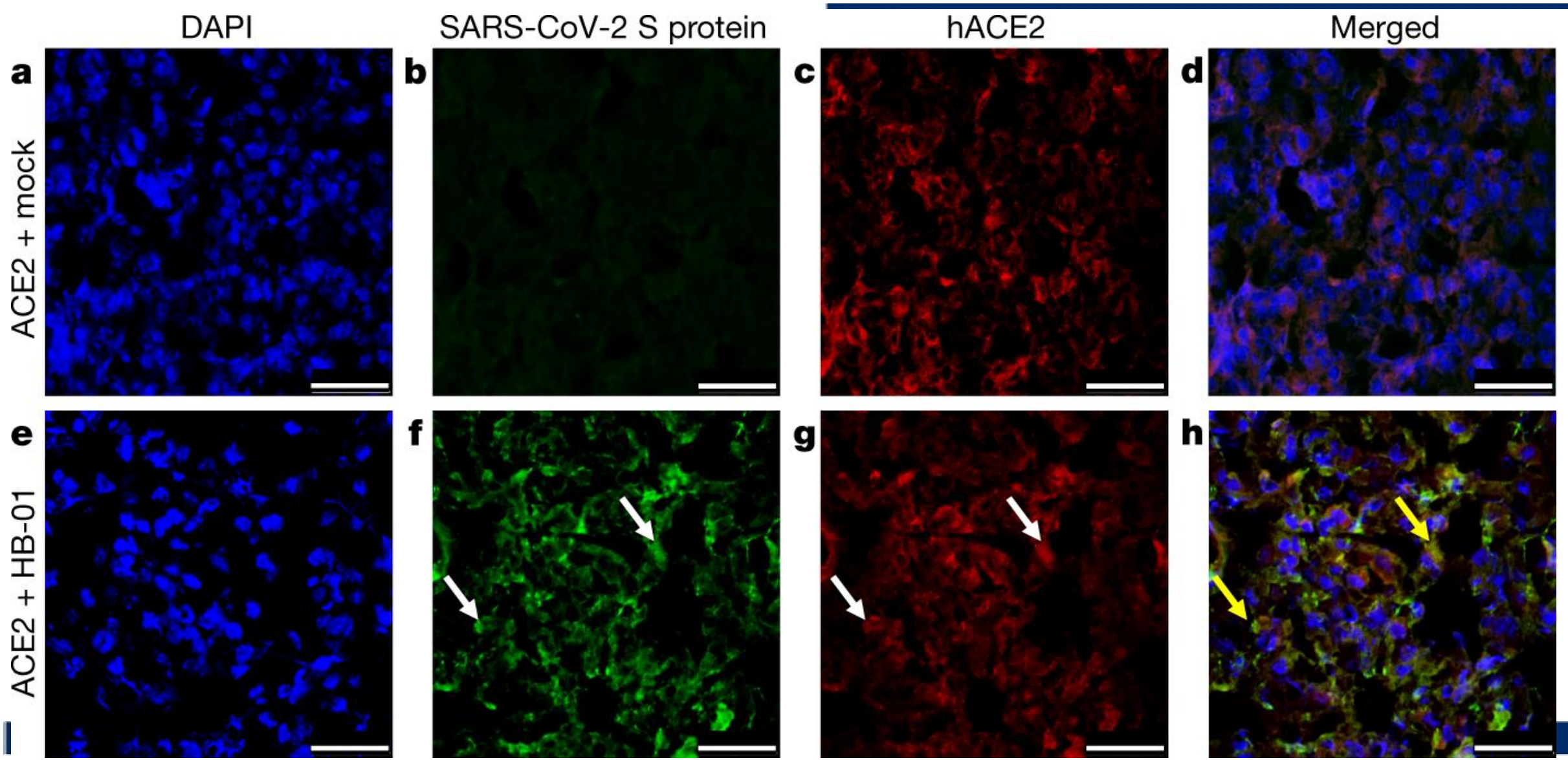
[a]*TCID50* 50% tissue culture infective dose

[b]The viral dosage used in the study, 2.3×10^{4} plaque-forming units (PFU), was converted to the estimated TCID50 by the conversion TCID50 ≈ 0.7 PFU [71].

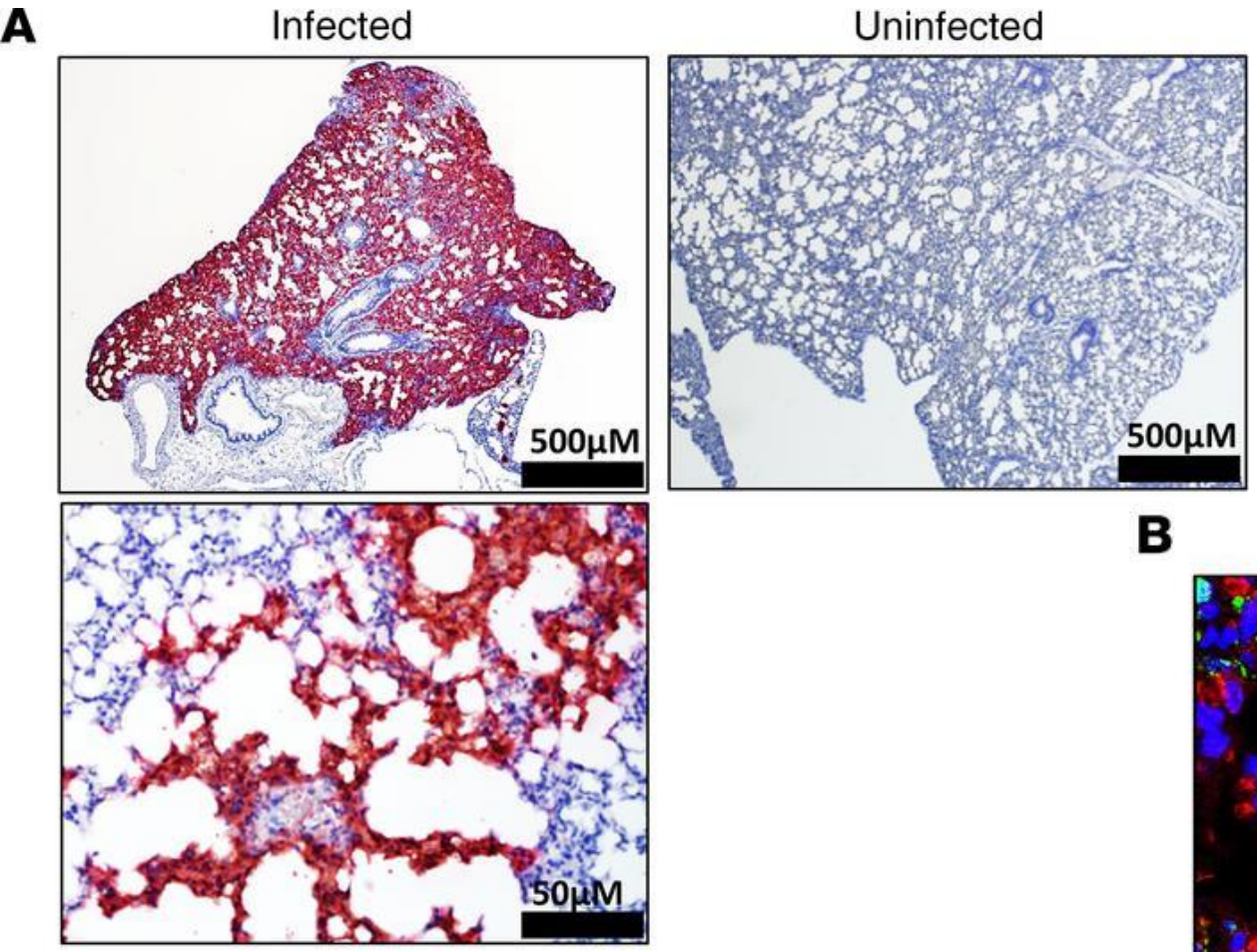
[c]The viral dosage used in the study, 10^{5} PFU, was converted to the estimated TCID50 by the conversion TCID50 ≈ 0.7 PFU [71].

