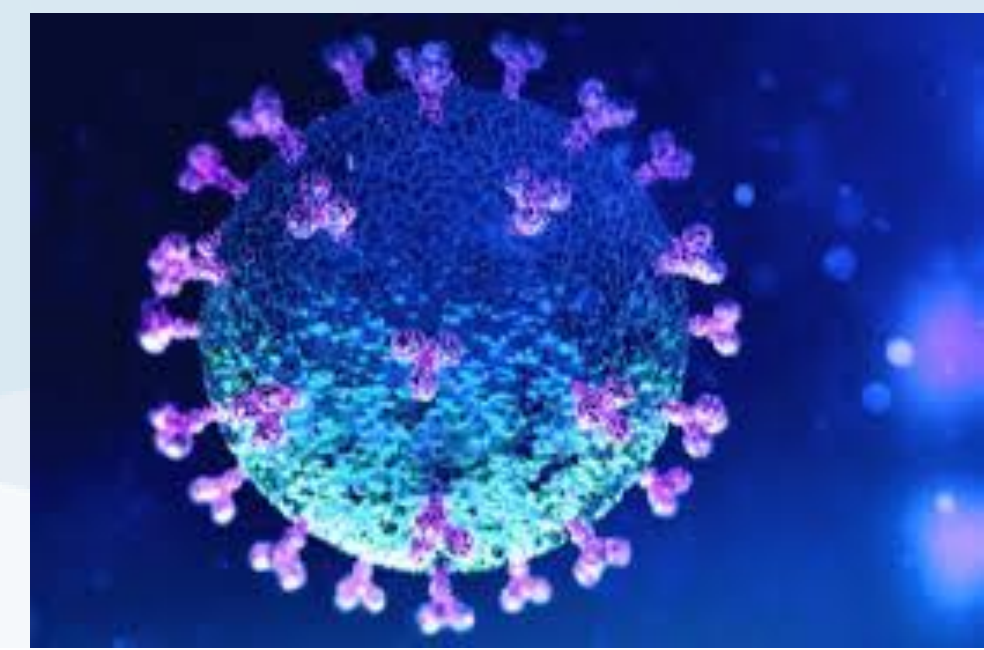


3D Human airway epithelial models
to study SARS-CoV-2 pathogenesis
and to discover antivirals

Samuel Constant, Ph.D., CEO
samuel.constant@epithelix.com

ASCCT/ESTIV, 17/03/2022



December 2019

- ✓ First cases recognized

January 2020

- ✓ Genome revealed + PCR diagnostic published

March 2020

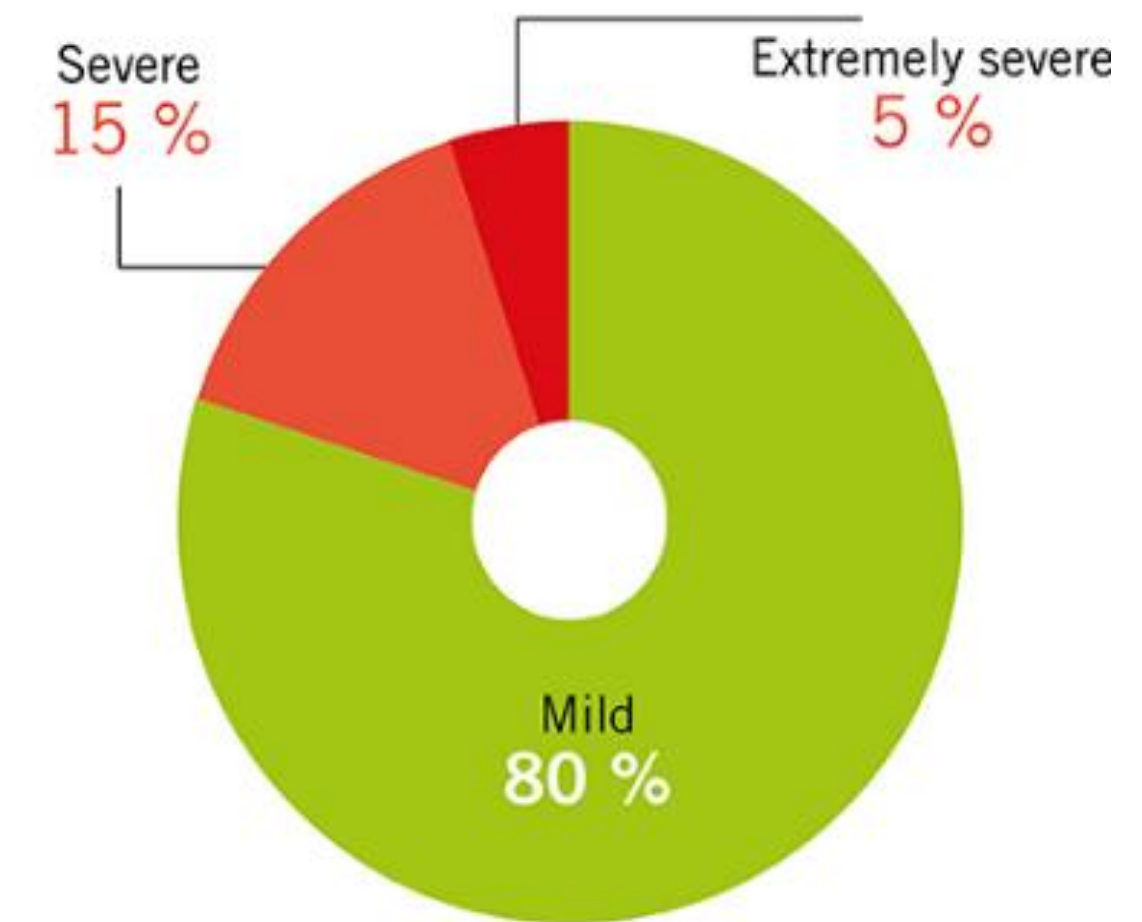
- ✓ Antibody tests

May 2020

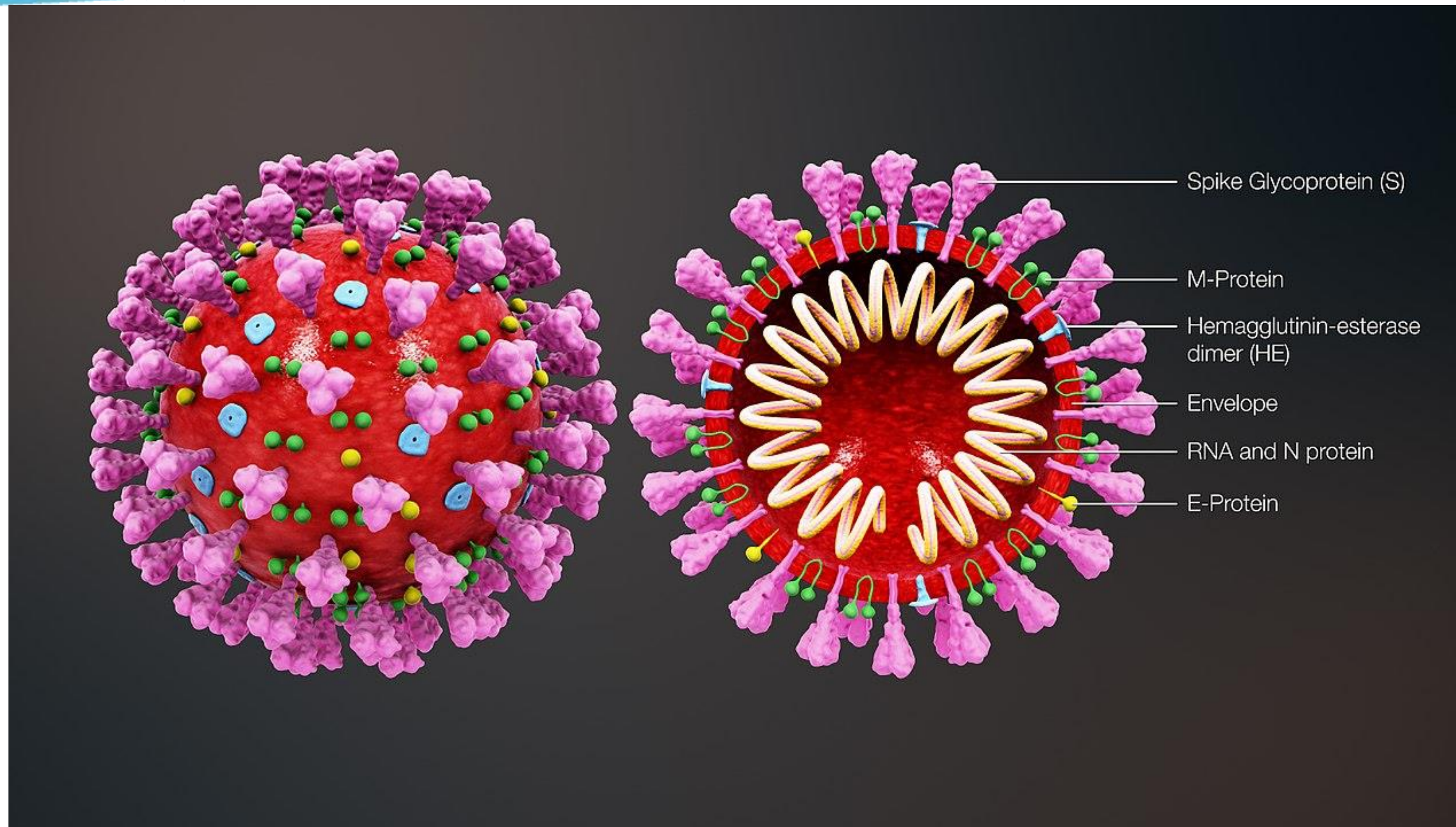
- ✓ First Antiviral Authorization (FDA) for emergency use (Remdesivir)

March 17th 2022

- ✓ 5 vaccines authorized in the EU (EMA)
- ✓ 2 Antivirals authorized: Paxlovid (FDA and EMA) and Molnupiravir (FDA)
- ✓ > 400'000 research articles on COVID-19 (WHO database)
- ✓ > 457 M Cases reported
- ✓ > 6 M deaths (1.3 % death rate)

