SUPPLEMENTARY FIGURE LEGENDS

SFig 1: Confocal microscopy images of Vero E6 (A) or Ace2-A549 (B) cells infected with SARS-CoV-2. At 24 hrs post-infection, cells were stained with antibodies against NP or against the dsRNA intermediate of replication (Scale bars, 20 μm).

SFig 2. SARS-CoV-2 infects Ace2-HEK293T cells and replication is inhibited by NTZ. Concentration-response curves for viral infectivity and for cell viability in Ace2-HEK293T cells treated with NTZ or RDV as described in the Figure 1 legend. Cells were infected with SARS-CoV-2 (isolate USA-WA1/2020) at an MOI of 0.25.

SFig 3. Functional validation of Ace2-A549 IFNAR-KO cells.

A. WT and IFNAR-KO Ace2-A549 cells were treated for 45 minutes with 1,000 U/ml of type I IFN before lysis. Expression of the indicated protein was determined by Western blot using actin as a loading control. **B.** WT and IFNAR-KO Ace2-A549 cells were stimulated for 24 hrs with 100 U/ml of type I IFN. The expression of IFITM3 mRNA was determined by qRT-PCR. IFITM3 mRNA levels relative to cyclophilin are shown.

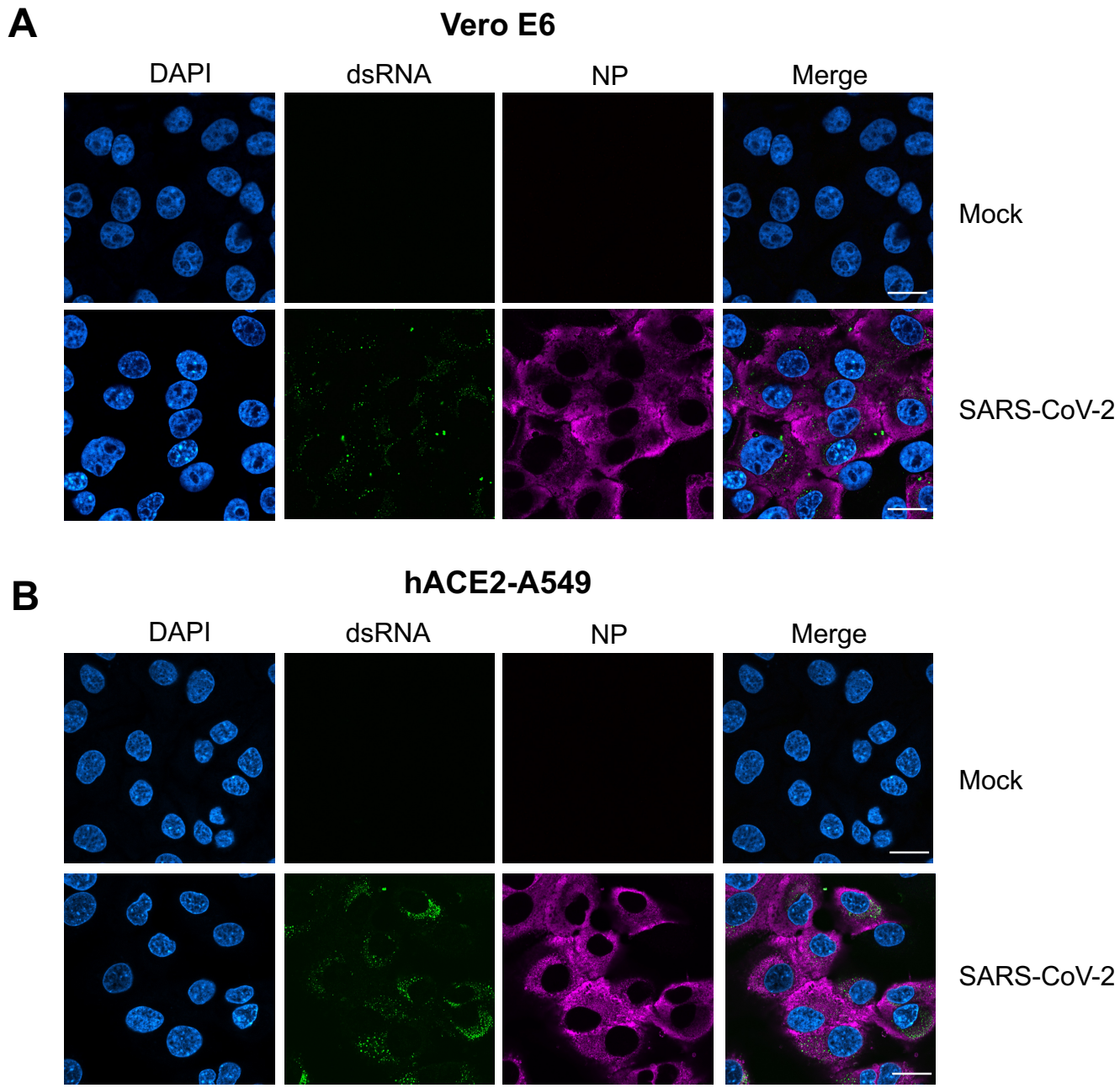
SFig 4. Infection of IAT2 cells with NG-SARS-CoV-2 shown by confocal microscopy. At 7 days post-plating 400,000 iAT2s/transwell were infected with NeonGreen-SARS-CoV-2 (NG-SARS-CoV-2) at an MOI of 0.01 for 2 days, fixed, and evaluated by confocal microscopy.