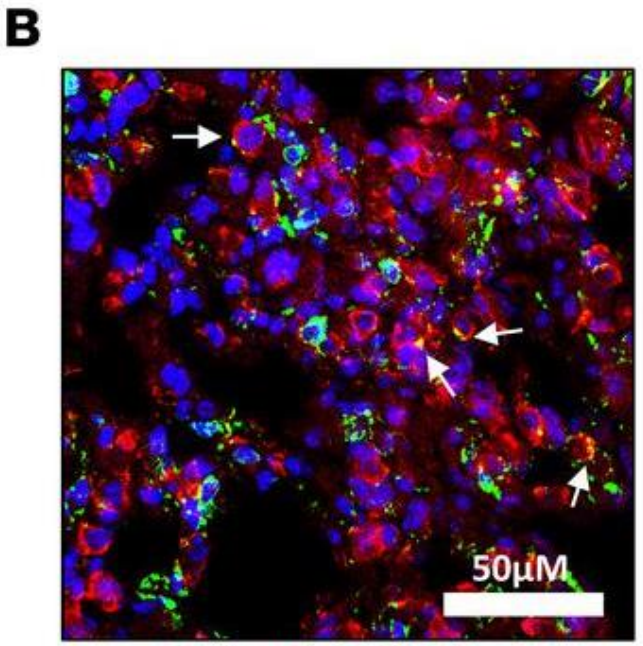
[d]Not applicable

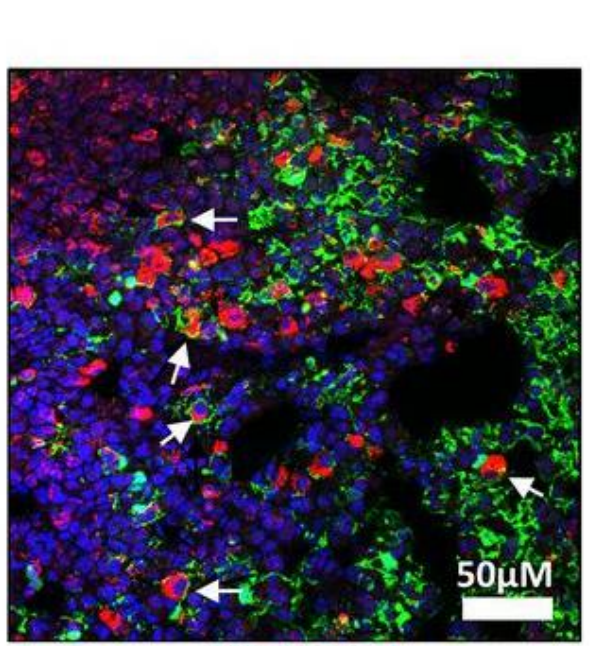
SARS CoV-2 Infection in K18-hACE2 Mice



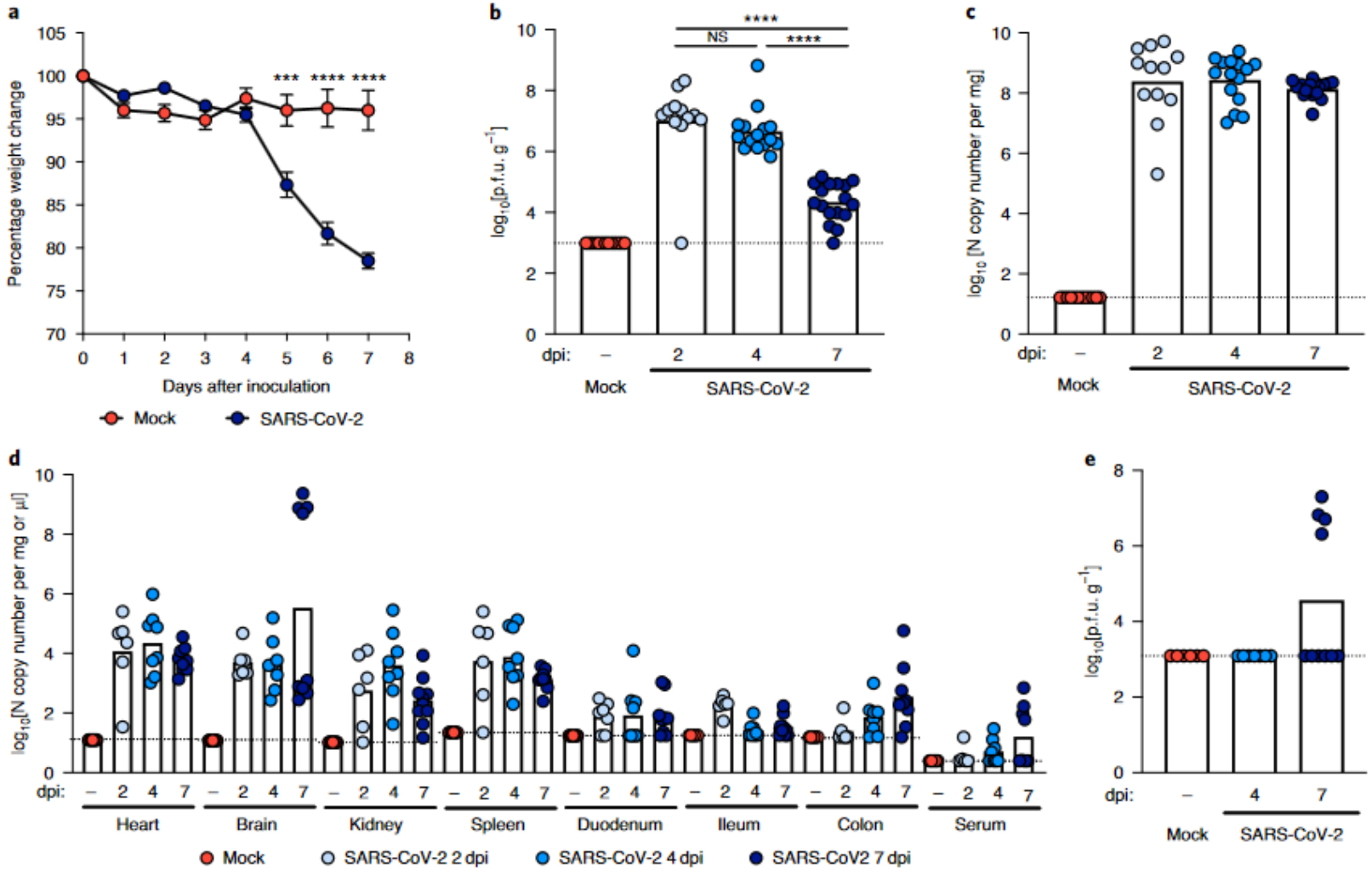
SARS CoV-2 Infection in K18-hACE2 Mice







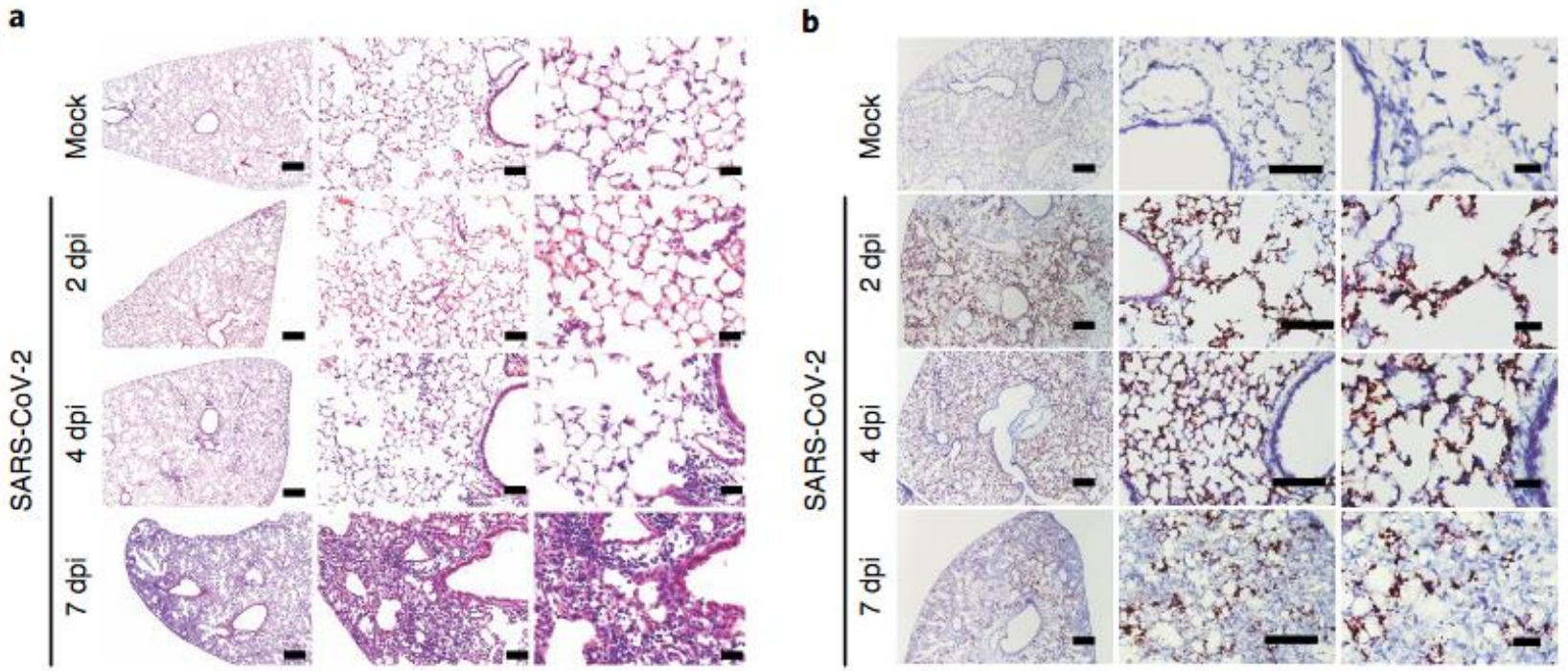
SARS CoV-2 Infection in K18-hACE2 Mice



Lung tissue

Fig. 1 |SARS-CoV-2 infection in K18-hACE2 mice.

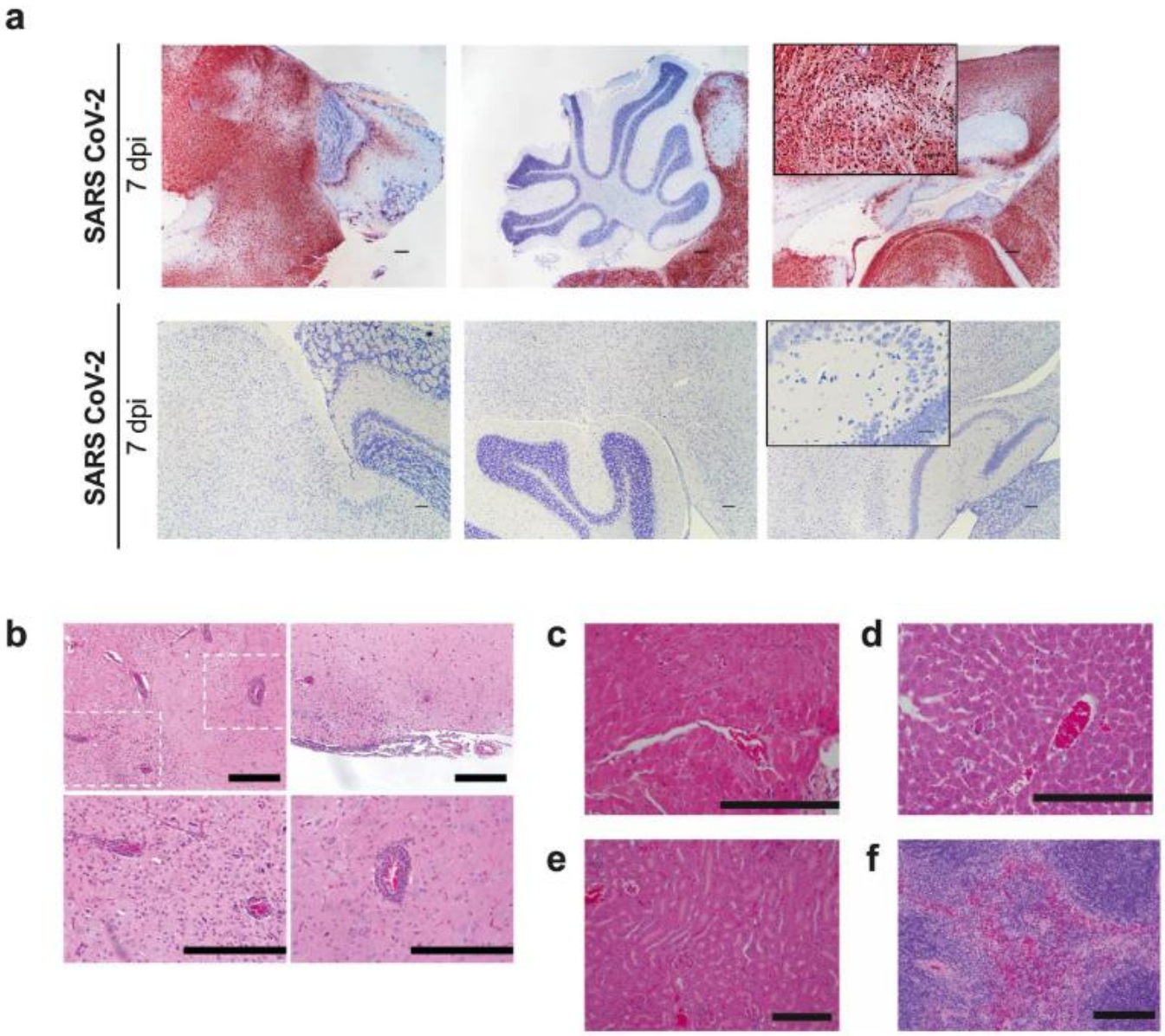
SARS CoV-2 Infection in K18-hACE2 Mice



Lung tissue

Histopathological analysis of SARS-CoV-2 infection in K18-hACE2 mice.a, Hematoxylin and eosin staining of lung sections from K18-hACE2 mice following mock infection or after intranasal infection with 2.5 × 104 p.f.u. SARS-CoV-2 at 2, 4 and 7 dpi.

SARS CoV-2 Infection in K18-hACE2 Mice

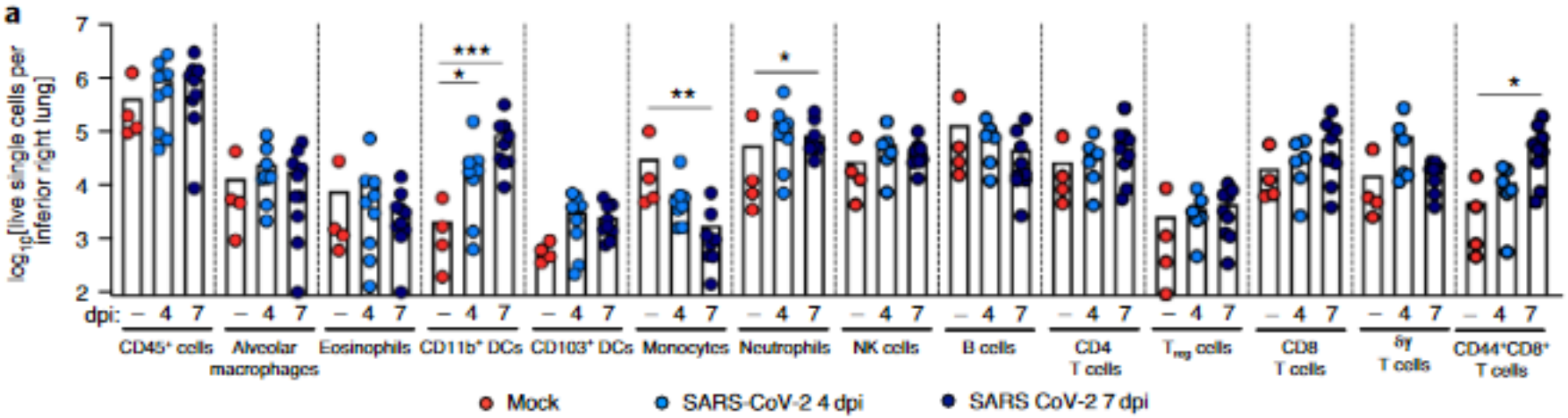


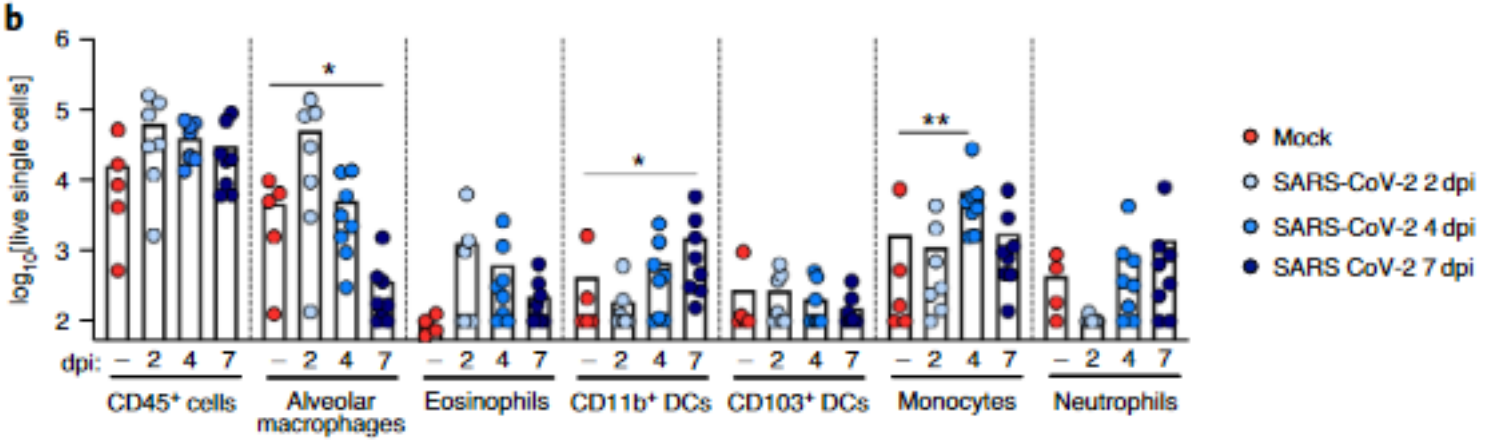
Brain

SARS-CoV-2 infection in extra-pulmonary organs.a. SARS-CoV-2 RNA in situ hybridization of brain sections from K18-hACE2 mice following intranasal infection with 2.5 x 104 PFU of SARS-CoV-2 at 7 dpi.

SARS CoV-2 Infection in K18-hACE2 Mice

Lung tissue

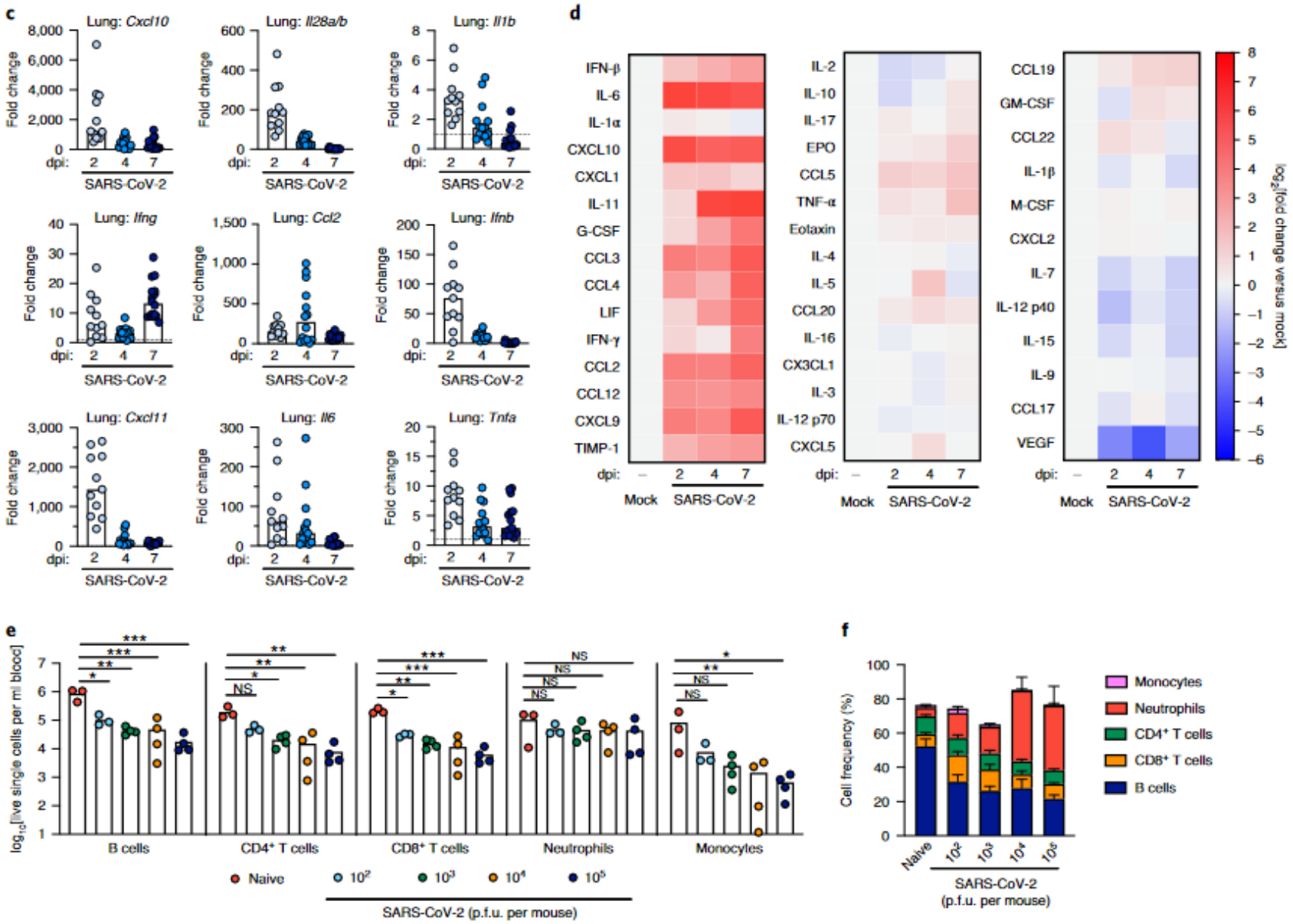




Bronchoalveolar lavage

Immune response to SARS-CoV-2 infection in the lungs of K18-hACE2 mice.a,b, Flow cytometric analysis of lung tissues (a) and BAL (b) at 2, 4 and 7 dpi with SARS-CoV-2.