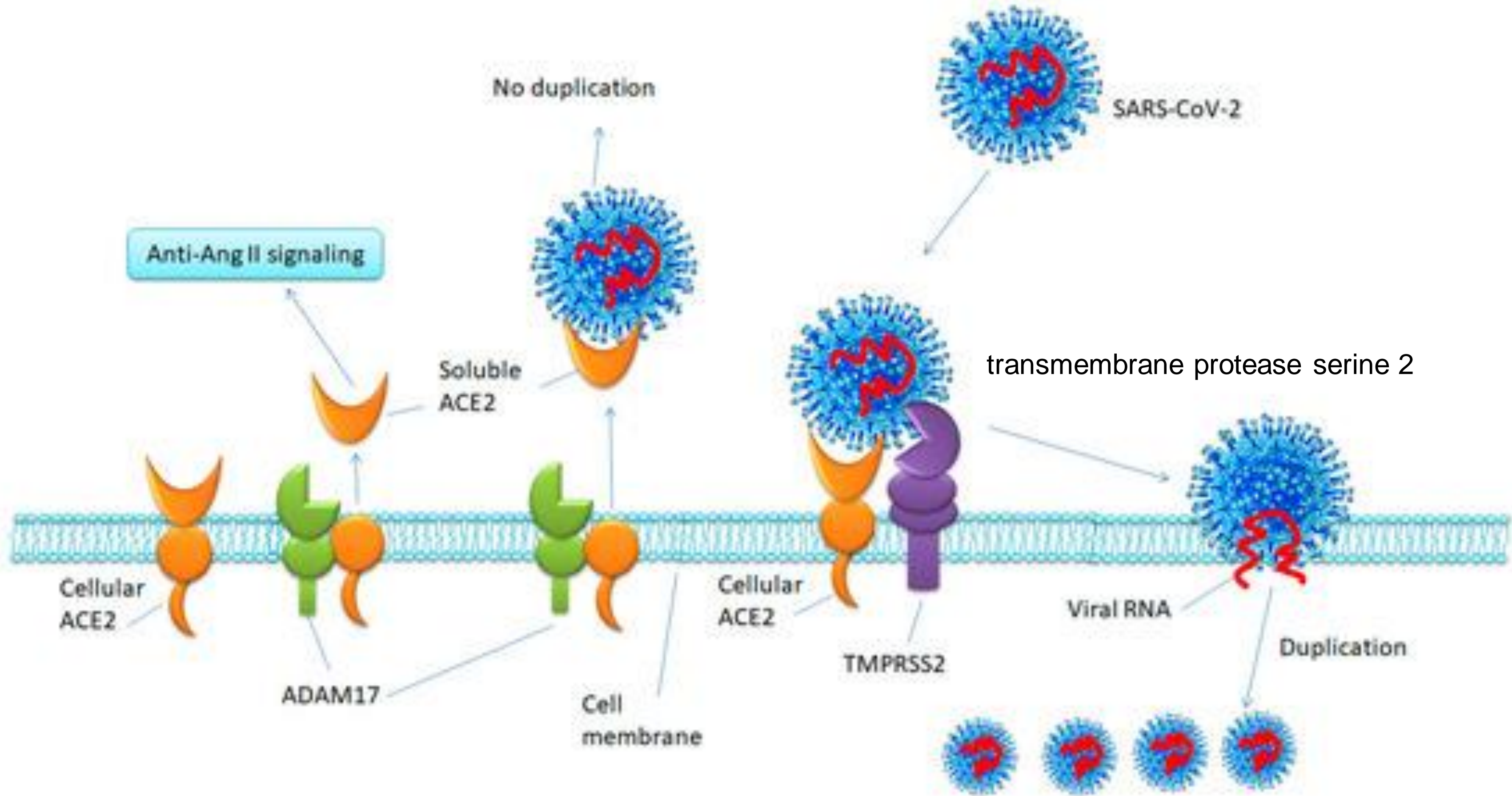


SARS-CoV-2 Structure

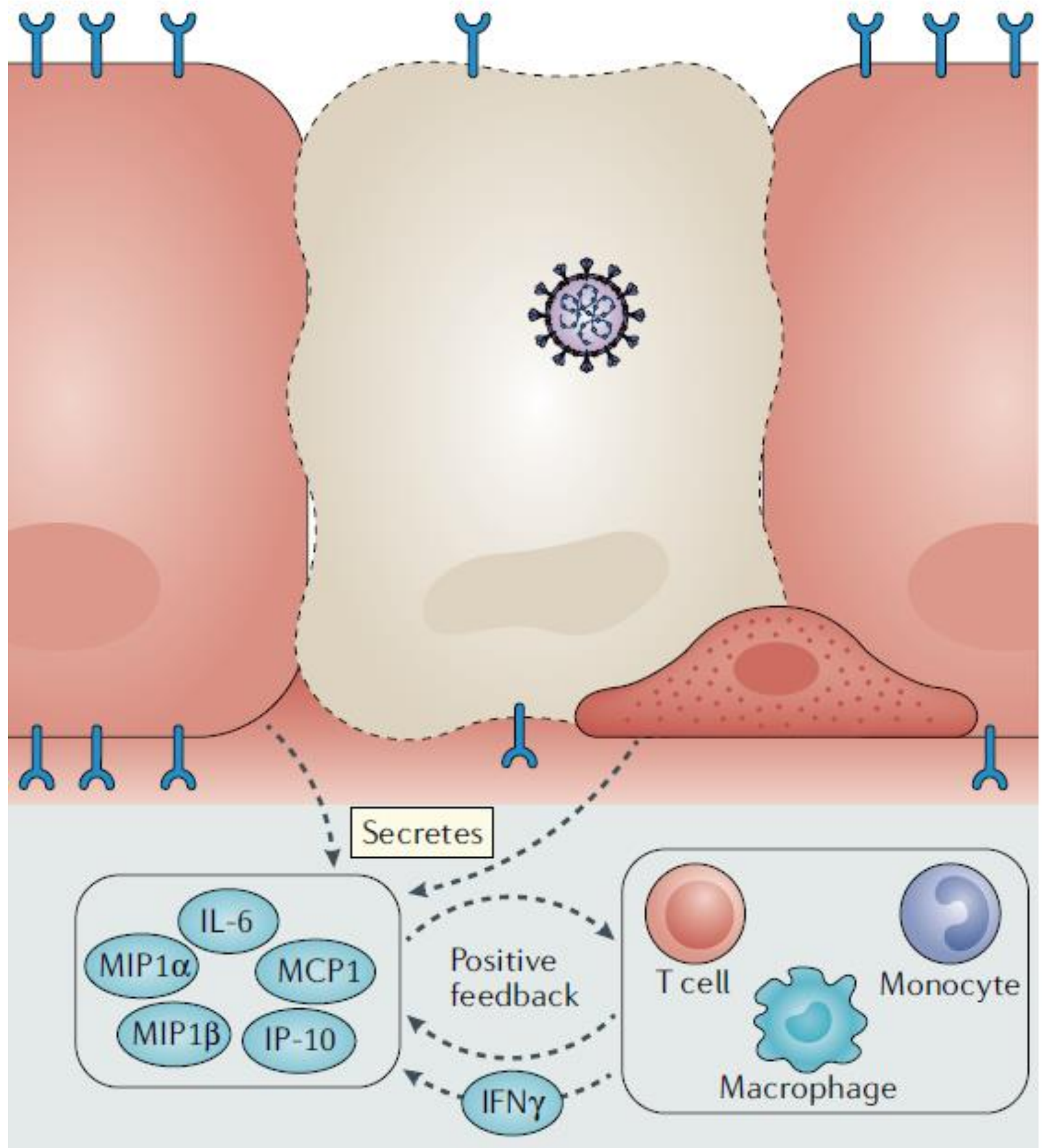
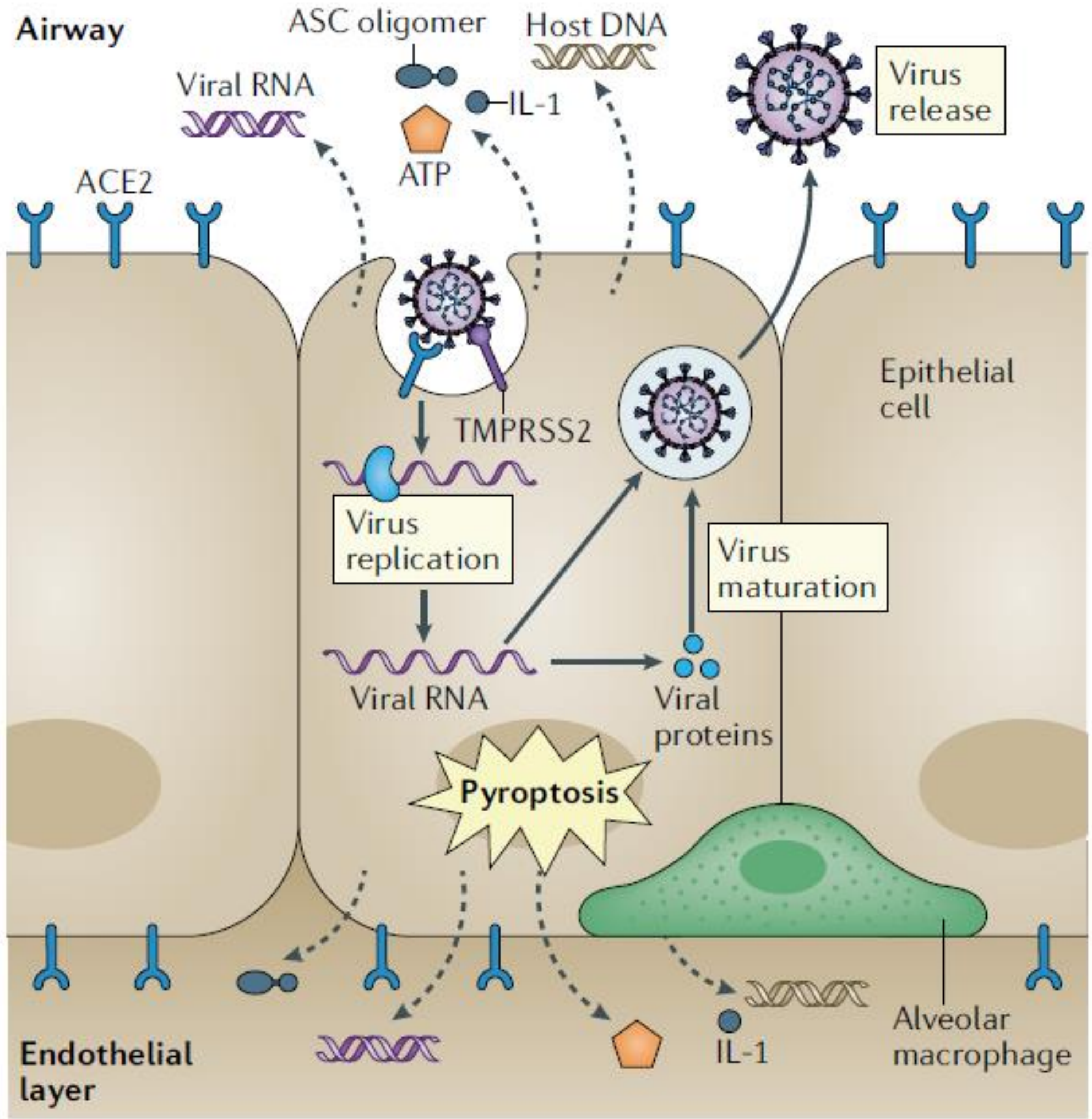


- Virion diameter : 50–200 nanometers
- S, E and M proteins form the viral envelope
- N protein holds the RNA genome
- Spike S protein allow the virus to attach to and fuse with the membrane of a host cell