SFig 5. High magnification of images shown in Figure 6 at day 2 and 14 of lung from naïve and from SARS-CoV-2+PBS/vehicle- vs. SARS-CoV-2+NTZ-treated animals at day 2 and 14 post-infection. Top: Bronchioles. At 2 dpi SARS-CoV-2 PBS/vehicle-treated: bronchioles (black arrows) are occluded by necrotic cellular debris and neutrophils and histiocytes, with

neighboring bronchiole epithelial apoptosis and/or necrosis represented by nuclear fragmentation (black hashed boxes). At 2 dpi SARS-CoV-2 NTZ-treated: segmental bronchiole epithelial degeneration and denuding represented by a hashed box, with less overall luminal exudate. **Bottom: Interstitium/Blood Vessels.** At 14 dpi SARS-CoV-2 PBS/vehicle-treated: mild-to-moderate residual perivascular lymphocytic infiltrate (see black box inset) neighboring areas of residual Alveolar type 2 (AT2) cell hyperplasia (blue arrows). At 14dpi SARS-CoV-2 NTZ-treated: minimal sporadic residual perivascular lymphocytic infiltrate (see black box inset at higher magnification) neighboring areas of residual AT2 cell hyperplasia (blue arrows). Scale bars: top row (bronchioles), 50 μm; bottom row: interstitium/blood vessels, 100 μm.

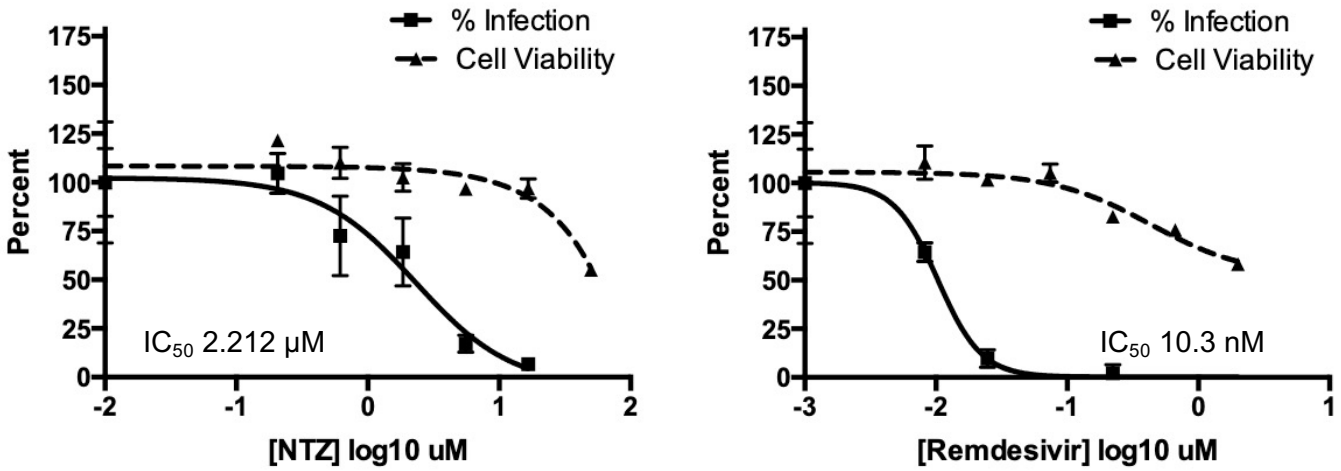
S Table 1. Monoplex SARS-CoV-2 Spike DAB Immunohistochemistry (IHC)