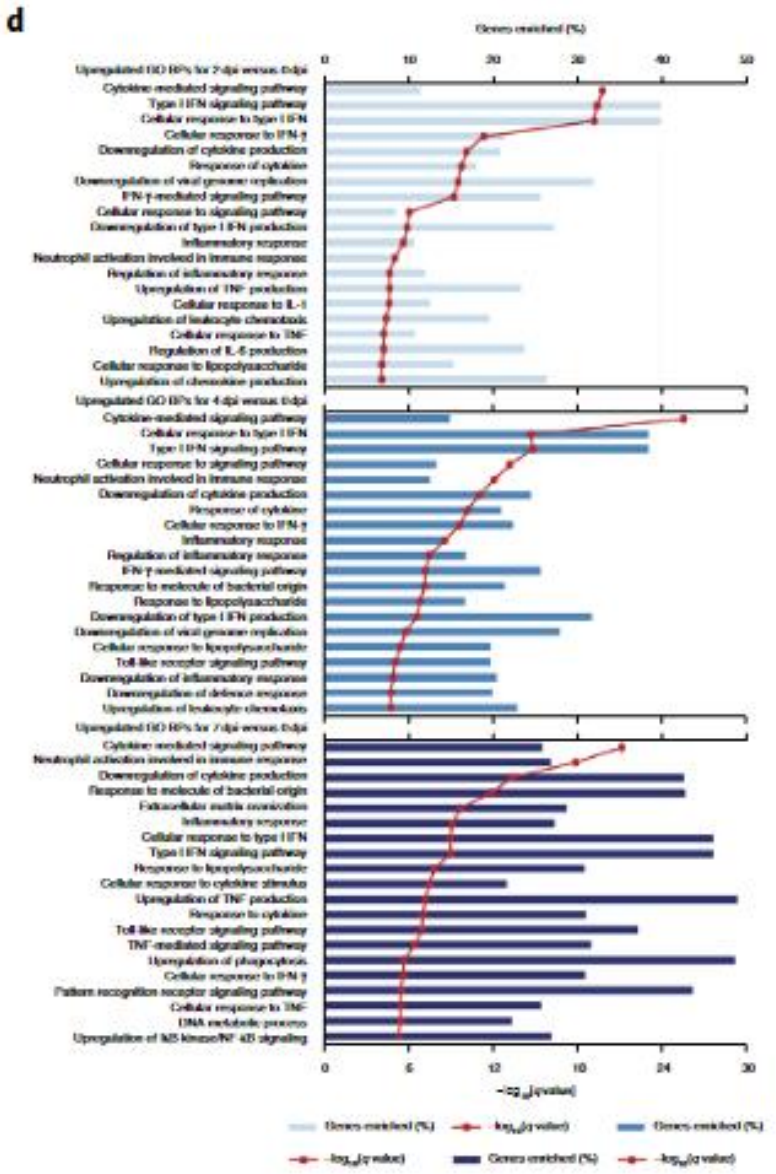
SARS CoV-2 Infection in K18-hACE2 Mice



Lung tissue

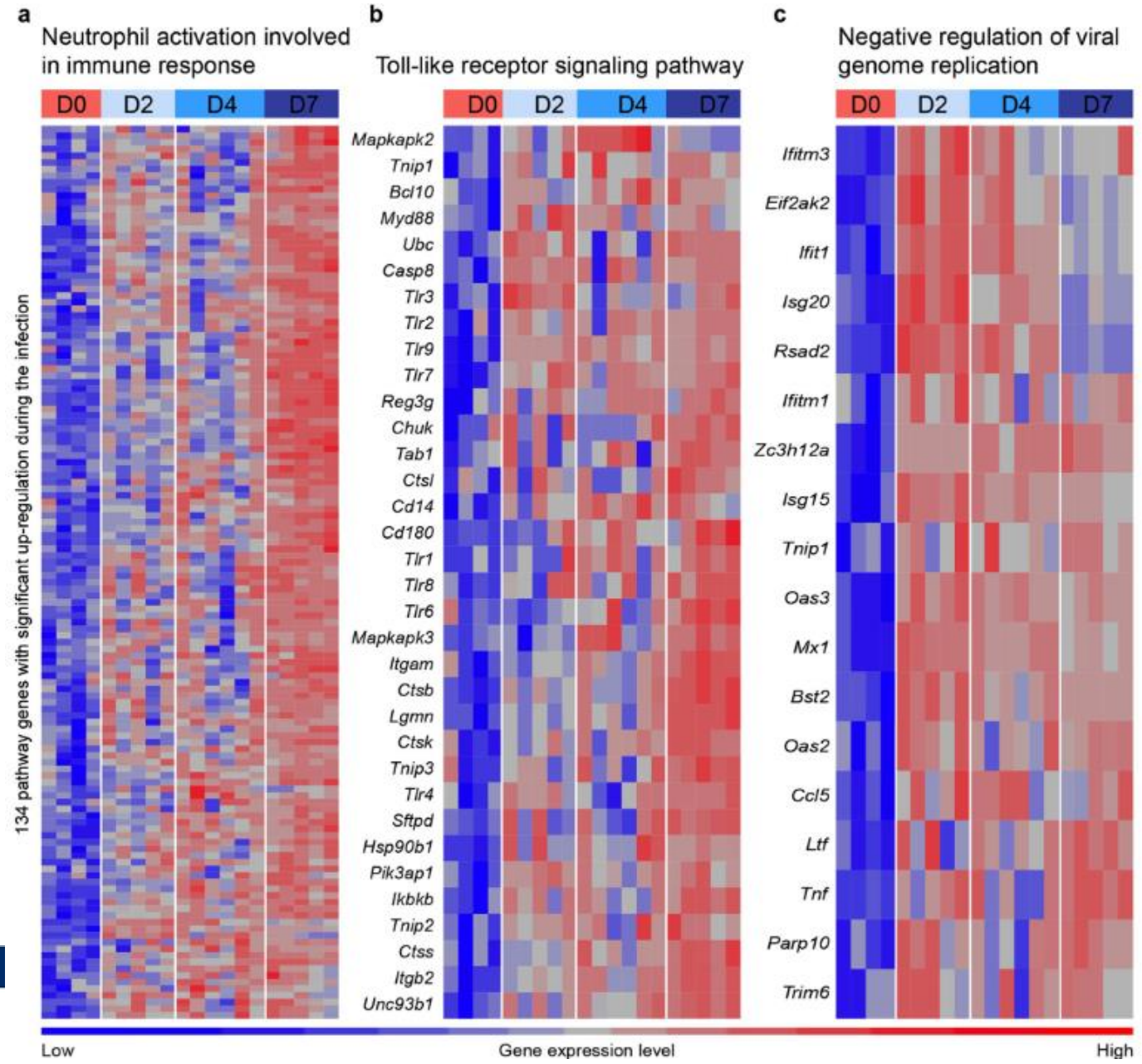
Immune response to SARS-CoV-2 infection in the lungs of K18-hACE2 mice. Inflammatory gene expression and Immune cell influx.

SARS CoV-2 Infection in K18-hACE2 Mice



Distinct transcriptional signatures are associated with early and late immune responses to SARS-CoV-2 infection.

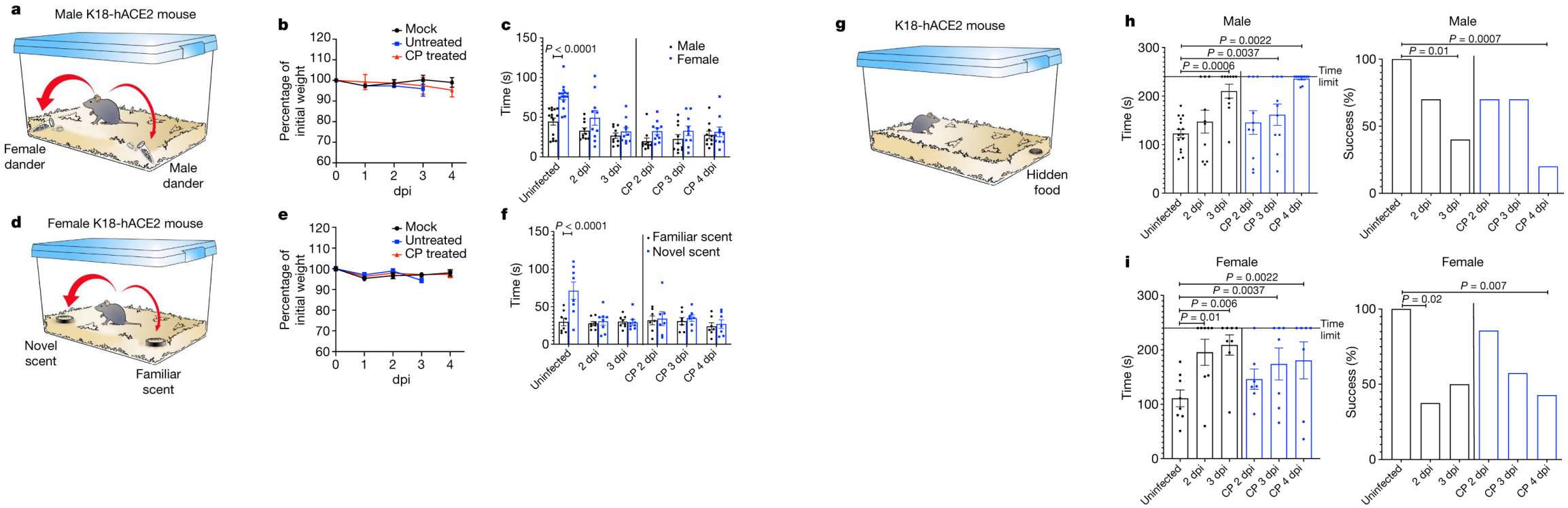
SARS CoV-2 Infection in K18-hACE2 Mice



Neutrophil activation

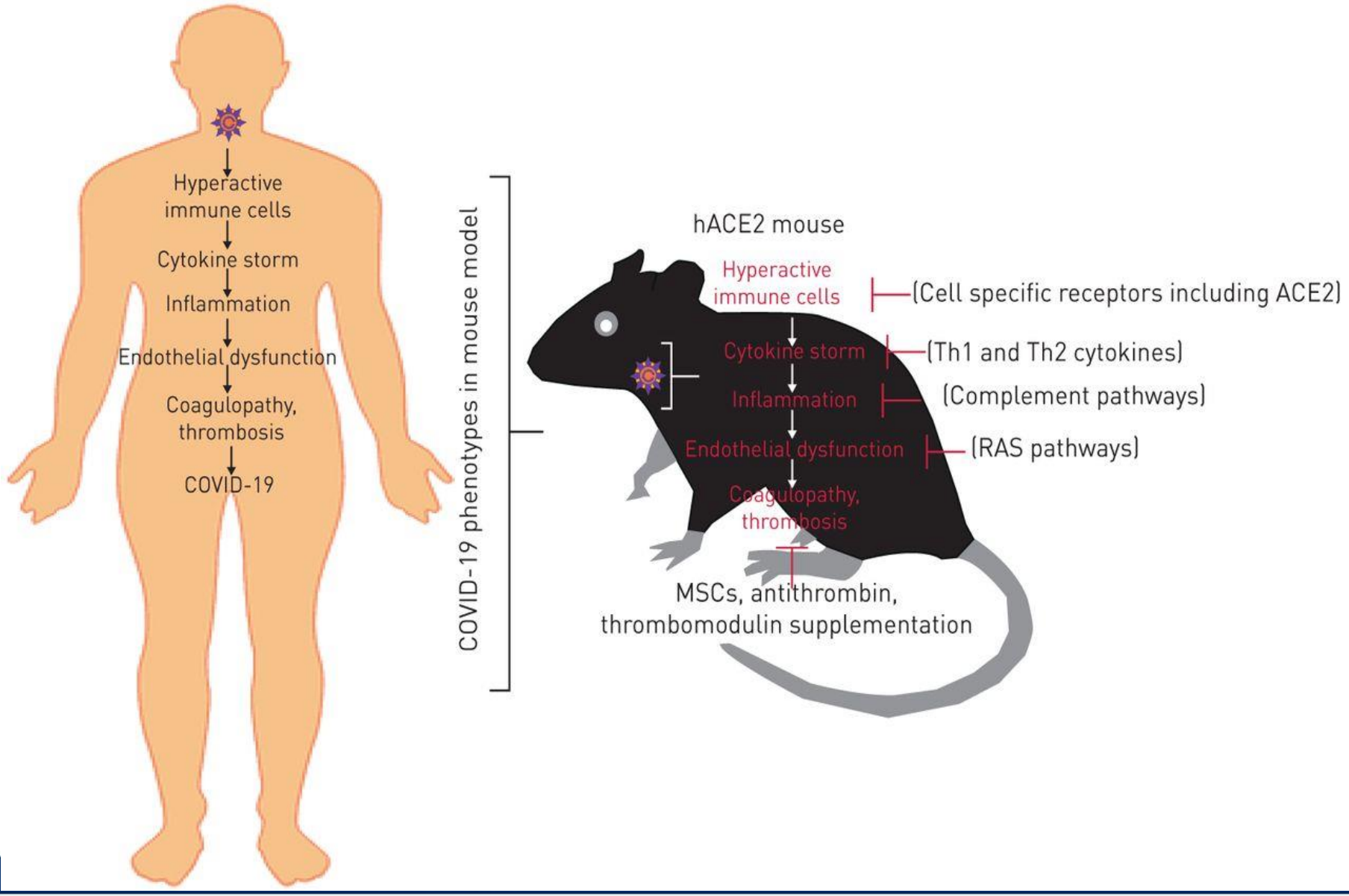
Transcriptional immune signatures following SARS-CoV-2 infection. Heat maps of significantly upregulated genes during SARS-CoV-2 infection enriched in neutrophil activation pathways