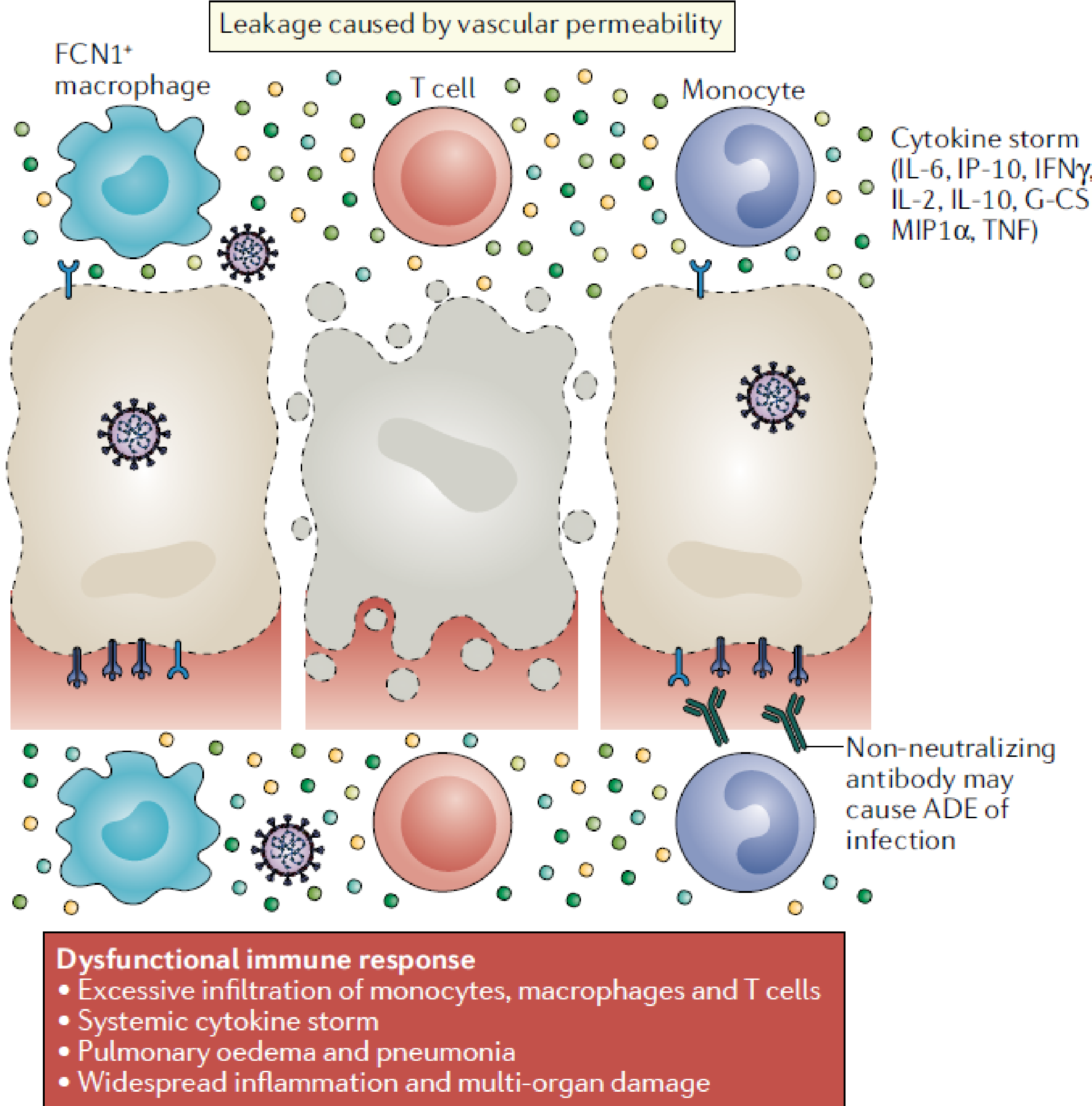
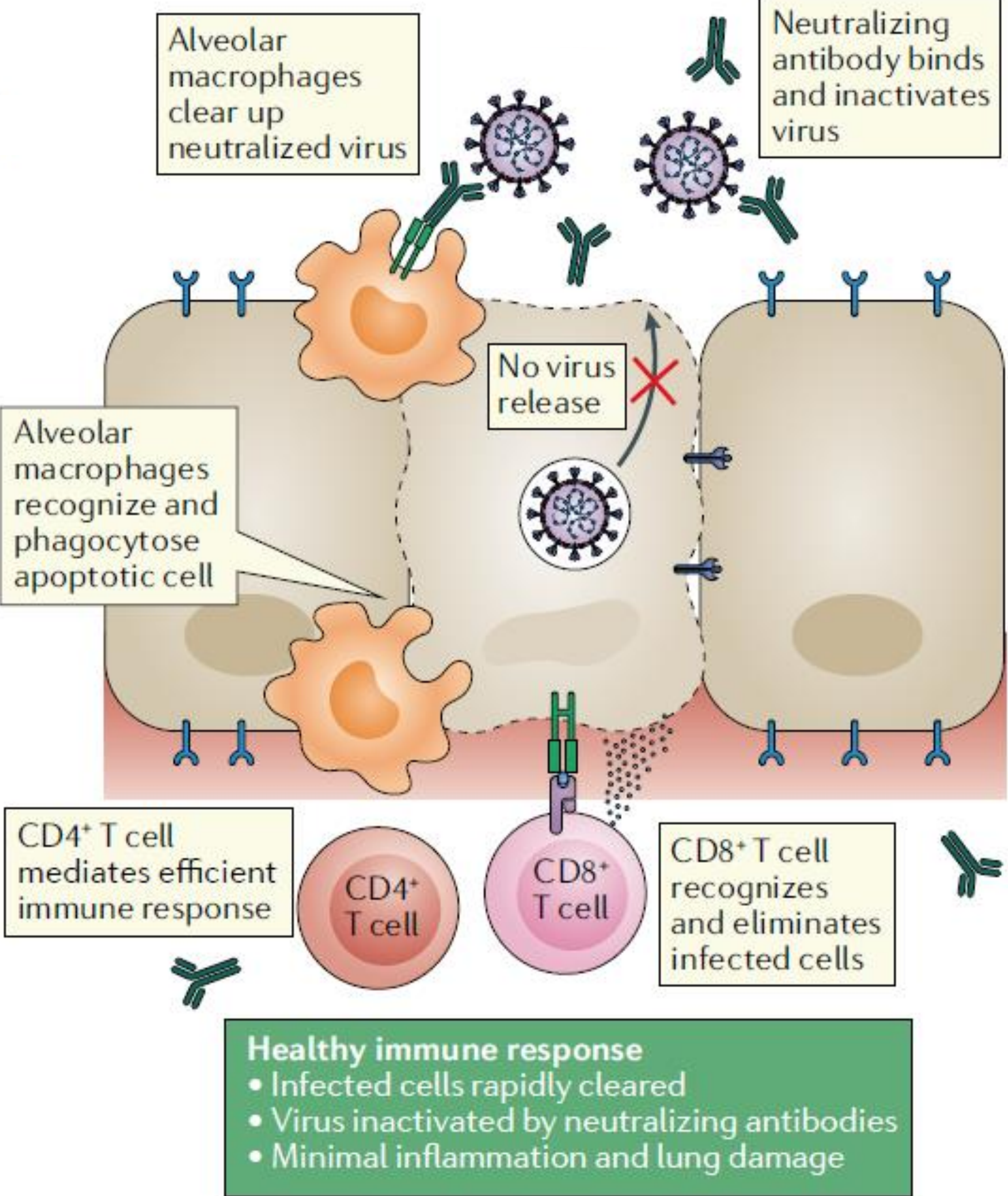
The virus entry: Angiotensin-converting Enzyme-2 (ACE2) receptor



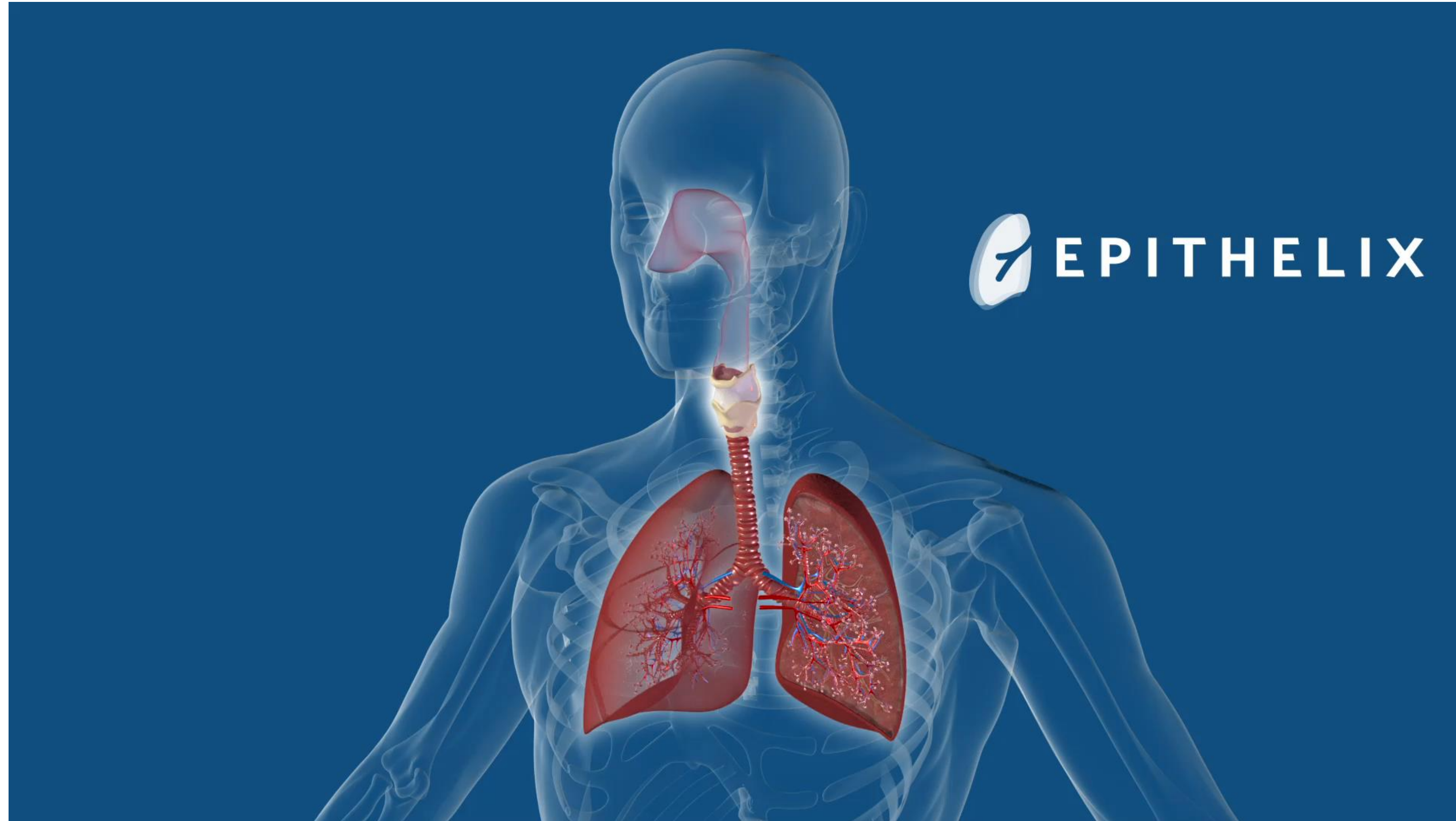
Chronology of events during SARS-CoV-2 infection



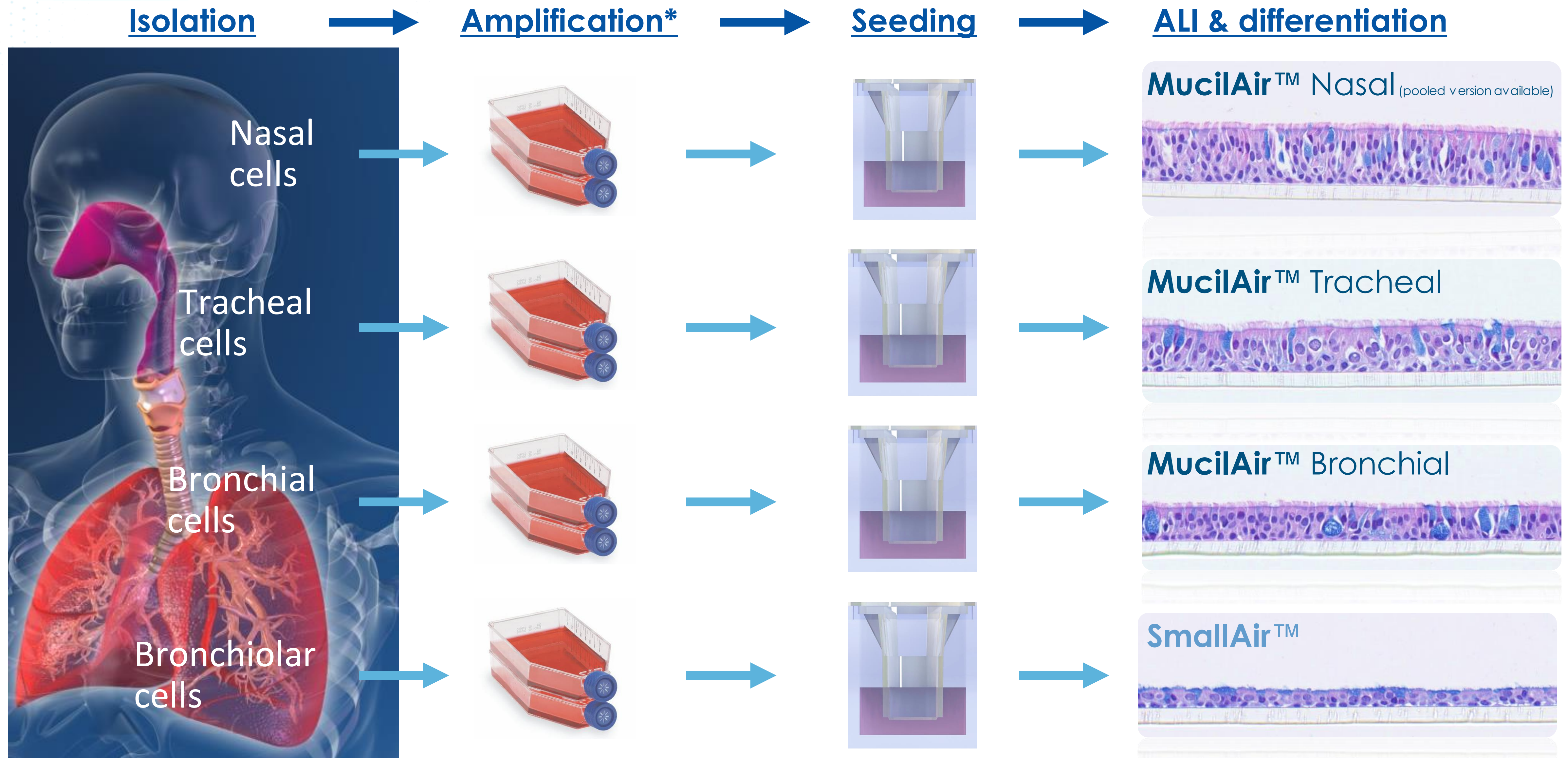
Chronology of events during SARS-CoV-2 infection