S Table 2. Lung Ordinal Scoring System

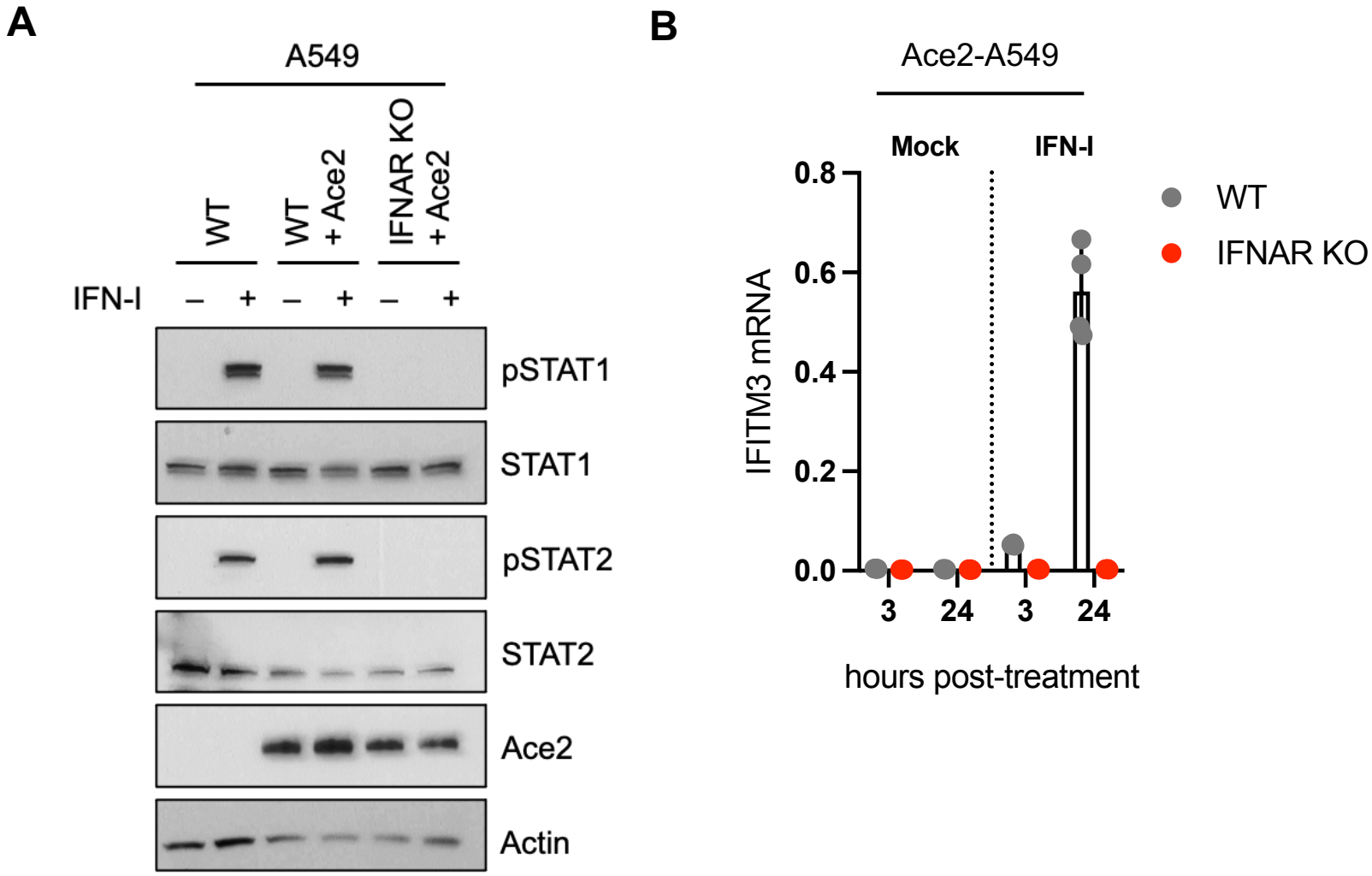

A
Vero E6
DAPI
dsRNA
NP
Merge
Mock
SARS-CoV-2
B
hACE2-A549
DAPI
dsRNA
NP
Merge
Mock
SARS-CoV-2