SARS CoV-2 Infection in K18-hACE2 Mice



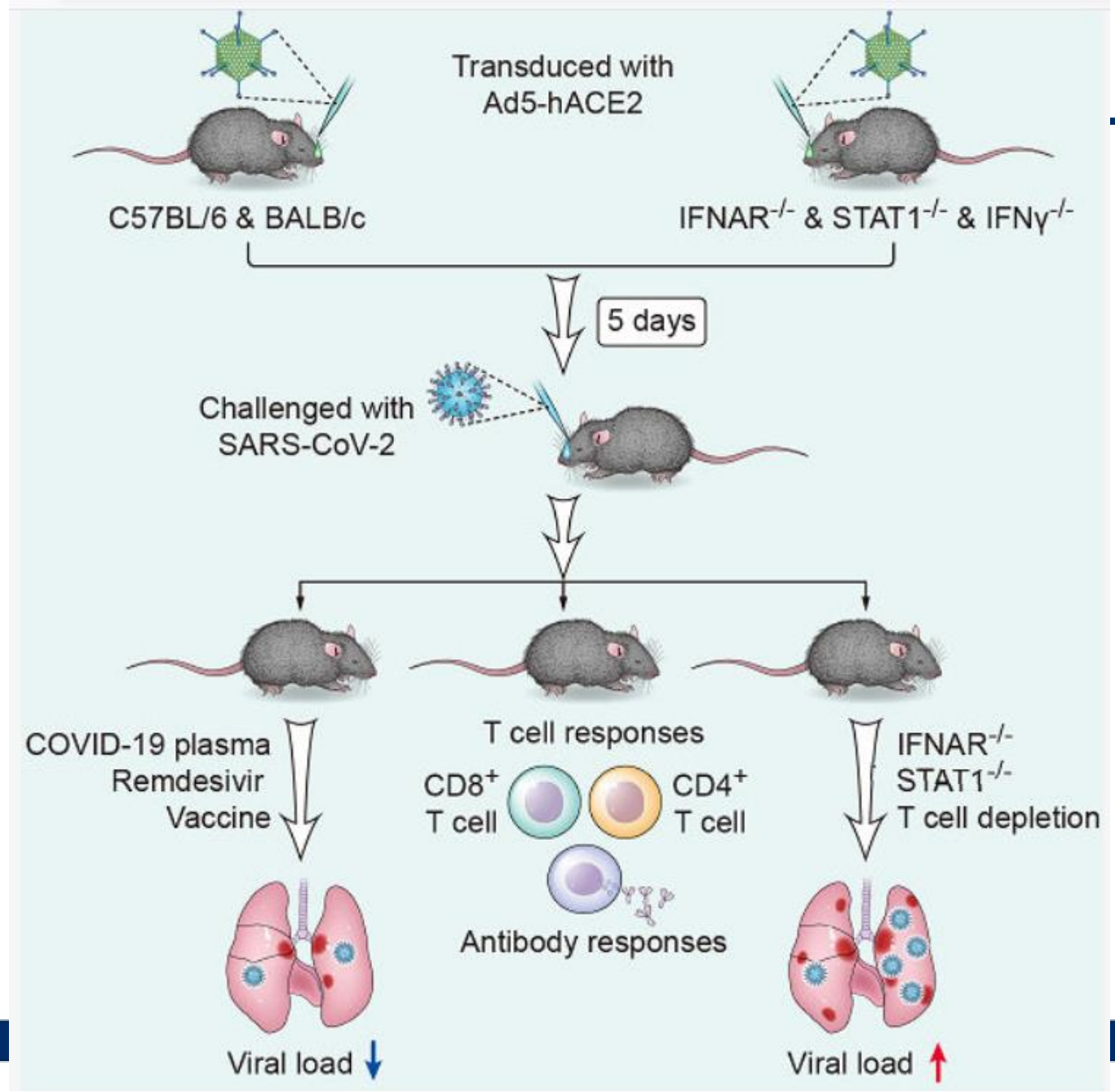
Anosmia

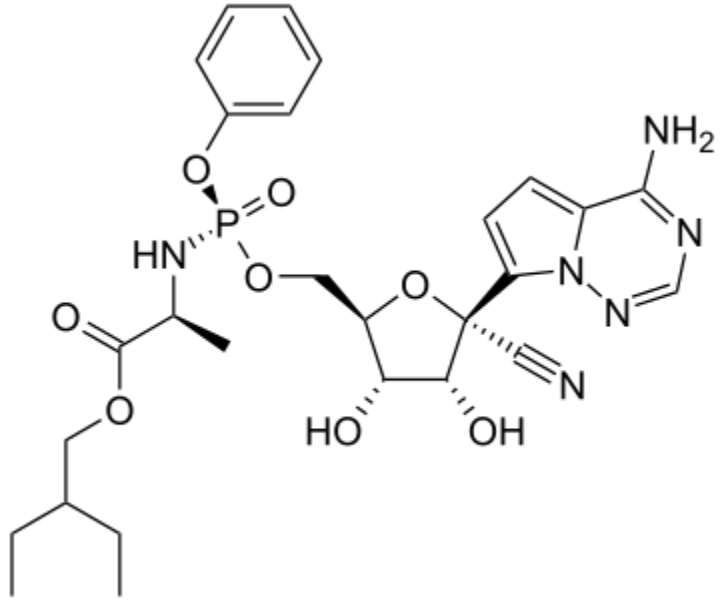
Potential Therapeutic Targets



Rahul Kumar et al. ERJ Open Res 2020;6:00405-2020

Remdesivir





As an adenosine nucleoside triphosphate analog (GS-443902), the active metabolite of remdesivir interferes with the action of viral RNA-dependent RNA polymerase and evades proofreading by viral exoribonuclease (ExoN), causing a decrease in viral RNA production.

Vaccine Development

Which animals are being used to develop a COVID-19 vaccine?

MICE

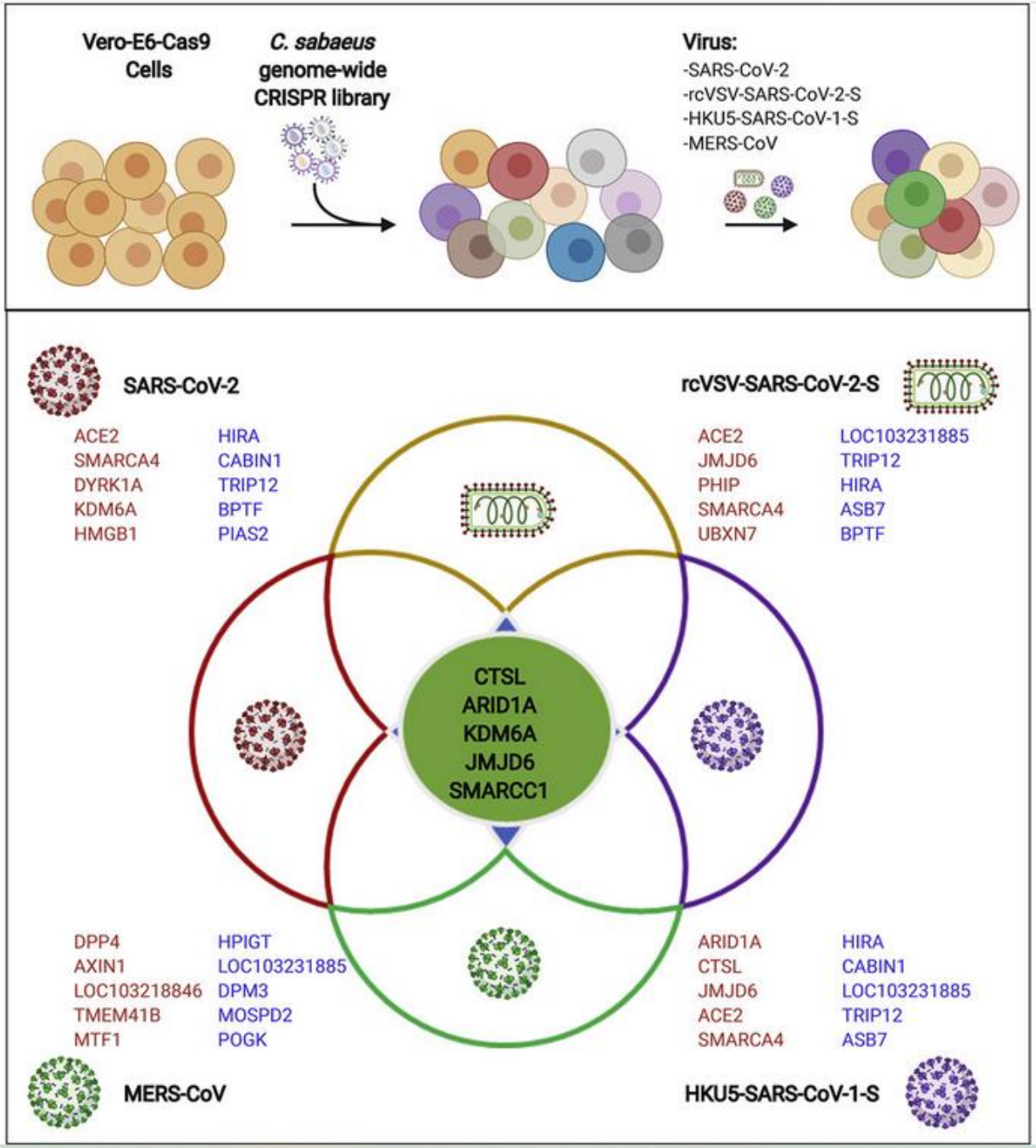
Mice are being used to test whether vaccine compounds are safe to be trialled in humans. There is only one strain of genetically altered mice that is susceptible to COVID-19. These mice were developed to research the SARS outbreak in 2003 and are now being bred for COVID-19 research.

MONKEYS

Non-human primates are our closest living relatives. Unlike mice, they can contract the COVID-19 virus. Researchers are using primates to test the safety of vaccine compounds, discover how the virus works inside the body, and whether it can re-infect people that have already recovered from the virus.

Understanding ANIMAL RESEARCH

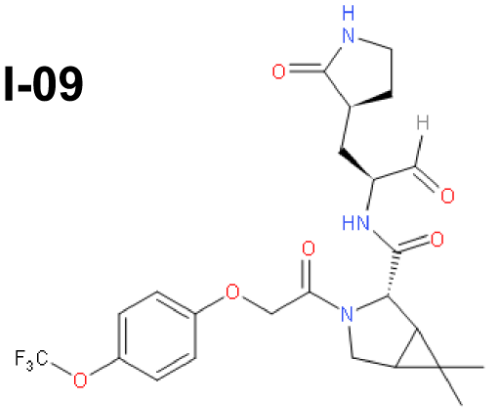
Novel Therapeutic Targets



Novel Therapeutic Targets

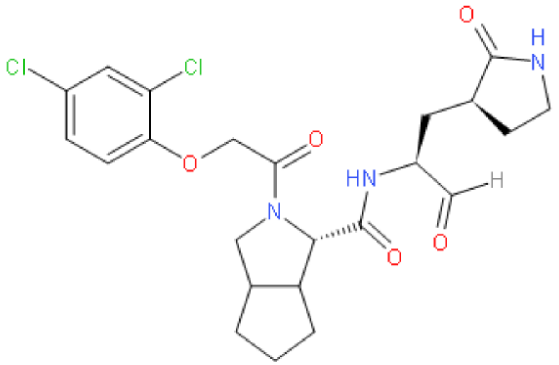
a

MI-09

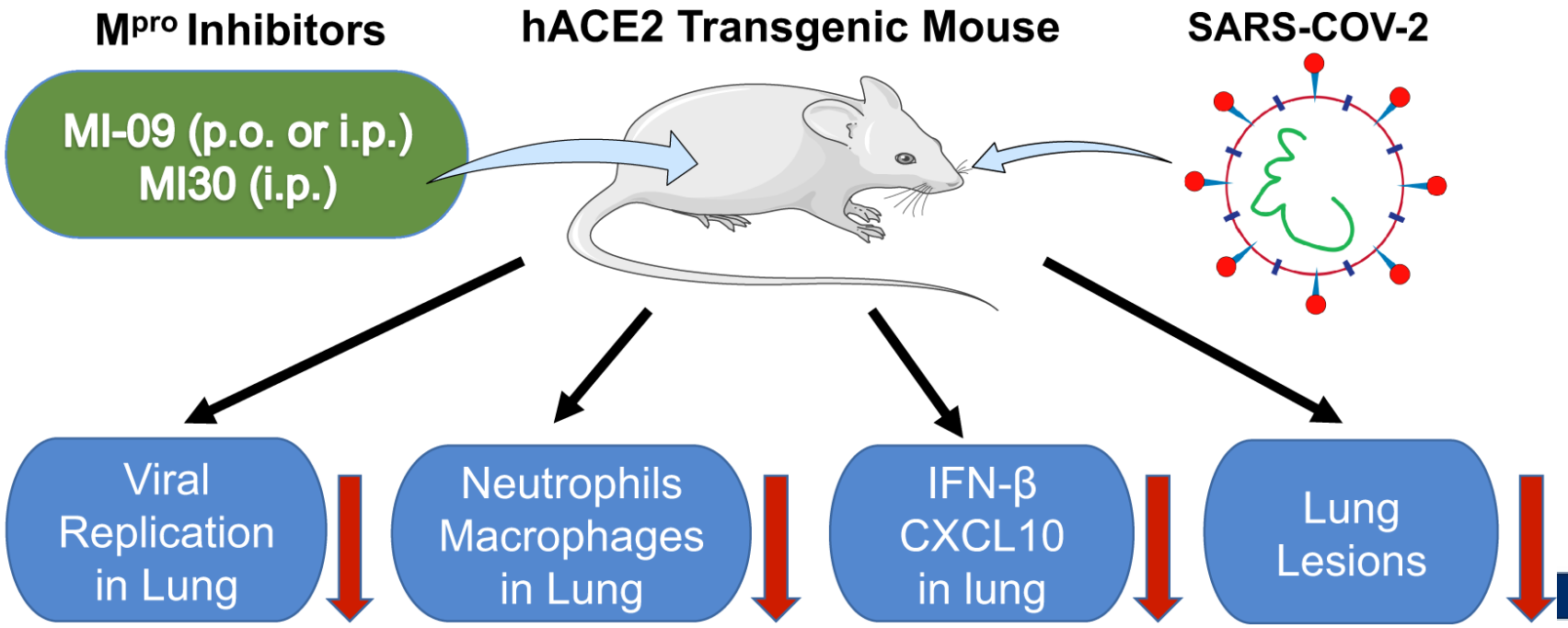


b

MI-30

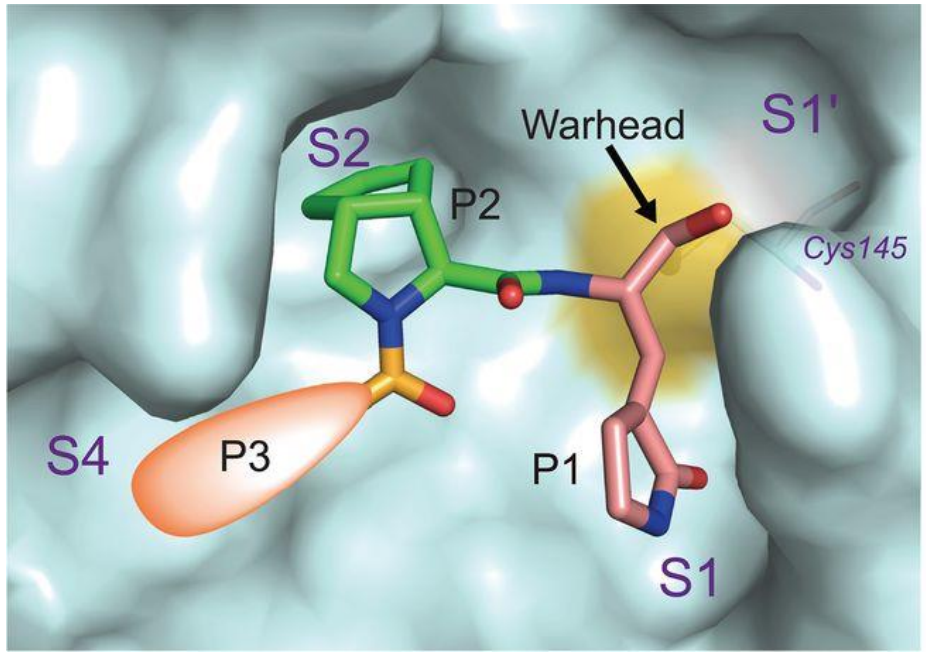


c



The main protease (M^{pro}, also known as 3CL^{pro}), is one of the coronavirus nonstructural proteins (Nsp5) designated as a potential target for drug development[7,8]. M^{pro} cleaves the viral polyproteins, generating 12 nonstructural proteins (Nsp4-Nsp16), including the RNA-dependent RNA polymerase (RdRp, Nsp12) and the helicase (Nsp13).