In vitro 3D human airway epithelia

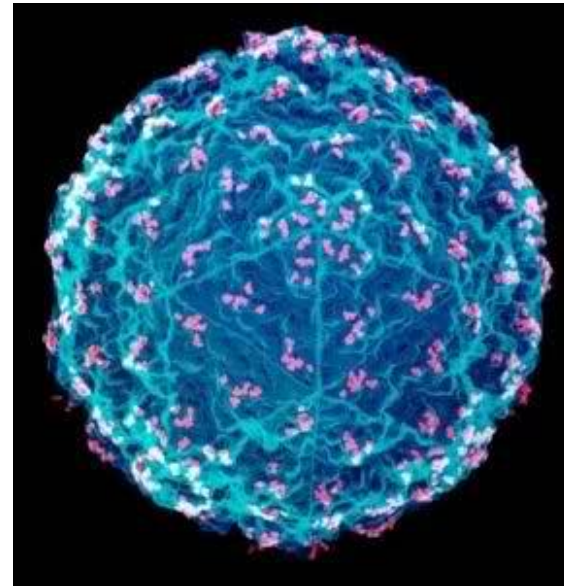


MucilAir™ & SmallAir™ : Long shelf life in vitro Airway models



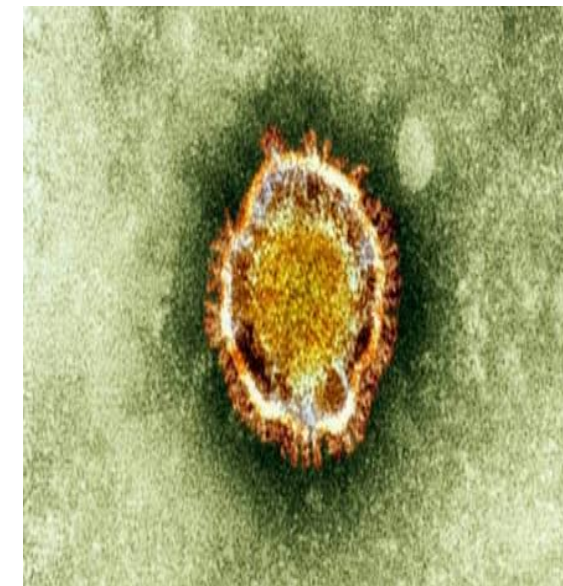
*Only one amplification (P1). Storage of isolated cells in liquid Nitrogen