S. Fig. 1

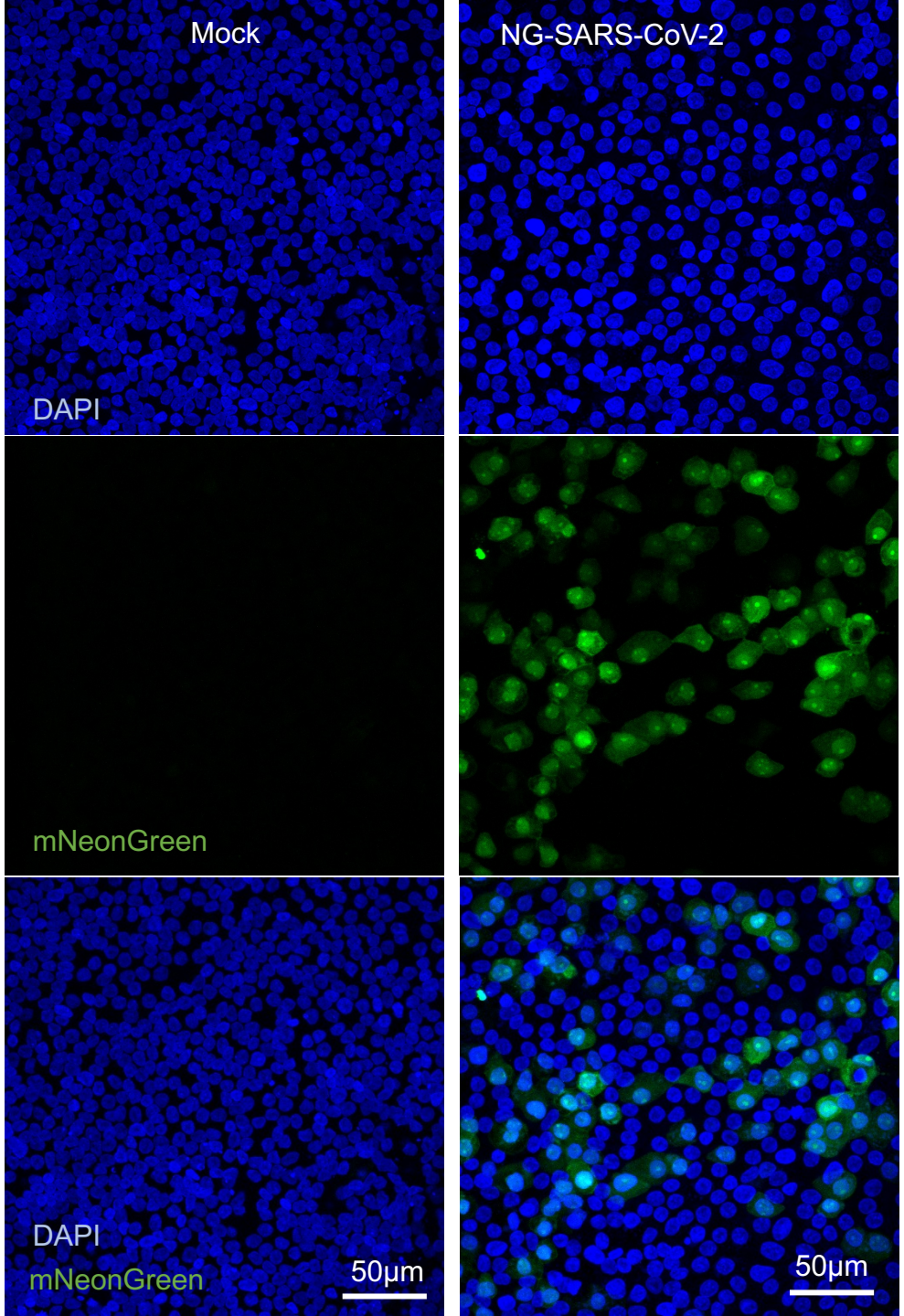
Ace2-HEK293T / SARS-CoV-2-WA1/2020



S. Fig. 2


A
A549
WT
WT + Ace2
IFNAR KO + Ace2
IFN-I
–
+
–
+
–
+
pSTAT1
STAT1
pSTAT2
STAT2
Ace2
Actin
B
Ace2-A549
Mock
IFN-I
IFITM3 mRNA
0.8
0.6
0.4
0.2
0.0
3
24
3
24
hours post-treatment
WT
IFNAR KO