Novel Therapeutic Targets



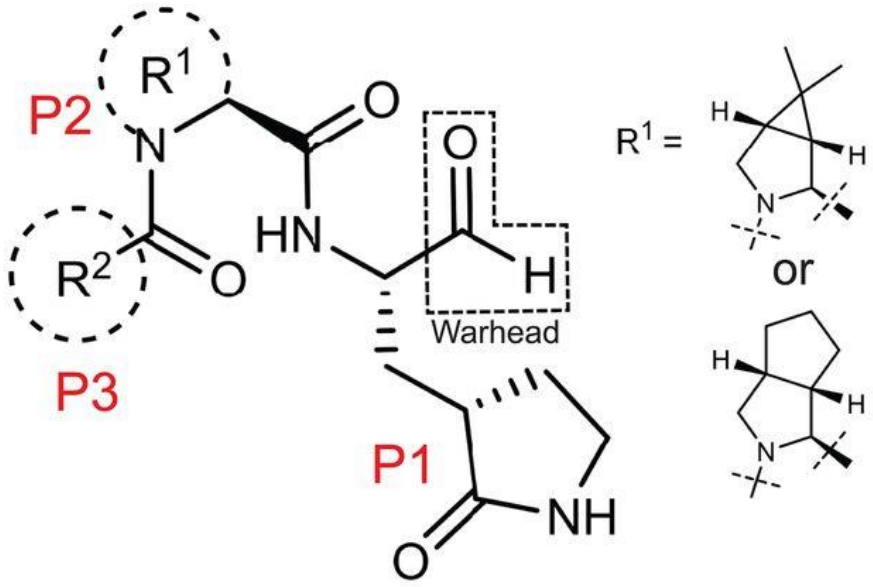


Fig. 1 Schematic diagram of the design of novel SARS-CoV-2 Mpro inhibitors.

Novel Therapeutic Targets

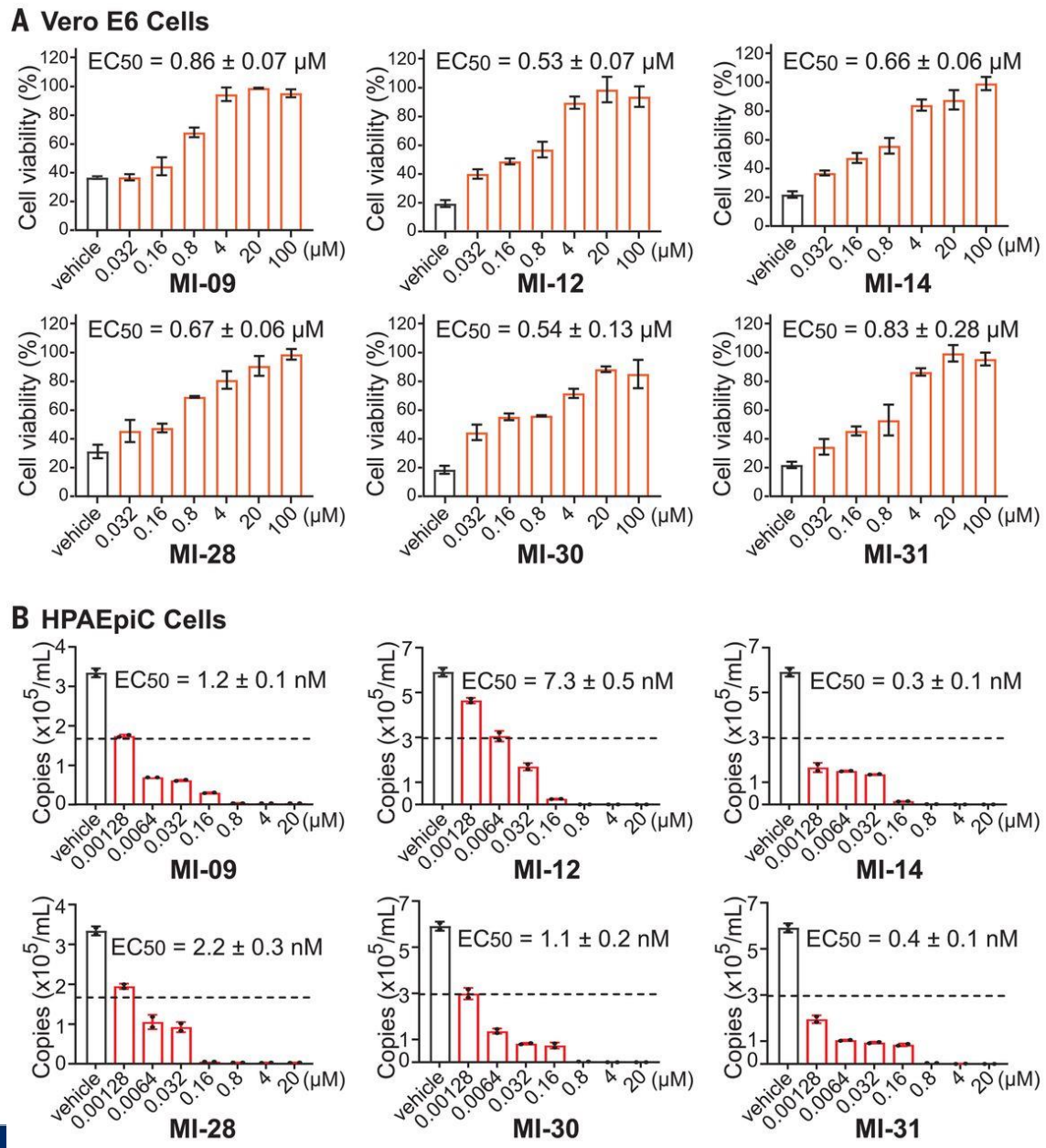
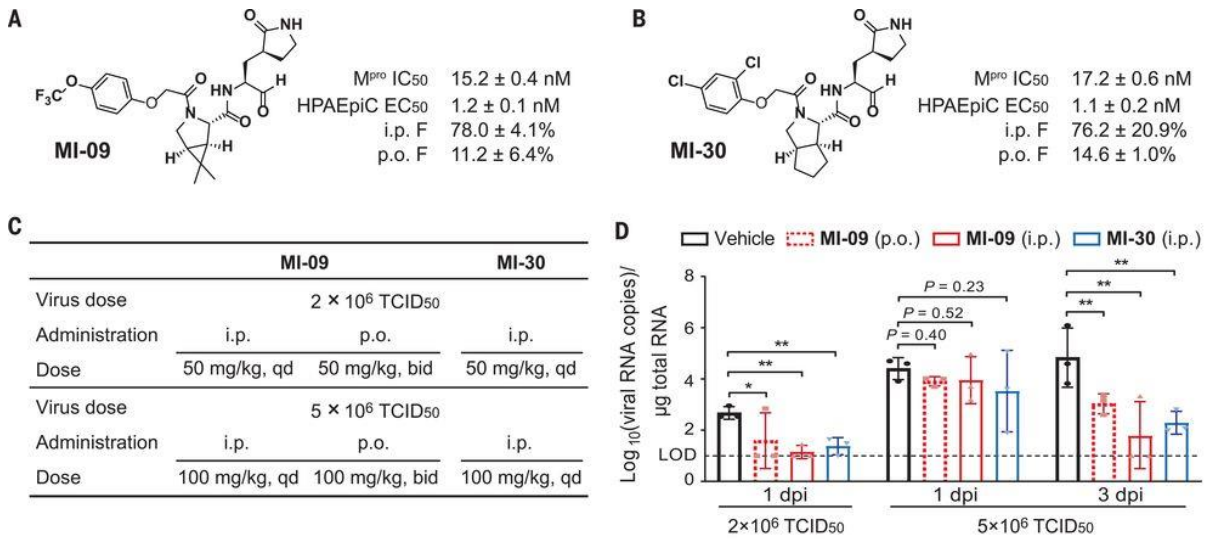


Fig. 3 Antiviral activity of six compounds against SARS-CoV-2 in cell-based assays.

Jingxin Qiao et al. Science 2021;371:1374-1378

Novel Therapeutic Targets



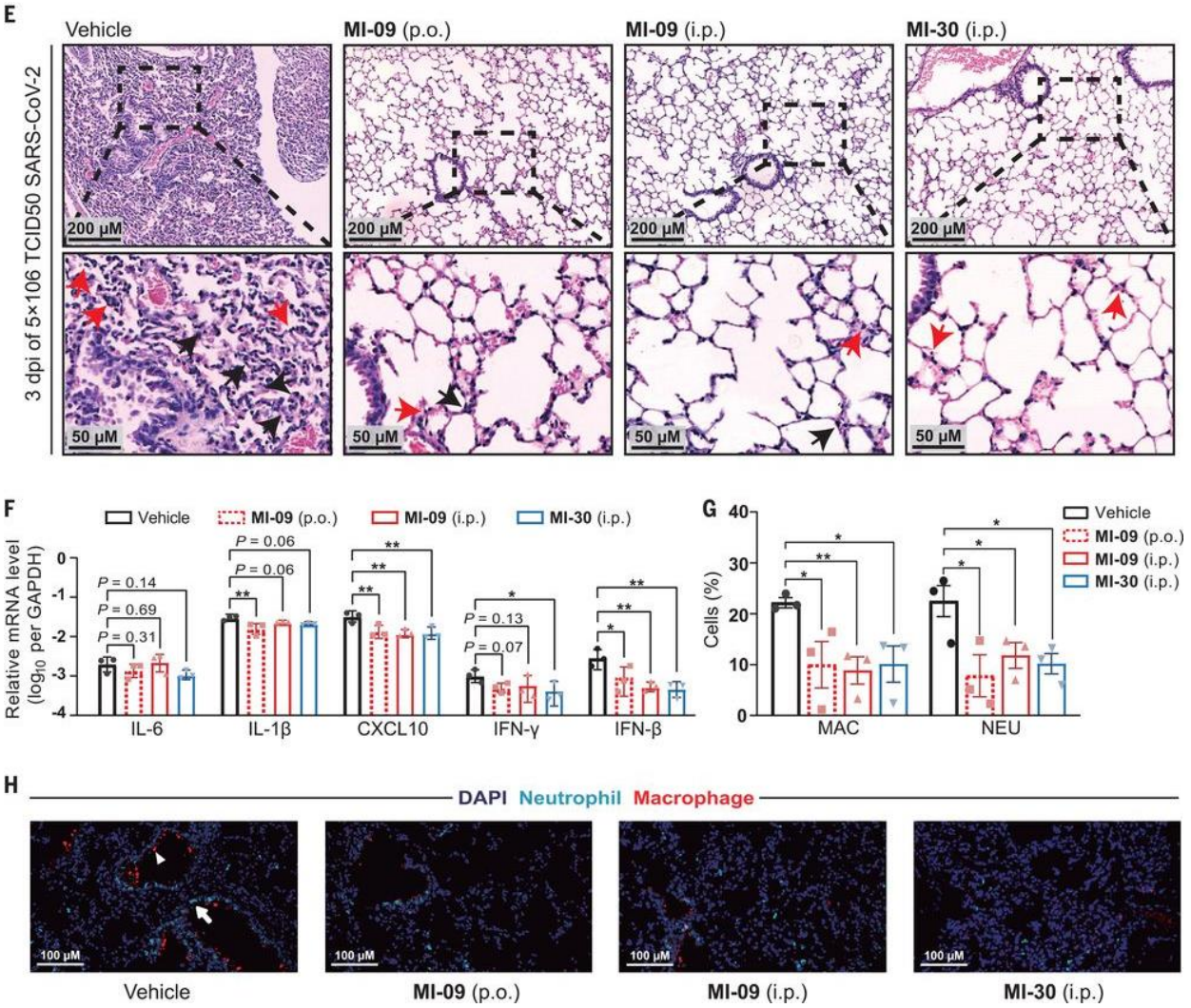
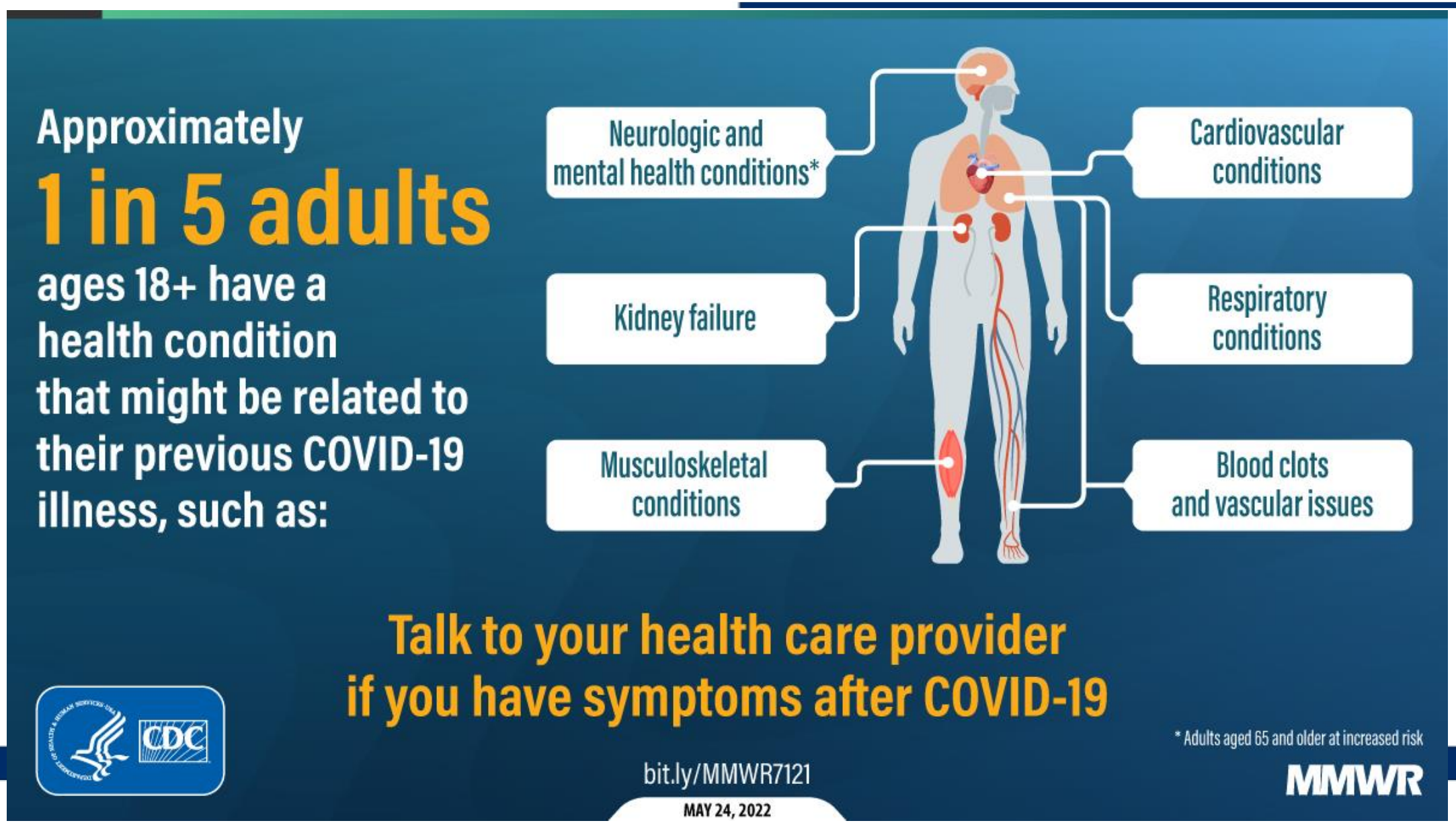