In vitro Antiviral Testing using MucilAir™ and SmallAir™



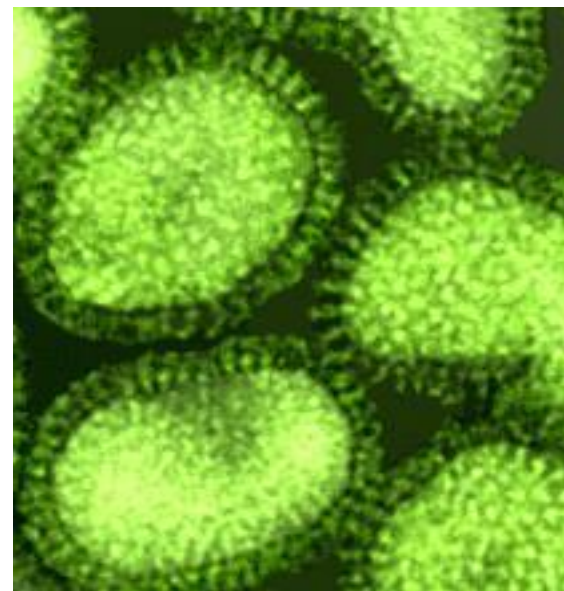
Rhinovirus

HRV-A16
HRV-B14
HRV-C15



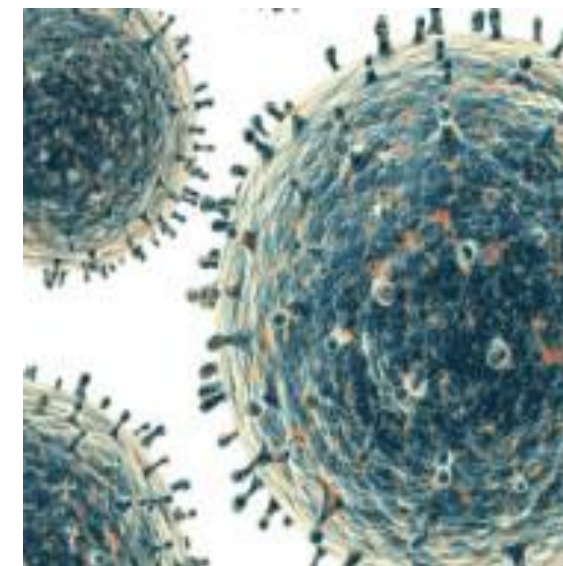
Coronavirus

OC 43
SARS-CoV-2



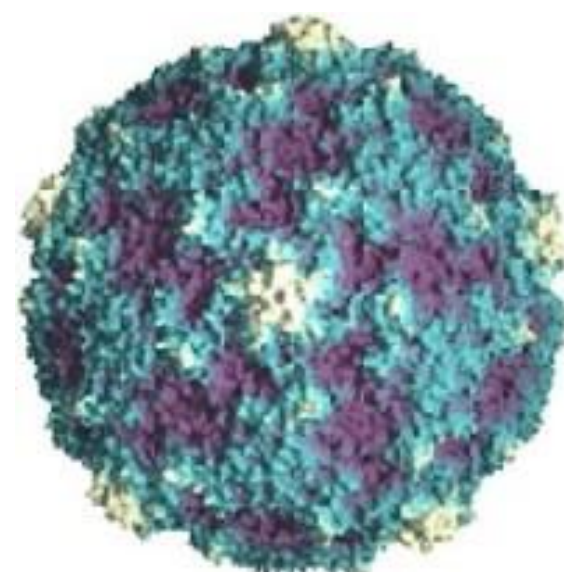
Influenza

Influenza A
(H1N1 and H3N2)
Influenza B



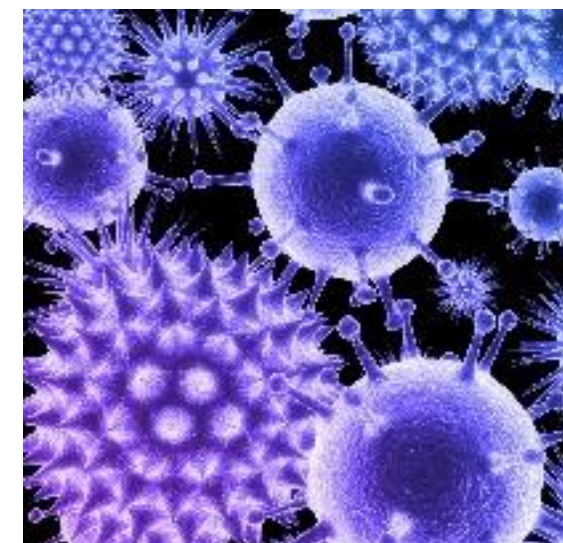
Respiratory Syncytial Virus

RSV-A
RSV-B



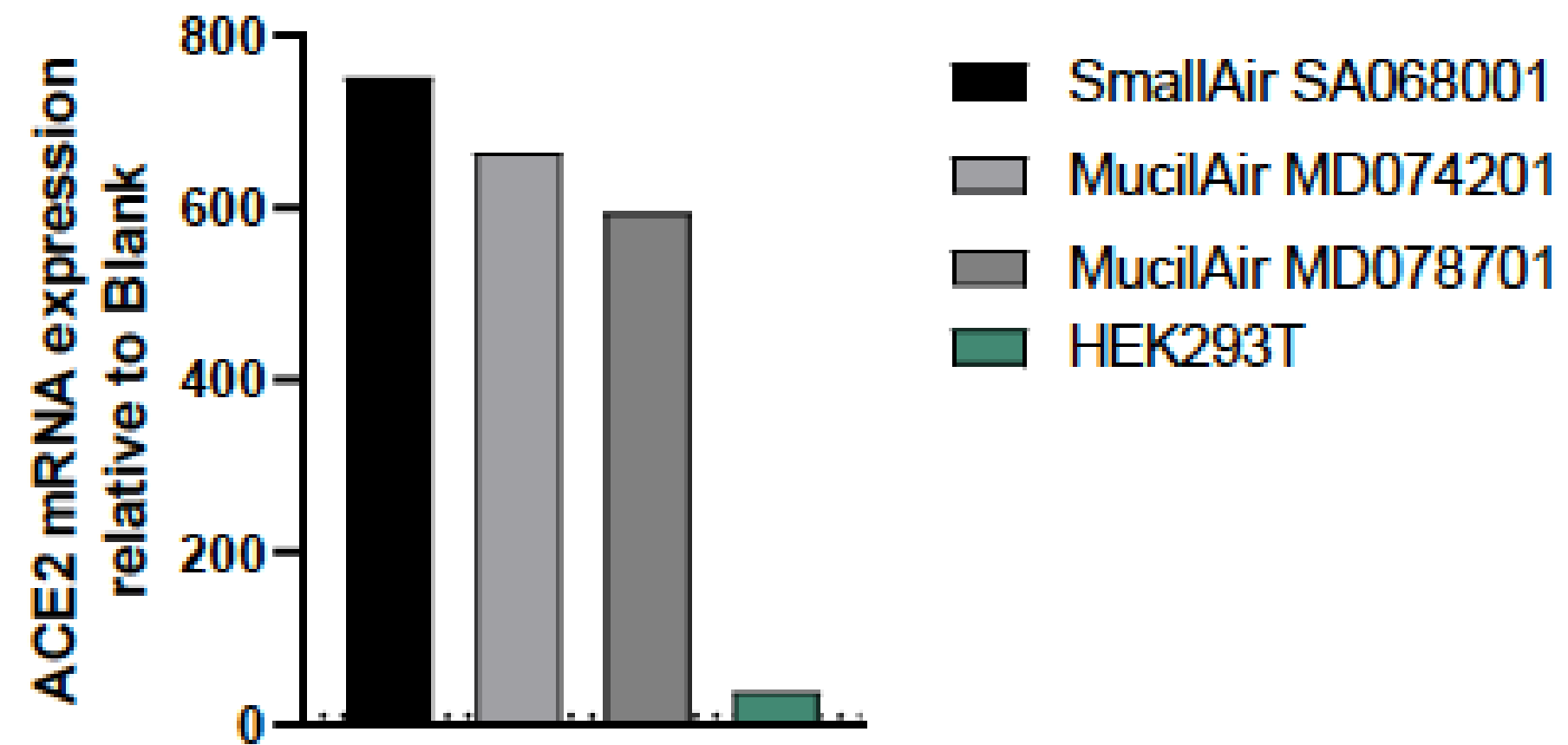
Respiratory Enterovirus

EV-68



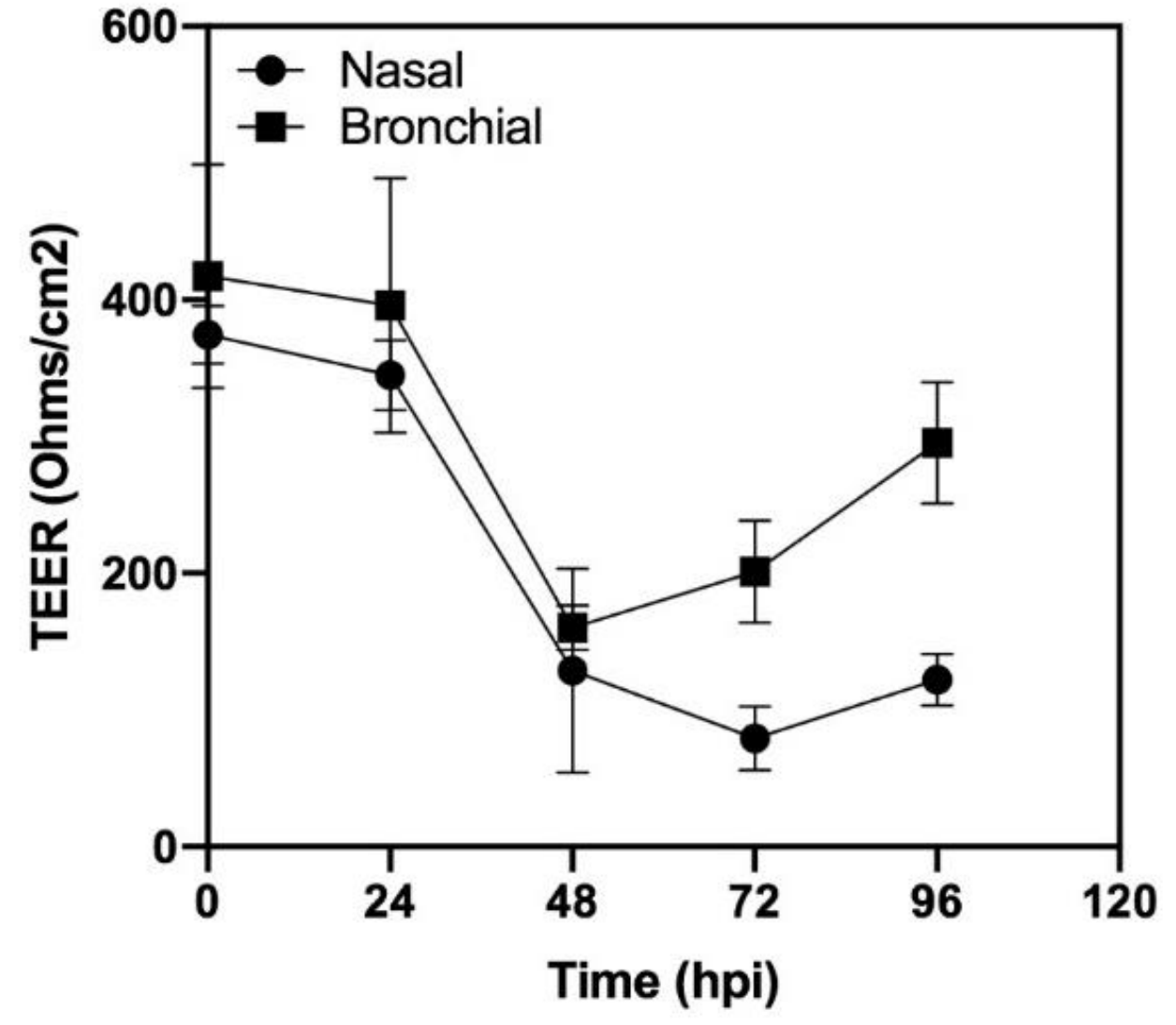
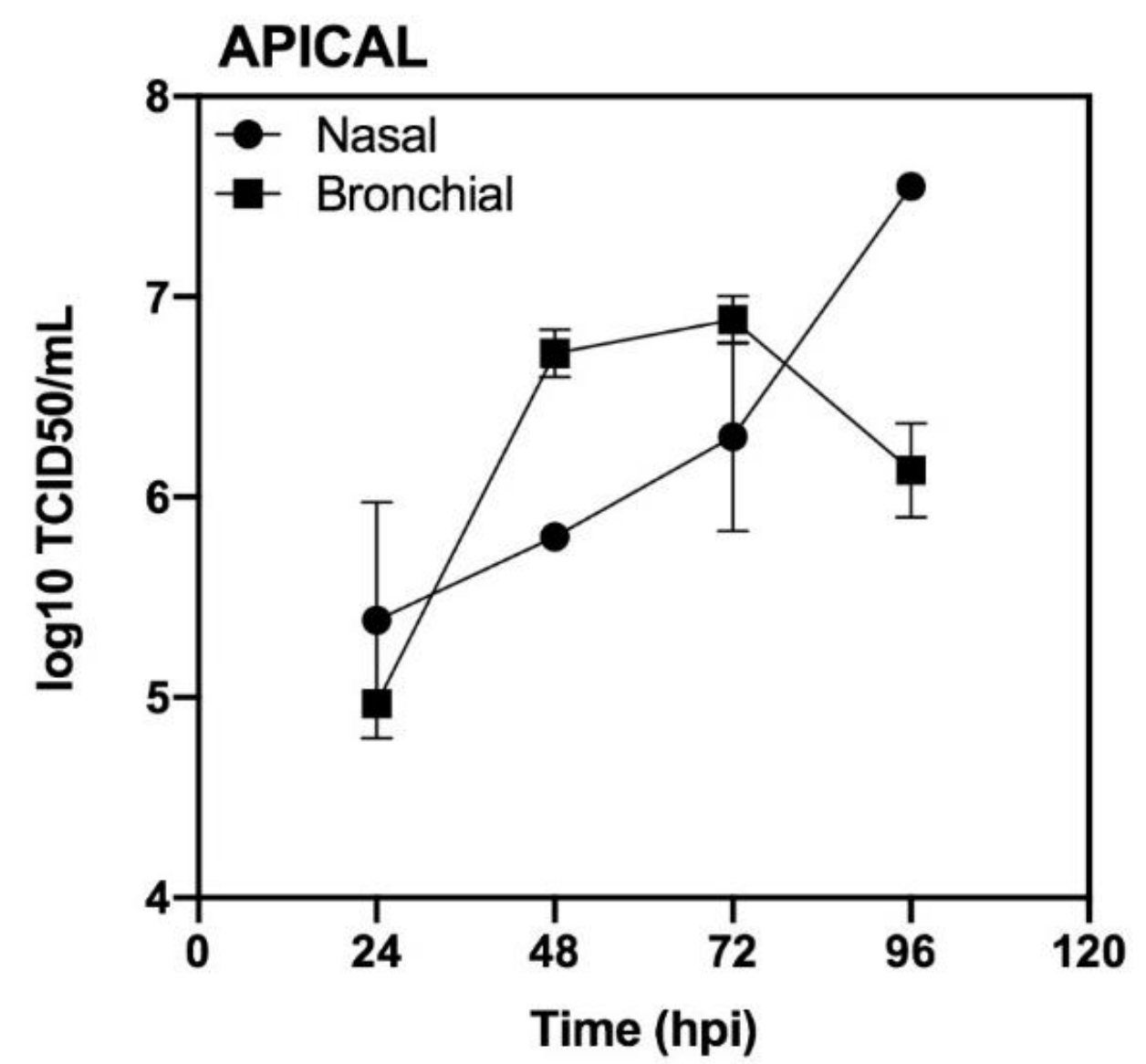
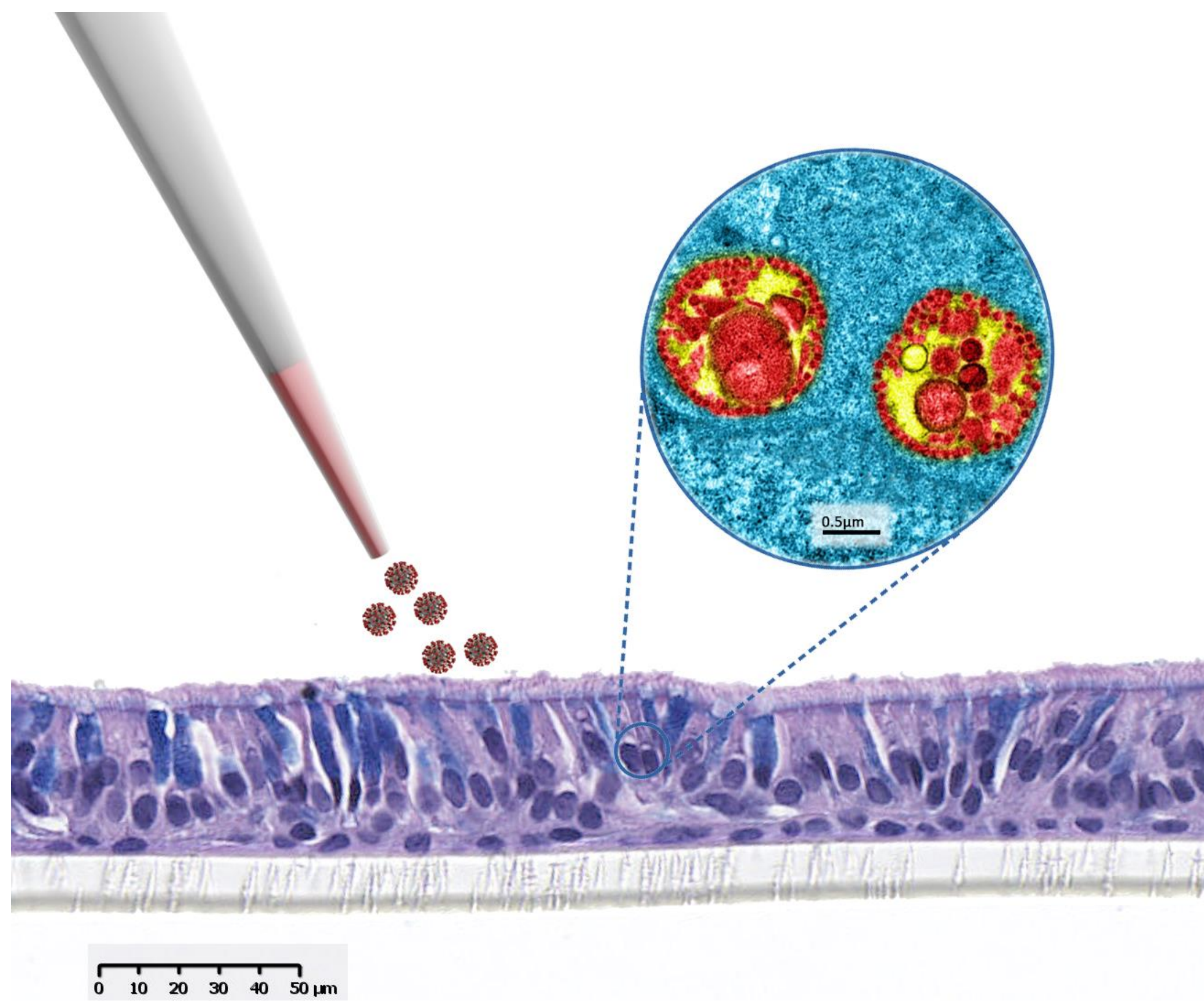
Others