S. Fig. 3


Mock
NG-SARS-CoV-2
DAPI
mNeonGreen
DAPI
mNeonGreen
50μm
50μm

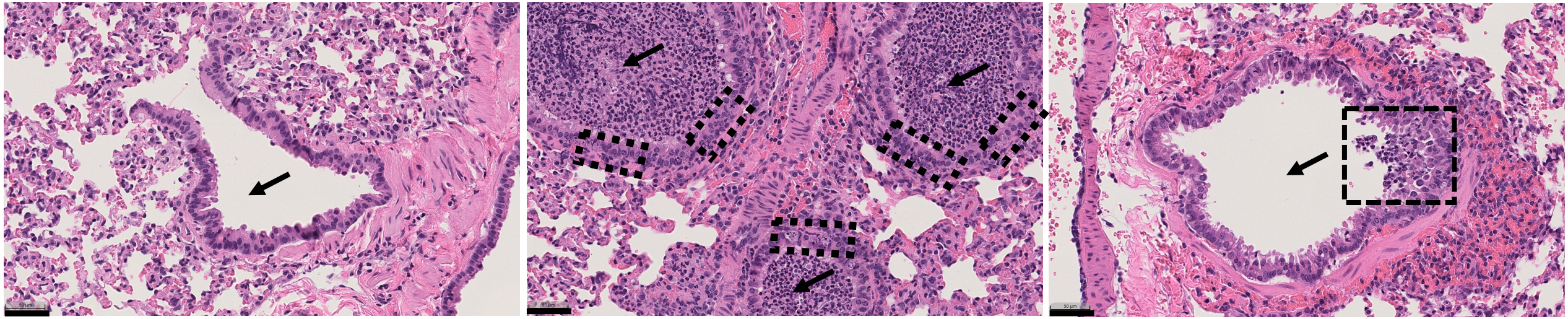
S. Fig. 4

Naive

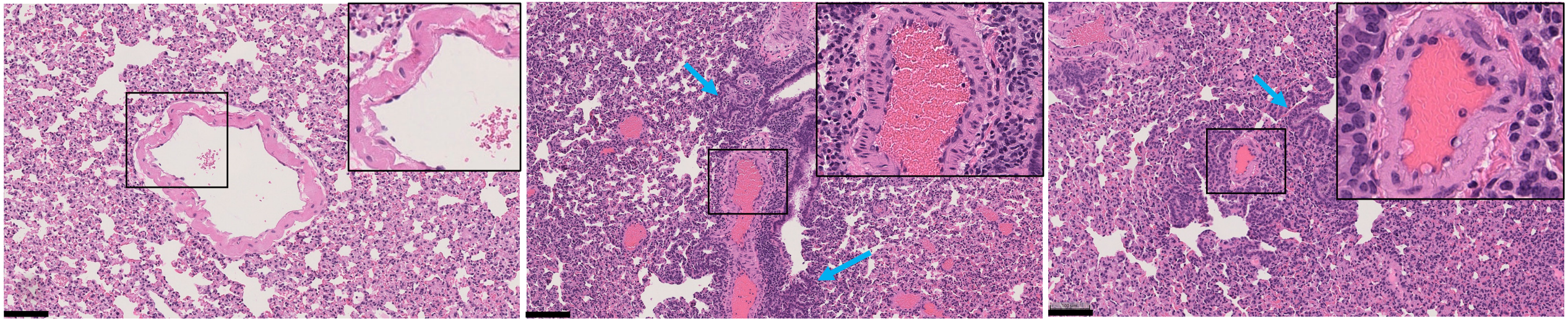
SARS-CoV-2-PBS

SARS-CoV-2 NTZ

2dpi Bronchioles



14dpi Interstitium/Blood Vessels



S. Fig. 5

Supplementary Tables

S Table 1. Monoplex SARS-CoV-2 Spike DAB Immunohistochemistry (IHC)				
Species	Antigen	Manufacturer and Clone	Primary Antibody Dilution	Chromogen
Ms monoclonal	SARS-CoV-2 Spike	Cell Signaling Technology E7U60	1:900	DAB
Diaminobenzidine-DAB; IHC-immunohistochemistry				

Suppl. Table 2. Lung Ordinal Scoring System	
Airways (bronchioles)	
0	Within normal limits.
1	Mild bronchiole epithelial degeneration/necrosis and hyperplasia/hypertrophy; mononuclear +/- neutrophil peribronchiolar and/or airway infiltrates
2	Moderate bronchiole epithelial degeneration/necrosis and hyperplasia/hypertrophy; mononuclear +/- neutrophil peribronchiolar infiltrates; infiltration of bronchiole airways with moderate mononuclear infiltrates, neutrophils, necrotic cellular debris, +/- erythrocytes.
3	Marked to severe bronchiole epithelial degeneration/necrosis and/or hyperplasia/hypertrophy with syncytial cells; mononuclear +/- neutrophil peribronchiolar infiltrates; +/- infiltration of bronchiole airways with mononuclear infiltrates, neutrophils, necrotic cellular debris, +/- erythrocytes.
Interstitium	
0	Within normal limits.
1-A (acute)	Mild focal to multifocal interstitial expansion and/or alveolar infiltration by mononuclear cells +/- neutrophils, with no observable edema, hemorrhage, and/or fibrin exudation.