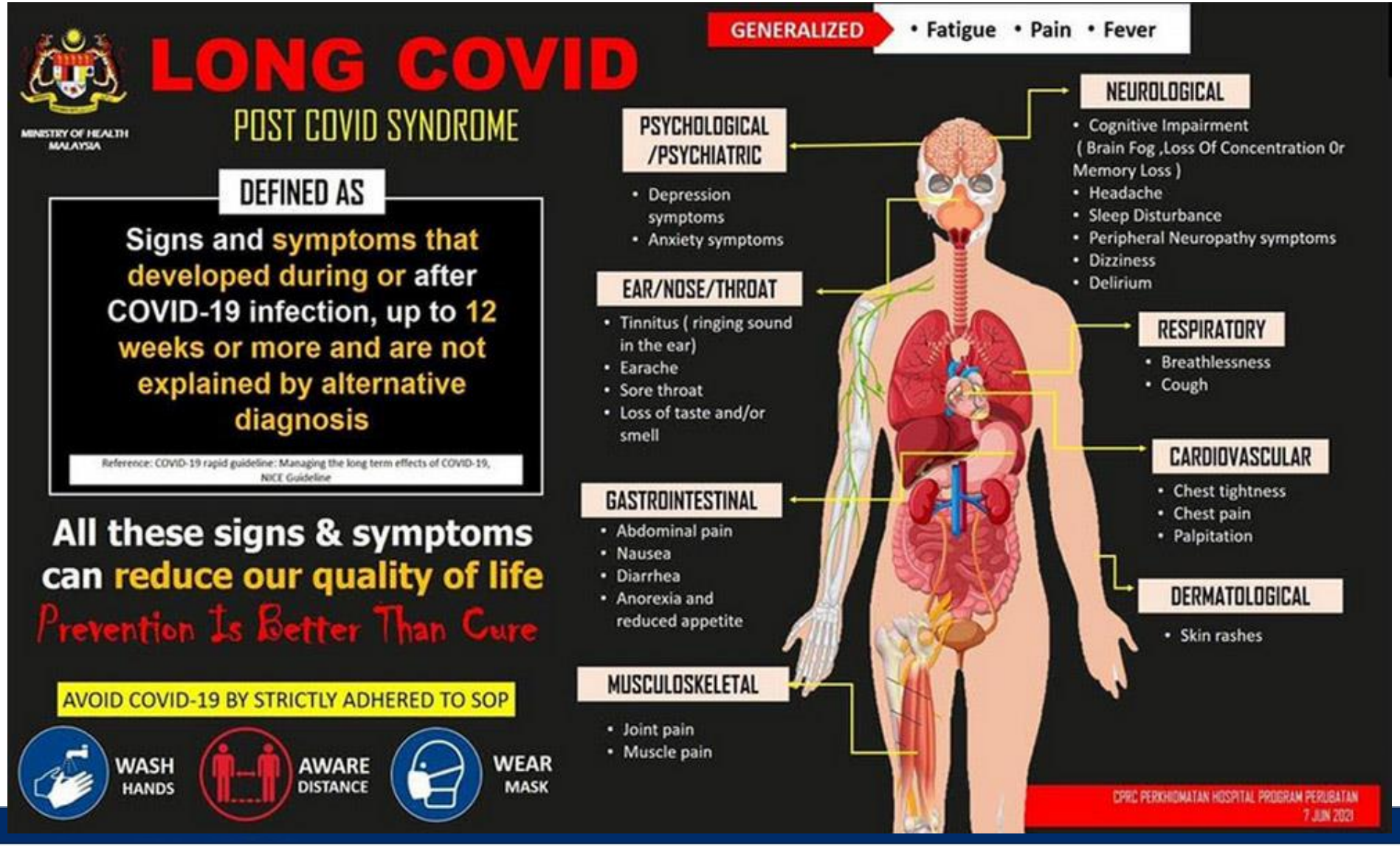
Fig. 4 MI-09 and MI-30 reduce lung viral loads and lung lesions in a SARS-CoV-2 infection transgenic mouse model.

Jingxin Qiao et al. Science 2021;371:1374-1378

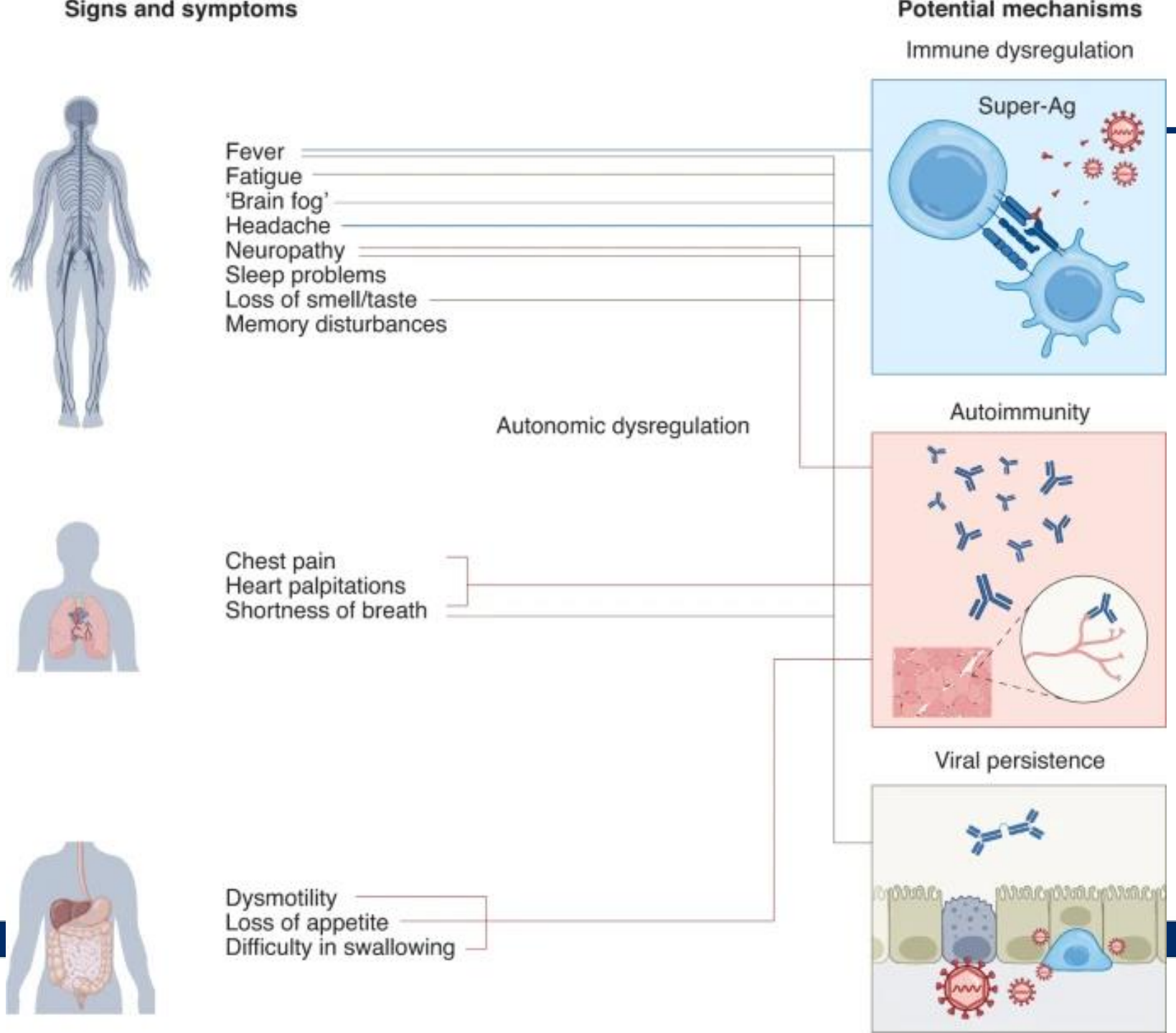
Long COVID


Approximately
1 in 5 adults
ages 18+ have a health condition that might be related to their previous COVID-19 illness, such as:
Neurologic and mental health conditions*
Kidney failure
Musculoskeletal conditions
Cardiovascular conditions
Respiratory conditions
Blood clots and vascular issues
Talk to your health care provider if you have symptoms after COVID-19
* Adults aged 65 and older at increased risk
bit.ly/MMWR7121
MAY 24, 2022
MMWR

Long COVID


MINISTRY OF HEALTH MALAYSIA
LONG COVID
POST COVID SYNDROME
DEFINED AS
Signs and symptoms that developed during or after COVID-19 infection, up to 12 weeks or more and are not explained by alternative diagnosis
Reference: COVID-19 rapid guideline: Managing the long term effects of COVID-19, NICE Guideline
All these signs & symptoms can reduce our quality of life
Prevention Is Better Than Cure
AVOID COVID-19 BY STRICTLY ADHERED TO SOP
WASH HANDS
AWARE DISTANCE
WEAR MASK
GENERALIZED
• Fatigue • Pain • Fever
PSYCHOLOGICAL /PSYCHIATRIC
• Depression symptoms
• Anxiety symptoms
EAR/NOSE/THROAT
• Tinnitus (ringing sound in the ear)
• Earache
• Sore throat
• Loss of taste and/or smell
GASTROINTESTINAL
• Abdominal pain
• Nausea
• Diarrhea
• Anorexia and reduced appetite
MUSCULOSKELETAL
• Joint pain
• Muscle pain
NEUROLOGICAL
• Cognitive Impairment (Brain Fog ,Loss Of Concentration Or Memory Loss)
• Headache
• Sleep Disturbance
• Peripheral Neuropathy symptoms
• Dizziness
• Delirium
RESPIRATORY
• Breathlessness
• Cough
CARDIOVASCULAR
• Chest tightness
• Chest pain
• Palpitation
DERMATOLOGICAL
• Skin rashes
CPRC PERKHIDMATAN HOSPITAL PROGRAM PERUBATAN
7 JUN 2021

Long COVID



https://www.dw.com/en/tracking-long-covid-in-the-blood/av-60658430

HEALTH AND SCIENCE

WHO says Covid remains a global emergency but pandemic could near its end in 2023

PUBLISHED MON, JAN 30 2023•11:17 AM EST

Spencer Kimball
@SPENCEKIMBALL

SHARE

KEY POINTS

- WHO chief Tedros Adhanom Ghebreyesus said Covid remains a global health emergency, though the world is in a much better place than it was a year ago.
- The WHO has estimated that at least 90% of the world's population has some level of immunity to Covid due to vaccination or infection.
- The WHO chief has previously said the end of the pandemic is in sight.

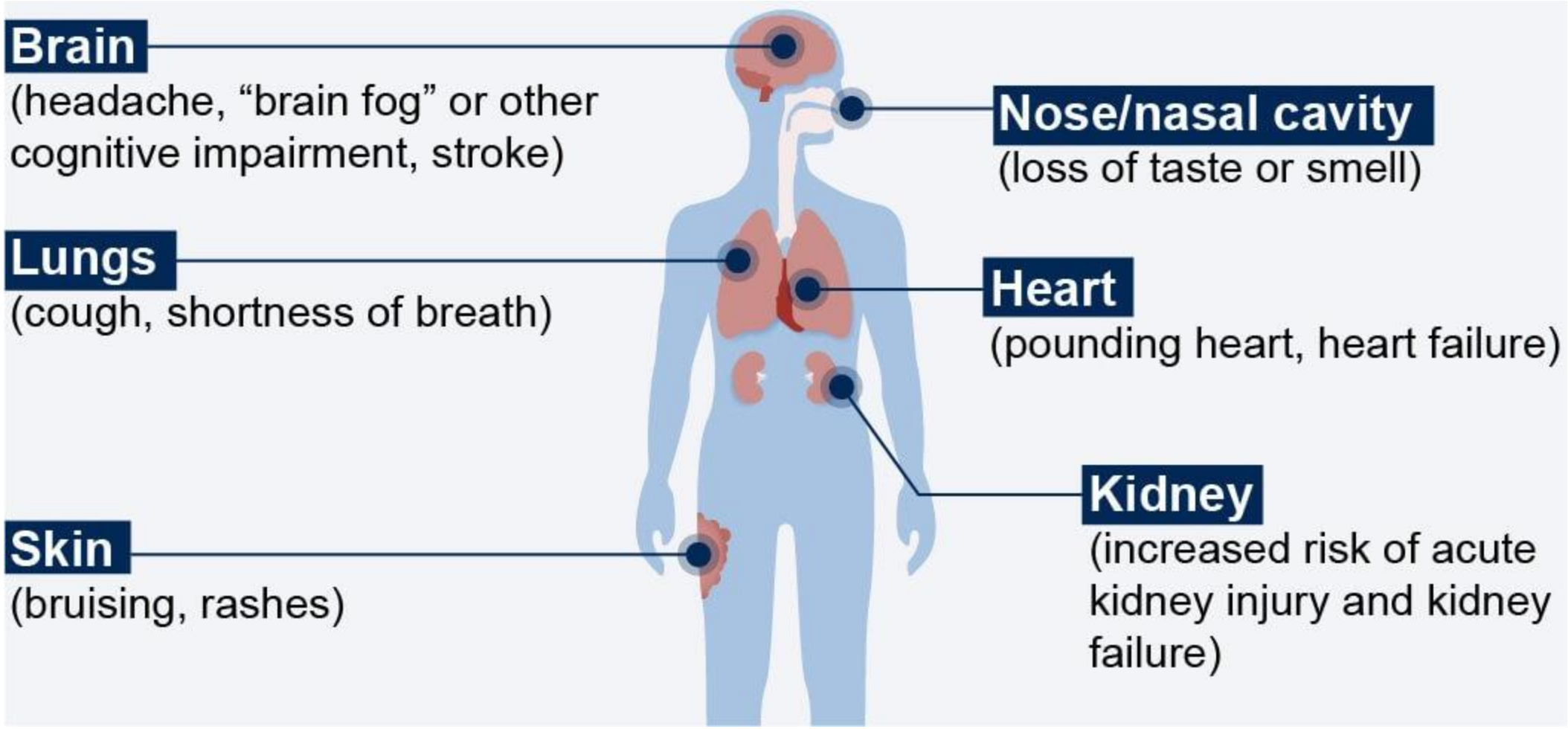
TRENDING NOW

31-year-old used her $1,200 stimulus check to start a business on track to bring in $1 million