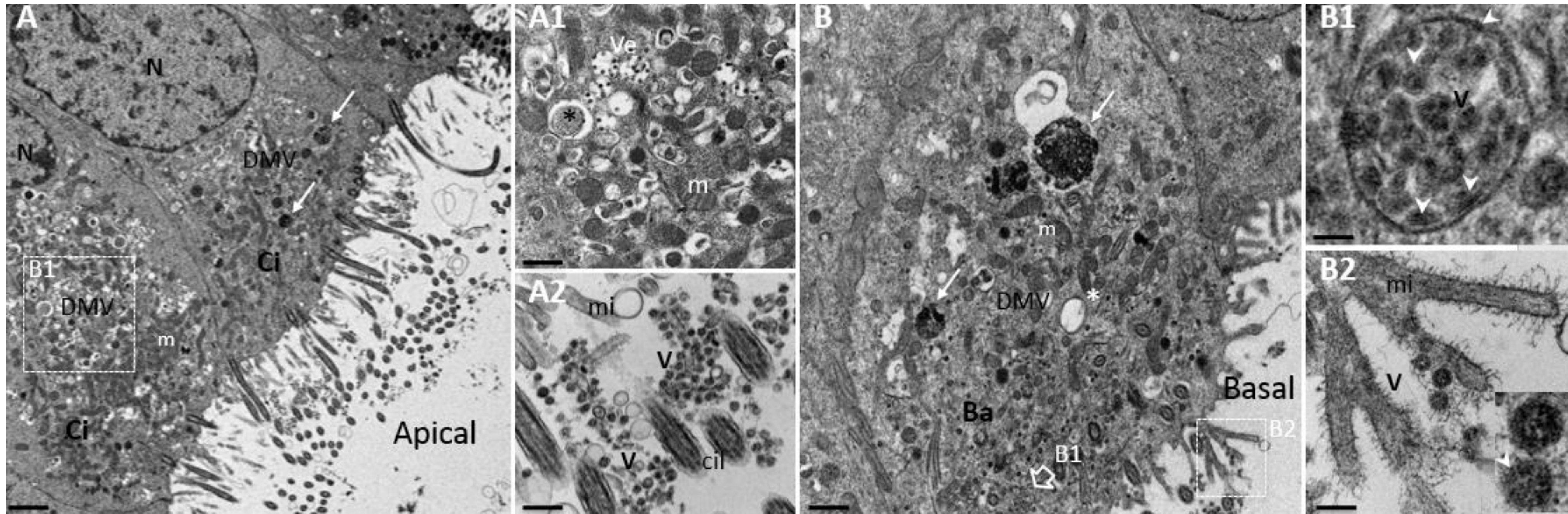
Metapneumovirus
Parainfluenza virus 3



- SmallAir™ SA068001: Small-Airways
- MucilAir™ MD074201: Nasal
- MucilAir™ MD078701: Bronchial

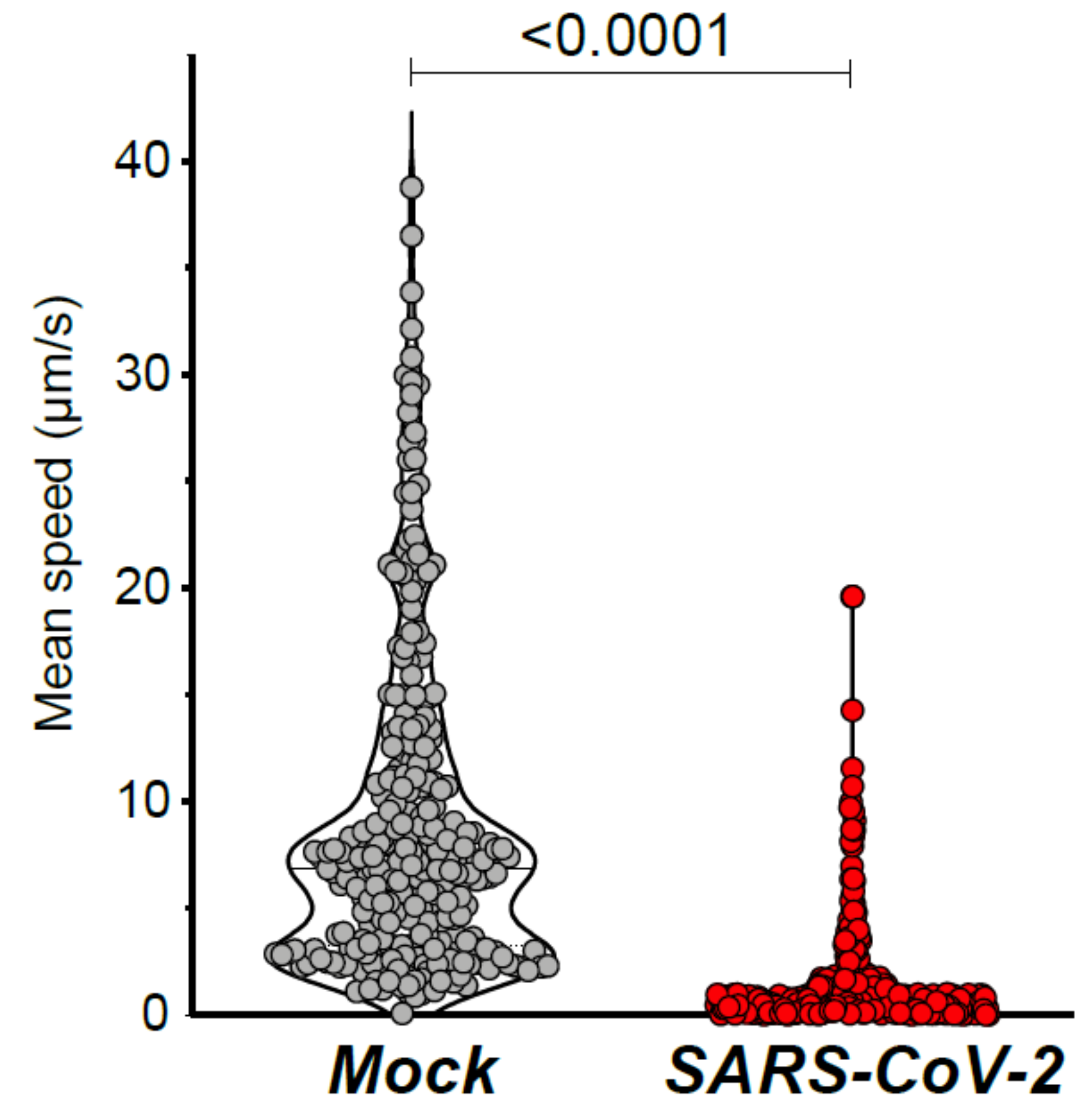
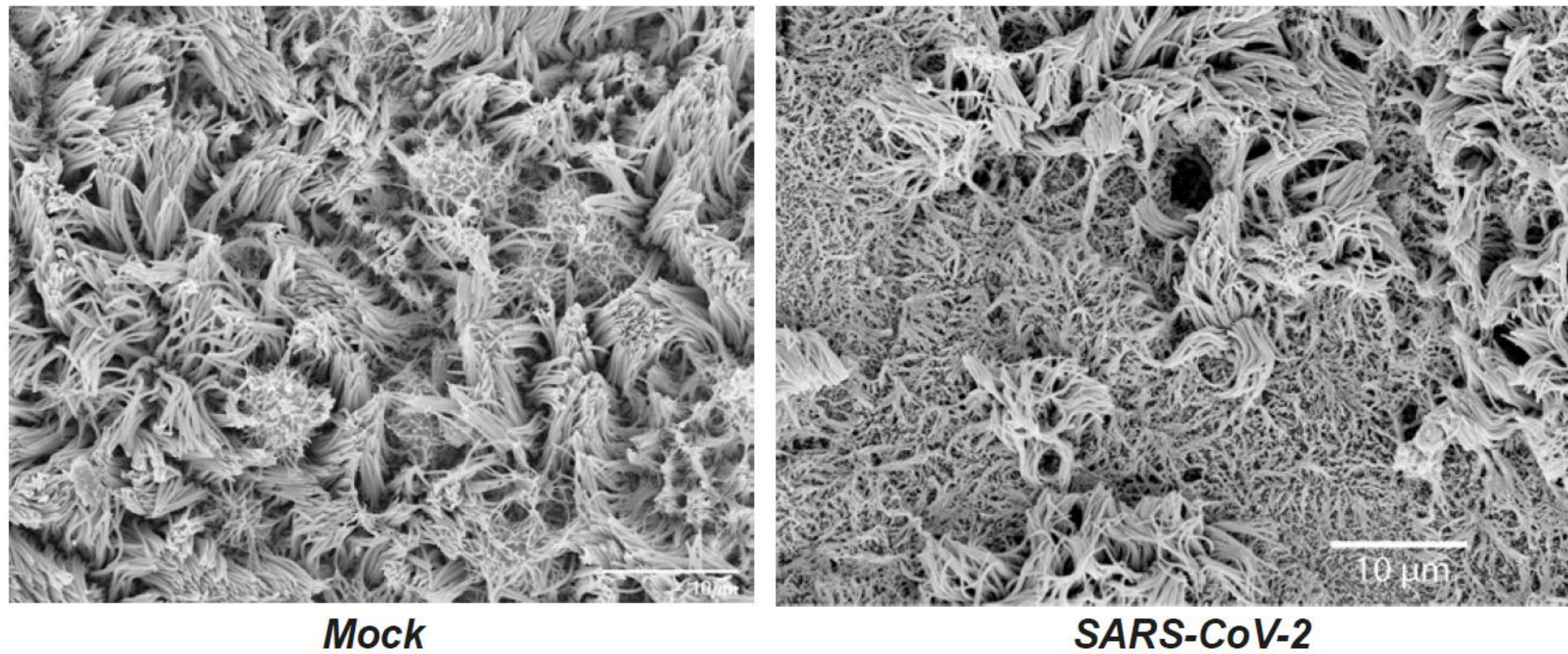
MucilAir™ and SmallAir™ express ACE2 mRNA at high levels





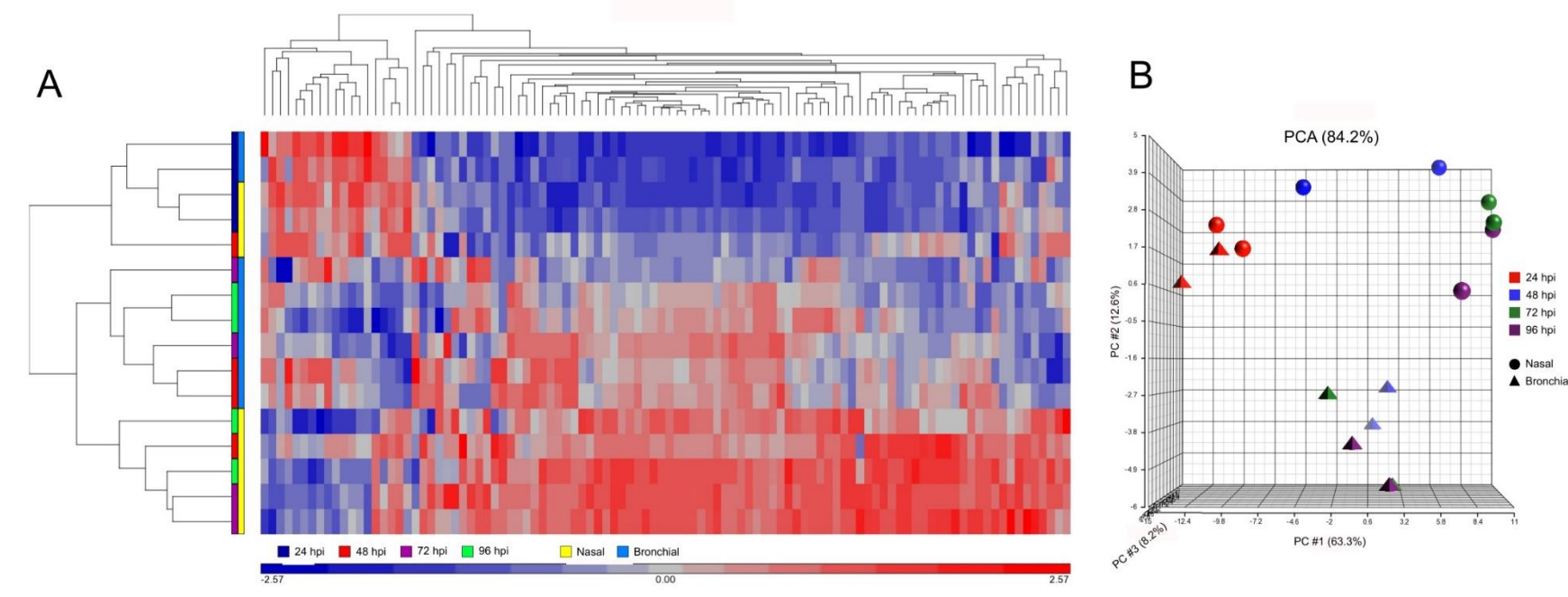
SARS-CoV-2 infects mainly ciliated and goblet cells