1-C (chronic)	Mild to moderate alveolar type 2 (AT2) pneumocyte hyperplasia, with mild interstitial or alveolar mononuclear infiltrates, +/- pleural and/or interstitial fibrosis.
2-A (acute)	Moderate multifocal interstitial expansion and/or alveolar infiltration by mononuclear cells (histiocytes and/or lymphocytes) and neutrophils, with mild edema, hemorrhage, and/or fibrin exudation, admixed with low amounts of cellular debris.
2-C (chronic)	Mild to moderate multifocal interstitial expansion and/or alveolar infiltration by mononuclear cells +/- neutrophils, with mild to moderate AT2 pneumocyte hyperplasia
3-A (acute)	Marked to severe multifocal interstitial expansion and/or alveolar infiltration by mononuclear cells and neutrophils, with moderate to regionally severe edema, hemorrhage, and/or fibrin exudation, with mild to moderate cellular debris.
3-C (chronic)	Severe alveolar type 2 (AT2) pneumocytes hyperplasia +/- alveolar bronchiolization. Prominent anisocytosis and cytomegaly of AT2 pneumocytes, with increased mitotic figures. Moderate to marked multifocal interstitial expansion and/or alveolar infiltration of mononuclear (histiocytes and/or lymphocytes) and neutrophils with mild edema, hemorrhage, and/or fibrin exudation, and mild cellular debris.
Blood vessels	
0	Within normal limits.
1	Mild mononuclear perivascular infiltrate +/- reactive endothelial hypertrophy.
2	Moderate mononuclear perivascular infiltrate +/- neutrophils, prominent reactive endothelium, +/- margination and/or transmigration of leukocytes.
3	Marked mononuclear infiltrate +/- neutrophils, prominent perivascular edema, reactive endothelium, and +/- margination and/or transmigration of leukocytes.