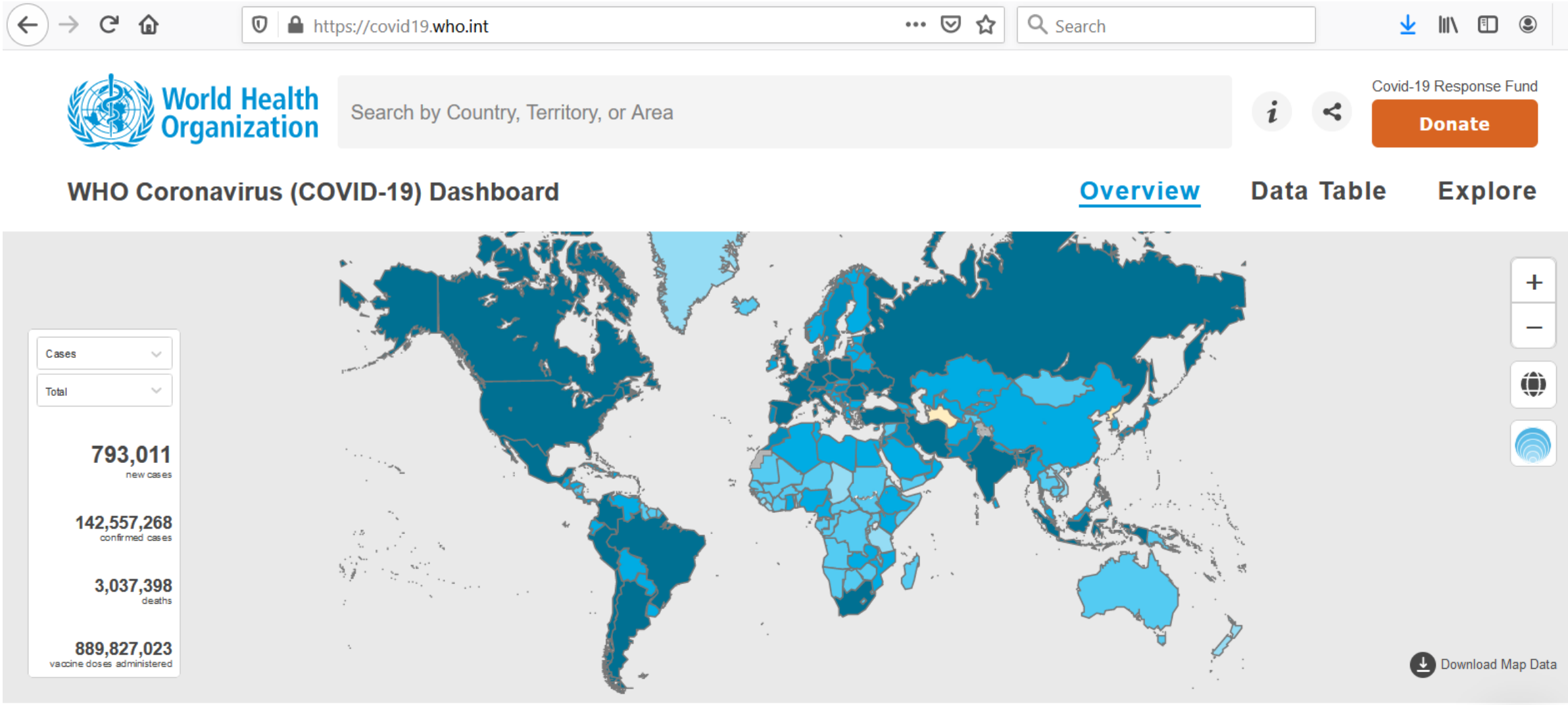
North Korea fires missiles as U.S. aircraft carrier set to arrive in South

Russia stirs outrage with plan for tactical nukes in

Long COVID


Brain
(headache, “brain fog” or other cognitive impairment, stroke)
Lungs
(cough, shortness of breath)
Skin
(bruising, rashes)
Nose/nasal cavity
(loss of taste or smell)
Heart
(pounding heart, heart failure)
Kidney
(increased risk of acute kidney injury and kidney failure)

WHO-COVID19



Globally, as of **7:19pm CEST, 21 April 2021**, there have been **142,557,268 confirmed cases** of COVID-19, including **3,037,398 deaths**, reported to WHO. As of **21 April 2021**, a total of **889,827,023 vaccine doses** have been administered.

WHO-COVID19

https://www.who.int/teams/health-care-readiness-clinical-unit/covid-19/data-platform

Global Regions Select language

World Health Organization

Health Topics Countries Newsroom Emergencies Data About Us

Global COVID-19 Clinical Data Platform for clinical characterization and management of patients with suspected or confirmed COVID-19

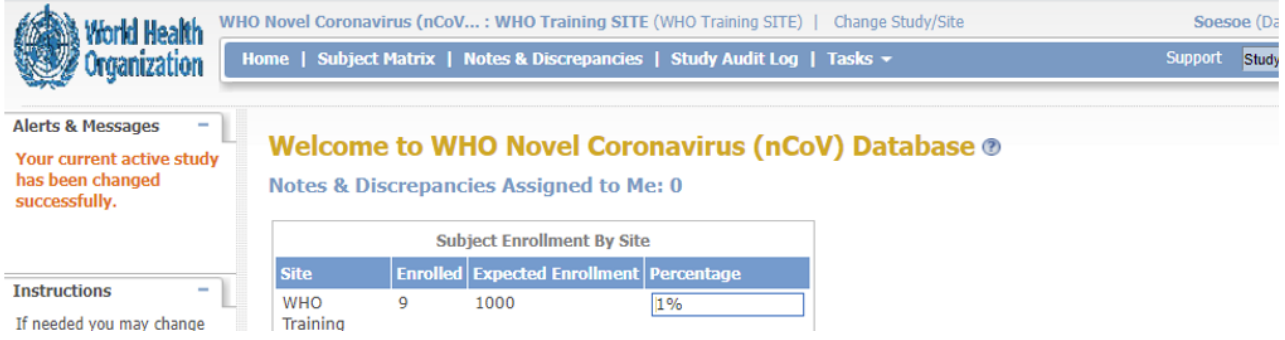
Global understanding of the severity, clinical features and prognostic factors of COVID-19 in different settings and populations remains incomplete. WHO therefore invites Member States, health facilities and other entities to participate in the global effort to collect anonymized clinical data relating to hospitalized suspected or confirmed cases of COVID-19 and contribute data to the Global COVID-19 Clinical Data Platform.

WHO will use the information to inform:

1. **Characterization of the key clinical features and prognostic factors** of cases of suspected or confirmed COVID-19, thereby increase understanding of the severity, spectrum, and impact of the disease in the hospitalized population globally, in different countries.
2. **Characterization of clinical interventions**, thereby facilitating global and national operational planning during the COVID-19 pandemic.

COVID-19 Clinical Data Platform

The platform is a secure, limited-access, password-protected platform hosted on OpenClinica. WHO will use the anonymized COVID-19 data solely for the permitted purpose(s) for which it is provided to WHO, and will protect the confidentiality and security of the Anonymized Data, in each case, in accordance with the Terms of Use applicable to the Global COVID-19 Clinical Data Platform.



About the Clinical Management team

Register to the platform

Acknowledgement of Clinical Platform contributors

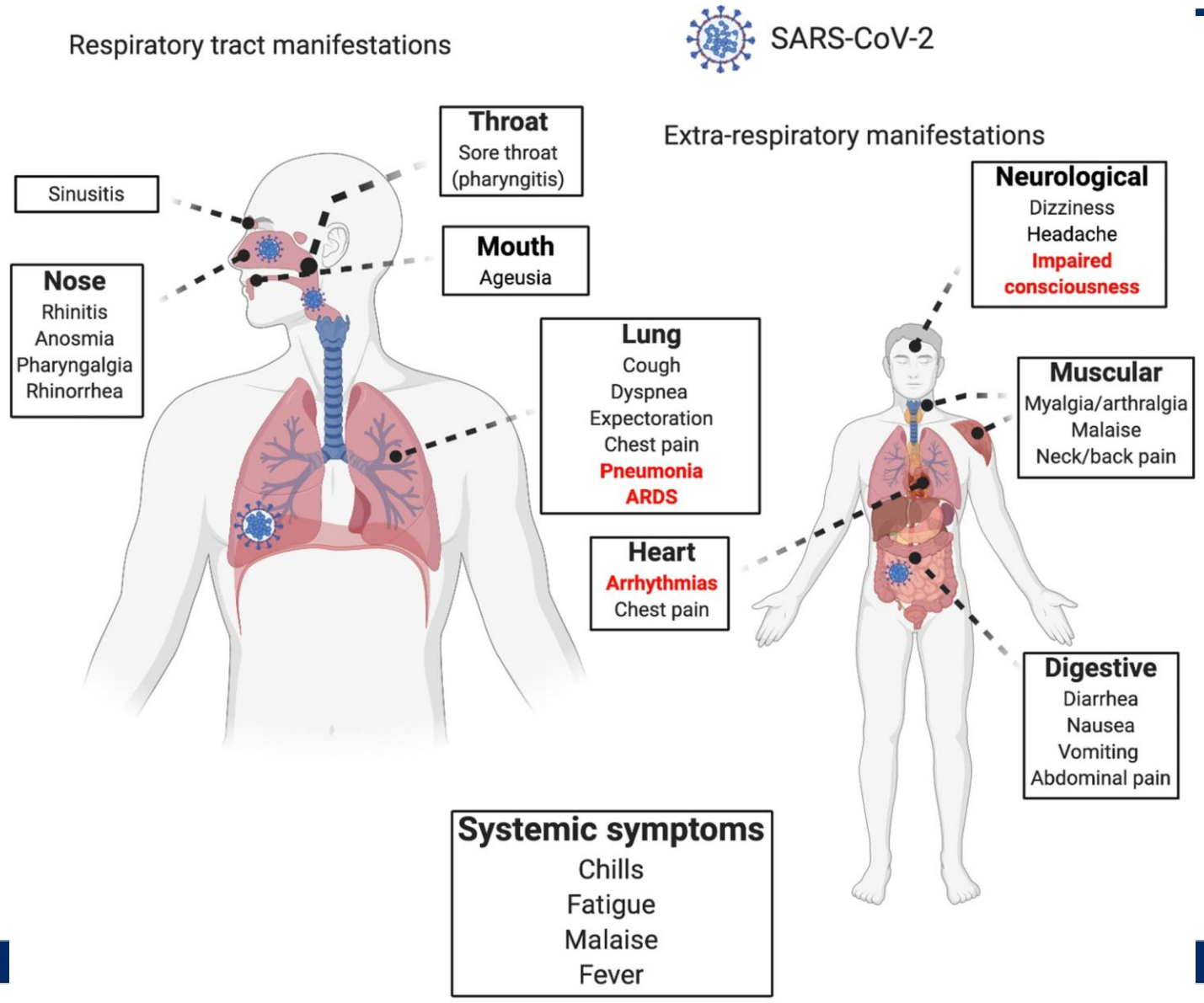
Core CRF

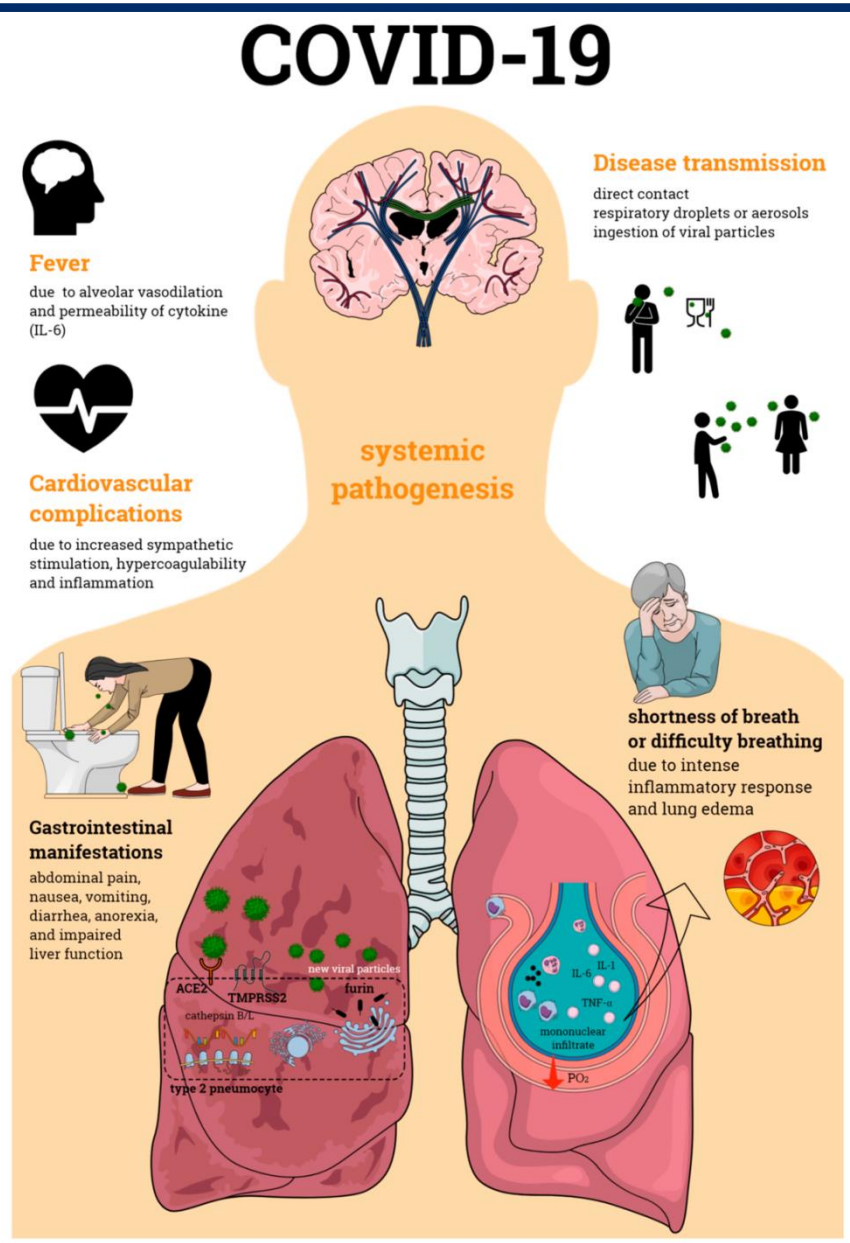
Arabic | Chinese | English | French | Russian | Spanish

Pregnancy CRF

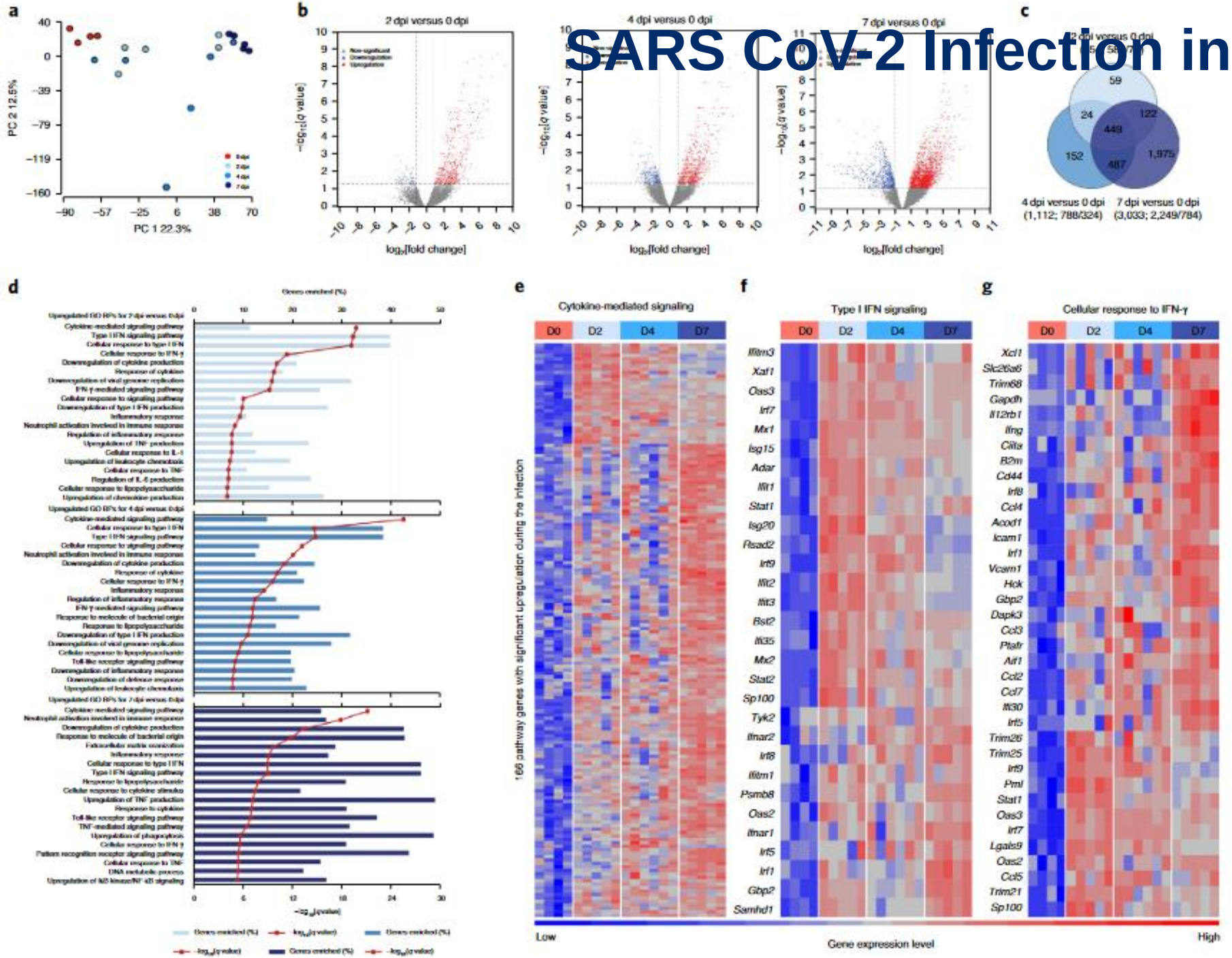
Arabic |Chinese | English | French | Russian | Spanish