SARS-CoV-2 impairs cilia function

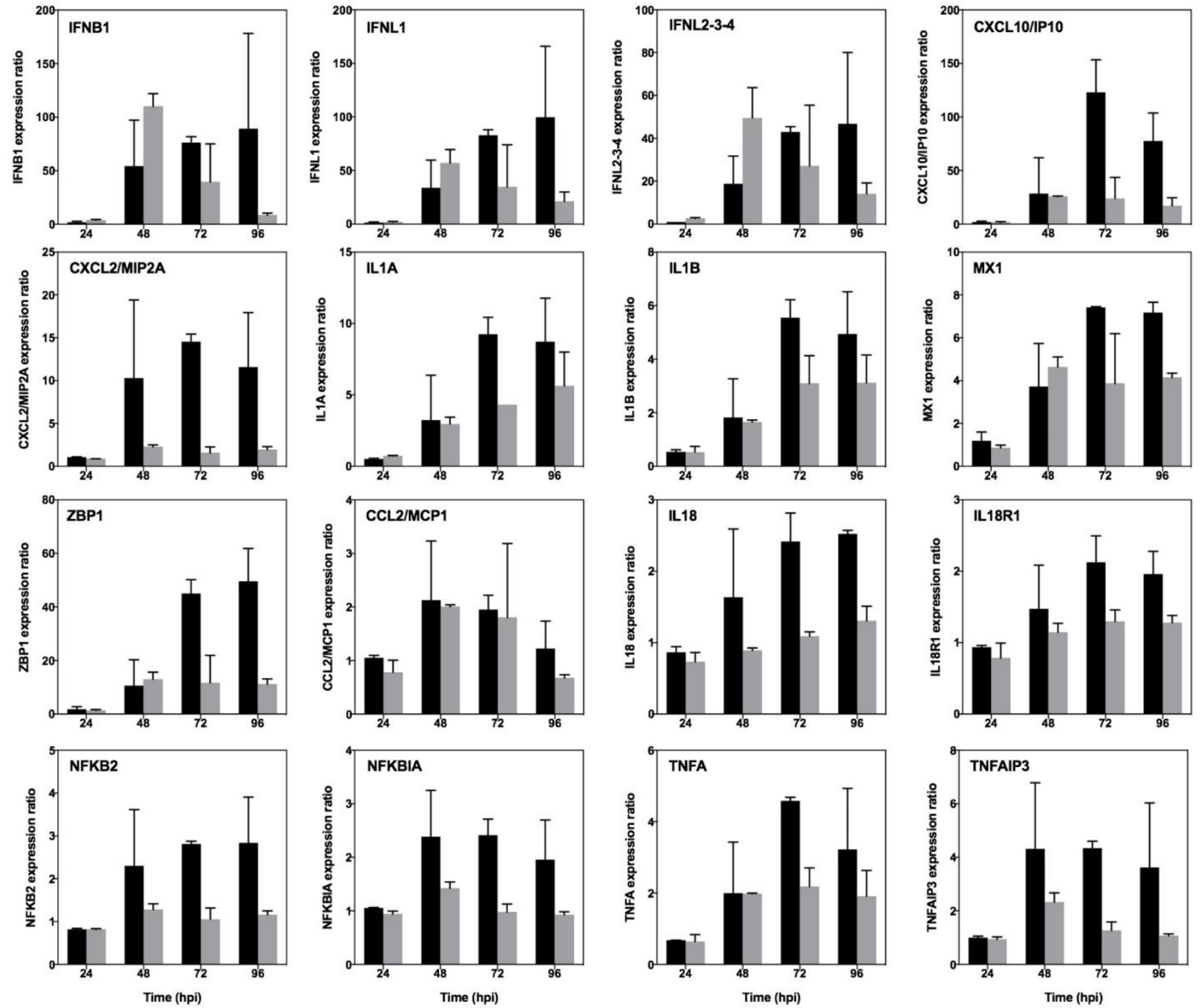


SARS-CoV-2 impairs mucociliary clearance on MucilAir™

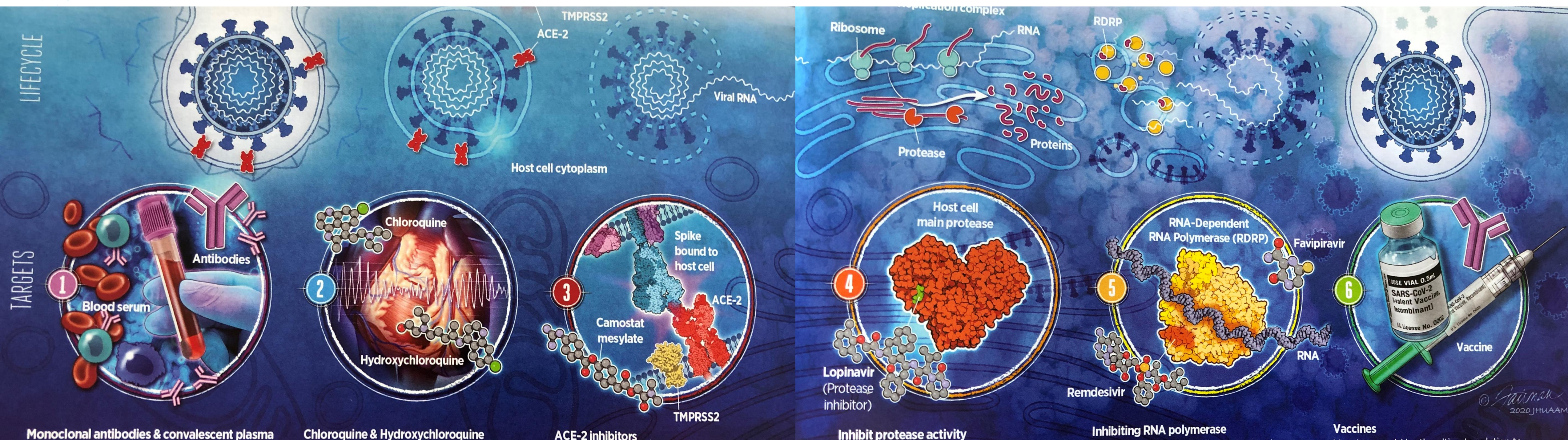
Innate immune transcriptional signature induced by SARS-CoV-2 on MucilAir™

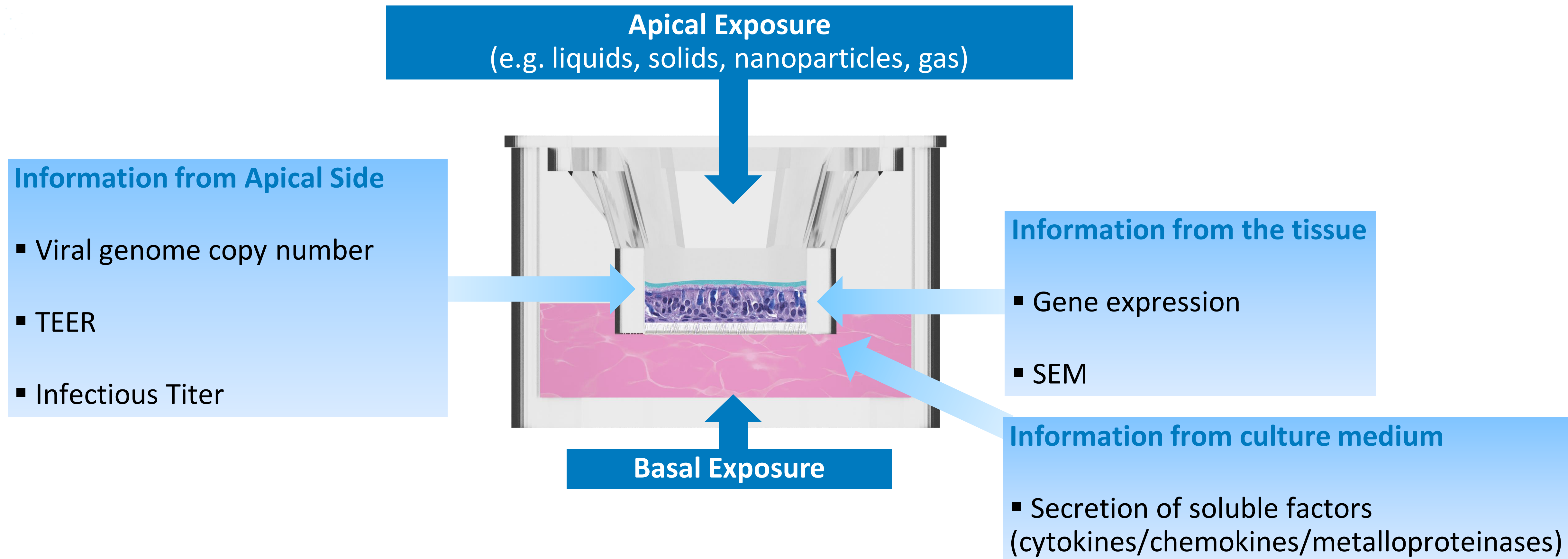


Strong upregulation of type I and III interferons and genes associated with NF- κ B and TNF- α is observed



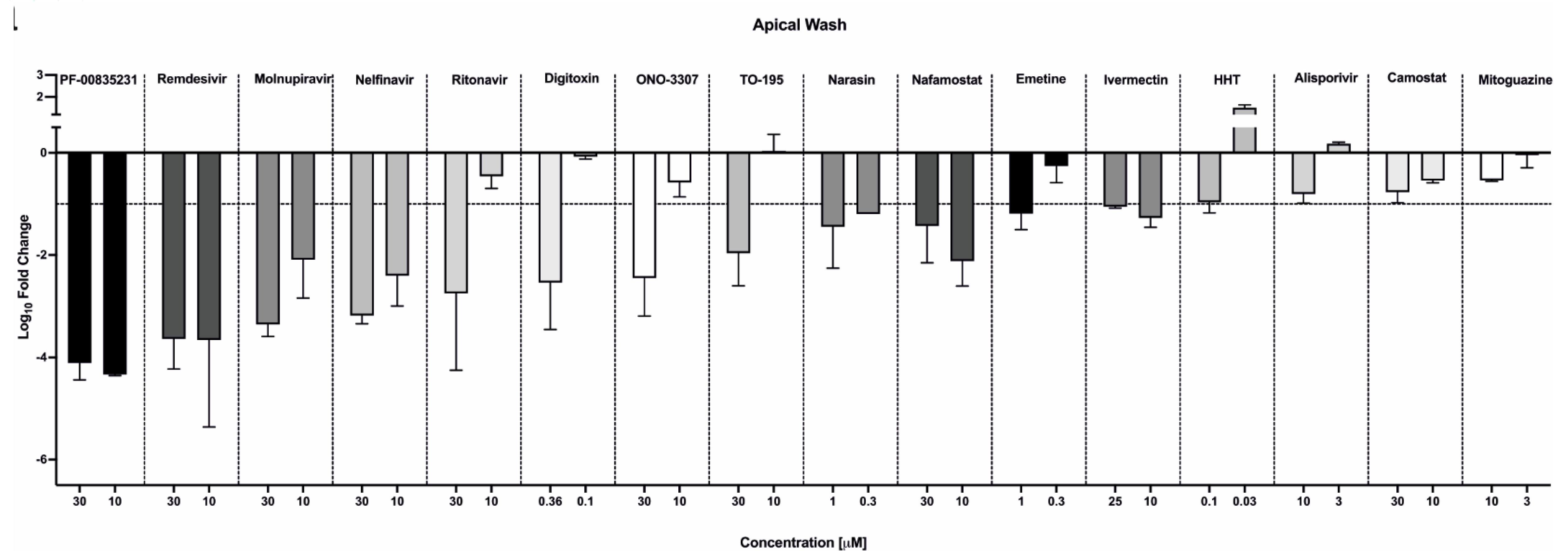
Current research strategies to stop SARS-CoV-2 infection





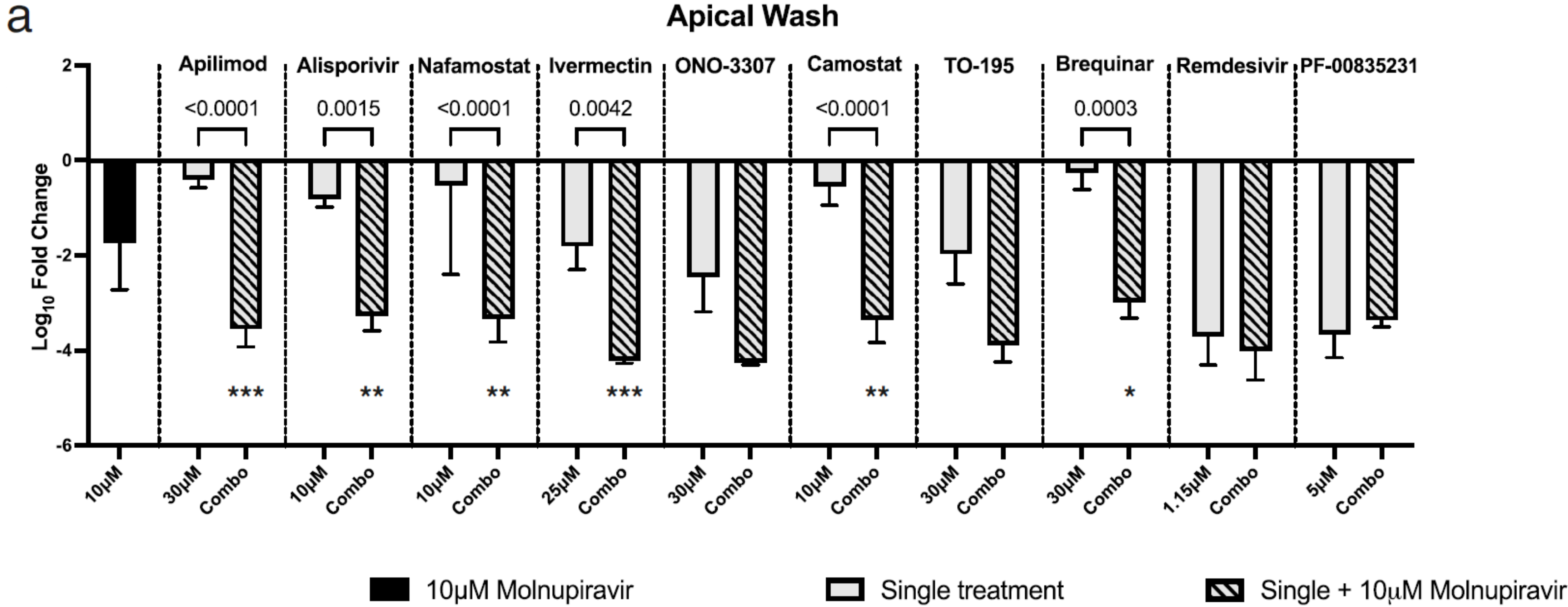
Aerosol therapies or systemic delivery can be easily studied

Antiviral evaluation of novel therapies against SARS-CoV-2 on MucilAir™



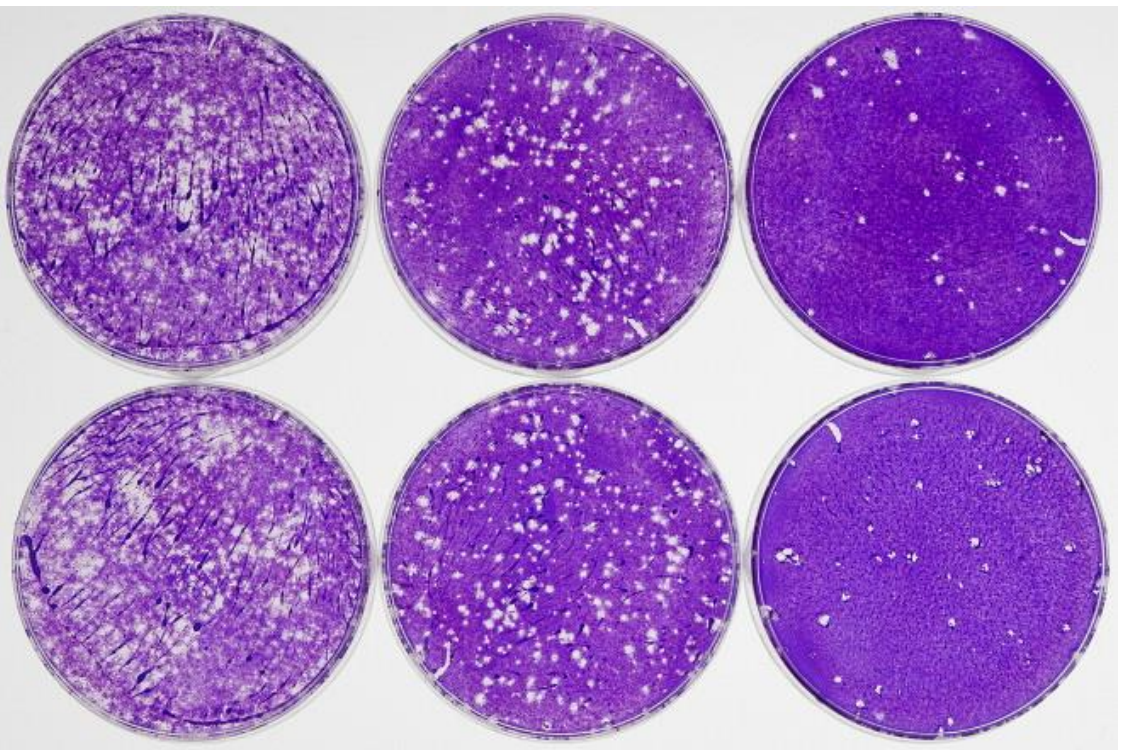
Molnupiravir and Paxlovid inhibit efficiently SARS-CoV-2 replication

Antiviral evaluation of combos against SARS-CoV-2 on MucilAir™



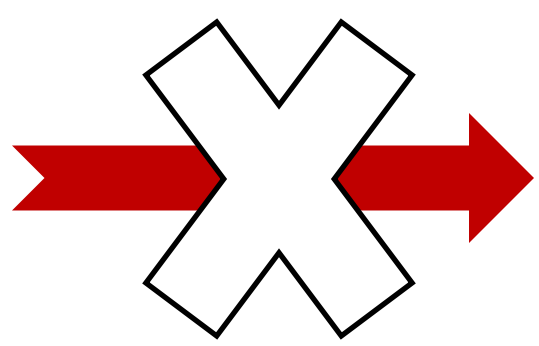
Combination therapy can enhance the antiviral activity of Molnupiravir

Vero E6 cells

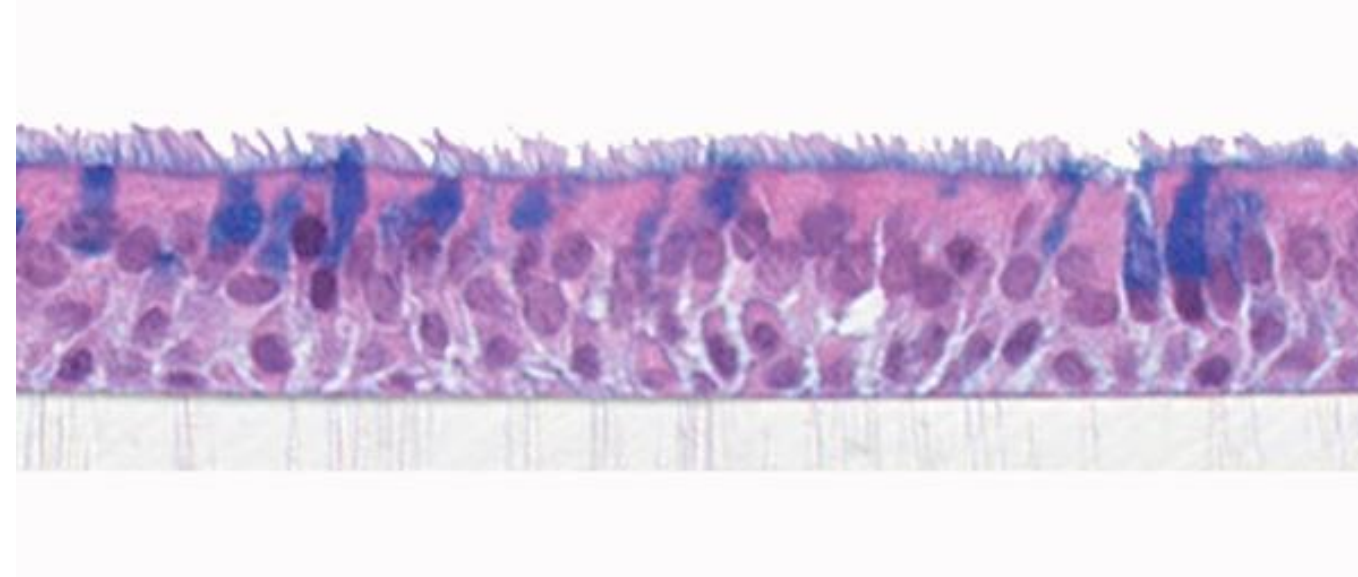


HCQ is effective

IC₅₀ = 2.2 μM (48h pi)
- 4.4 μM (72h pi)



MucilAir™



HCQ is not effective at subtoxic doses



Cynomolgus Macaques



HCQ is not effective against SARS-CoV-2

ALI 3D Human Airway Models like MucilAir™ and SmallAir™ are useful tools to study SARS-CoV-2 pathogenesis

- ✓ Isolation, characterization and amplification of circulating strains
- ✓ Identification of transcriptional and secreted innate immune signature
- ✓ Pathway identification of the pathogenesis
- ✓ Screening platform to test antivirals (repositioning of marketed drugs or evaluation of novel therapies and combinations delivered systematically or through aerosol therapy) -> **Local toxicity & efficacy assessment!**

Thanks for your attention



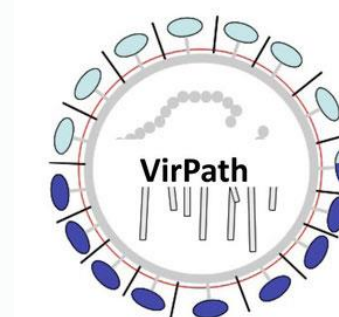
French Lab

- Carole Bertinetti
- **Mendy Bouveret**
- Christine CaulFuty
- **Mireille CaulFuty**
- Ophélie Verbeke
- Laurent Wiszniewski
- Dr. Ludovic Wiszniewski



Swiss Lab

- Paul Alouani
- Guy Barbin
- **Sacha Benaoudia**
- **Dr. Bernadett Boda**
- **Rosy Bonfante**
- Caroline Chojnacki
- Cindia Ferreira
- Emilie Ferreira
- Ina Fureraaj
- Matia Gojun
- **Dr. Song Huang**
- Xiao-Yann Huang
- Faten Hussein
- Gowsinth Gunasingam
- Marc Lanzillo
- Melany Monachino
- Rebecca Pimenta
- Florian Shala
- Jimmy Vernaz
- Karin Weber



▪ **Dr. Manuel Rosa-Calatrava**

▪ **Dr. Olivier Terrier**



▪ **Prof. Caroline Tapparel**

▪ **Dr. Manel Essaidi-Laziosi**



▪ **Dr. Olivier Engler**

▪ **Dr. Hulda Jonsdottir**



▪ **Dr. Rob Jordan**

▪ **Dr. Monalisa Chatterji**

Interested in new updates on *in vitro* lung models approaches ?

13-14 JUNE NICE - FRANCE

LIVE 2022
LUNG IN VITRO event
for innovative & predictive models