COVID-19 Manifestations





SARS CoV-2 Infection in K18-hACE2 Mice



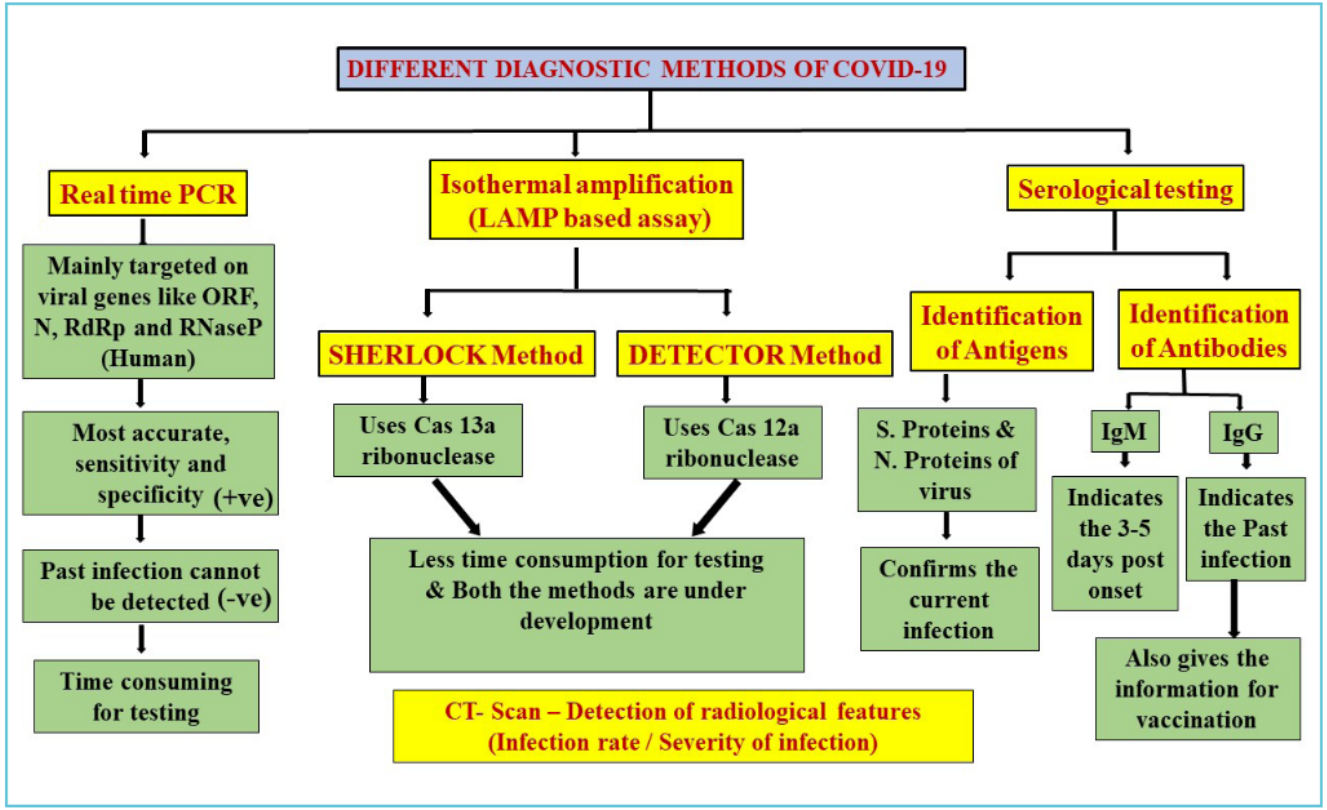
Distinct transcriptional signatures are associated with early and late immune responses to SARS-CoV-2 infection.

Detection Methods

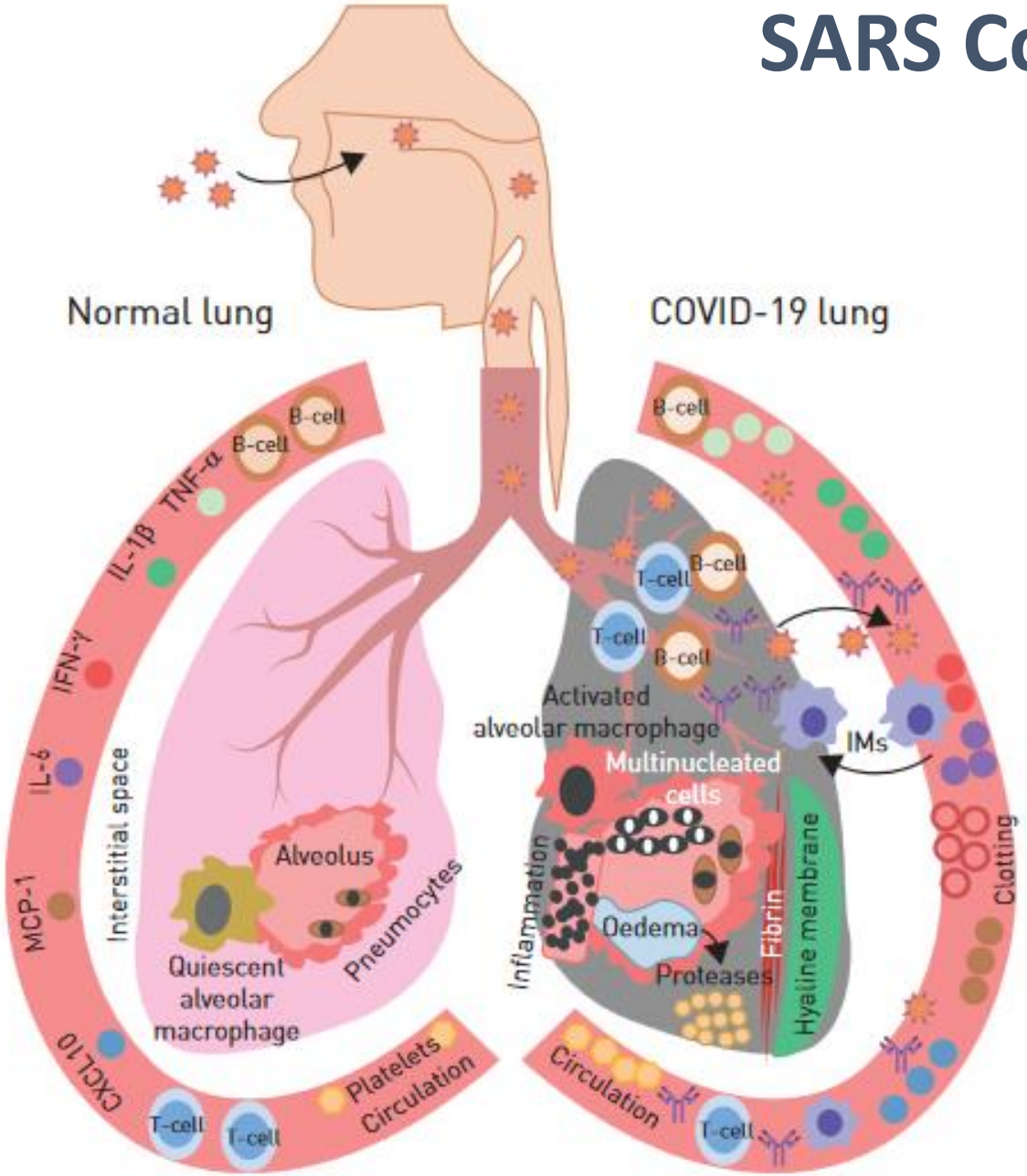
Table 1 Currently targeting different genes by the different country protocol as per WHO

Country	Institute	Targeting gene	References
China	China CDC	ORF 1ab and N genes	(4)
Hong Kong SAR	Hong Kong University	ORF 1b-nsp14, N genes	(5)
Germany	Charitè	RdRp, E, N genes	(6)
Japan	National Institute of Infectious Diseases	N gene	(7)
Thailand	National Institute of Health	N gene	(8)
USA	US CDC	Three targets in N gene (N1, N2, and N3) RP-RNase	(9)

Figure 1 Different diagnostic methods of COVID-19



SARS CoV-2: Excessive Lung Inflammation



Lymphopenia ↑
(CD4+ T, CD8+ T, NK and B-cell number) ↓

Lymphocyte activation and dysfunction
Cytokine production, TNF-α, INF-γ, IL-2 ↑

T-cells exhaustion markers
(PD-1, TIM3, NKG2A) ↑

Granulocytes
Neutrophil ↑ Eosinophil ↓ Basophils ↓

Monocytes ↓

Cytokine storm ↑
Inflammatory cytokines, IL-1β, IL-2, IL-6, IL-7, IL-8, IL-10; G-CSF, GM-CSF, IP10, MCP1, IFY-γ and TNF-α

Complement activation
(C3a, C5a, C5b–9) ↑

Antibodies
(IgM and IgG) ↑

COVID-19: Treatment

Table 1. Leading therapeutic agents against COVID-19, evaluated and described across common parameters

Drug	Parameters	Details
Azithromycin	Status/Remarks	No improvement on clinical outcomes, but no significant increase in detrimental side-effects either
	Drug type/ Original purpose	Antibiotic
	Mode of Administration	Oral/Intravenous
	Mechanism of Action	Inhibits mRNA translation by binding to 50s subunit of bacterial ribosome
	References	Furtado *et al.* (2020), Oldenburg and Doan (2020)
Baricitinib	Status/Remarks	Improvement in patient status observed, no adverse side-effects reported. Currently in phase III clinical trials conducted by Eli Lilly and Co
	Drug type/ Original purpose	For rheumatoid arthritis treatment
	Mode of Administration	Oral
	Mechanism of Action	Janus kinase inhibitor. Shows anti-inflammatory activity
	References	Cantini *et al.* (2020)
CD24Fc	Status/Remarks	In phase III clinical trials. Preliminary results suggest effective management of COVID-associated symptoms
	Drug type/ Original purpose	nonpolymorphic regions of CD24 attached to the Fc region of human IgG1
	Mode of Administration	Intravenous
	Mechanism of Action	Immunomodulator, tempers inflammatory responses
	References	OncoImmune (2020)
Colchicine	Status/Remarks	Has been hypothesized to address inflamatory responses in COVID-19 infection, but concerns regarding adverse side-effects have been raised. Currently under clinical trial
	Drug type/ Original purpose	Anti-gout agent
	Mode of Administration	Oral
	Mechanism of Action	Inhibits microtubule polymerization, proinflammatory responses, neutrophil migration, and mitosis
	References	Cumhur Cure *et al.* (2020), Dalili (2020)
Dexamethasone	Status/Remarks	Shown to lower mortality rate in a recent trial, currently being provisionally approved for patient treatment in certain regions. May be effective in critically ill patients
	Drug type/ Original purpose	Corticosteroid
	Mode of Administration	Oral/Intravenous/Intramuscular
	Mechanism of Action	Immunosuppresant. Shows anti-inflammatory effects
	References	Horby *et al.* (2020)
EIDD-2801	Status/Remarks	Potent antiviral activity observed in mouse models and primary human cells. Currently under phase 2 clinical trial
	Drug type/ Original purpose	Antiviral drug. Nucleoside derivative N4-hydroxycytidine
	Mode of Administration	Oral
	Mechanism of Action	Interferes with viral replication by introducing mutations
	References	Ridgeback Biotherapeutics (2020), Sheahan *et al.* (2020)

Table 1 (continued)

Drug	Parameters	Details
Favipiravir	Status/Remarks	Clinical studies show faster viral clearence and improvement in chest imaging. A recent clinical trial from India by Glenmark showed faster and more effective recovery rate
	Drug type/ Original purpose	Pyrazinecarboxamide derivative
	Mode of Administration	Oral/Intravenous
	Mechanism of Action	Inhibits the viral RNA-dependent RNA polymerase
	References	Glenmark (2020), Irvani (2020)
Hydroxychloroquine	Status/Remarks	Discontinued as a recommended drug for treatment. Clinical studies show no significant benefit for patients. Adverse cardiovascular effects have been reported. However, the study by Mehra *et al.*, claiming no significant benefits of HCQ administration, has since been withdrawn
	Drug type/ Original purpose	Chloroquine derivative. Antimalarial drug
	Mode of Administration	Oral
	Mechanism of Action	Increases lysosomal pH. Also dampens inflammatory response
	References	Chen *et al.* (2020c), Gautret *et al.* (2020), Li *et al.* (2020a, b, c, d, e, f), Mahevas *et al.* (2020), WHO (2020b)
Ivermectin	Status/Remarks	Emerging candidate against COVID-19. Initial concerns were raised over its high effective dosage concentration by Caly *et al.*, but this is being explored as a safer and more effective alternative to HCQ
	Drug type/ Original purpose	Avermectin derivative
	Mode of Administration	Oral/topical
	Mechanism of Action	Targets ligand-gated ion channels of invertebrate neural cells
	References	Caly *et al.* (2020), Gupta *et al.* (2020), Heidary and Gharebaghi (2020)
Lopinavir–ritonavir	Status/Remarks	Clinical studies have demonstrated no significant benefits of lipinavir-ritonavir in COVID-19 affected patients
	Drug type/ Original purpose	Antiretroviral drug
	Mode of Administration	Oral
	Mechanism of Action	HIV protease inhibitor
	References	Cao *et al.* (2020b), WHO (2020b)
Remdesivir	Status/Remarks	Significant benefits from administration of this drug are doubtful. Clinical studies have reported a marginal improvement in critically ill patients
	Drug type/ Original purpose	Nucleoside analog
	Mode of Administration	Intravenous
	Mechanism of Action	Inhibits the viral RNA-dependent RNA polymerase
	References	Grein *et al.* (2020), Wang *et al.* (2020a, b)

COVID-19: Treatment

NEWS

Inhaled interferon beta therapy shows promise in COVID-19 trial

SNG001 diminished the risk of COVID-19 patients developing severe symptoms, reduced breathlessness and improved recovery rates.

By Hannah Balfour (European Pharmaceutical Review)

20 July 2020

No comments yet

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