



Mucosal immunity: What do we need for protection?

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Host and virological factors contributing to breakthrough infection following vaccination

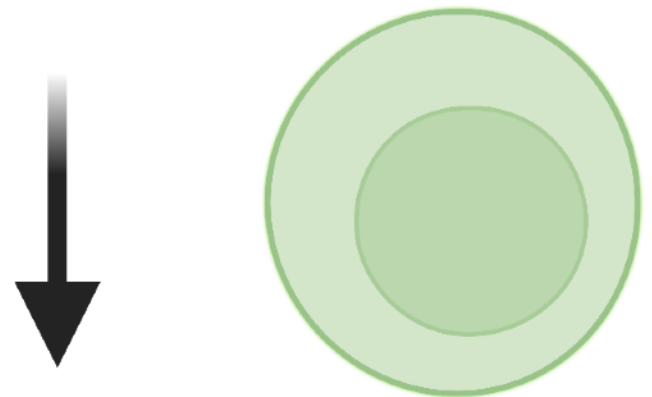
Waning immunity



Antibody

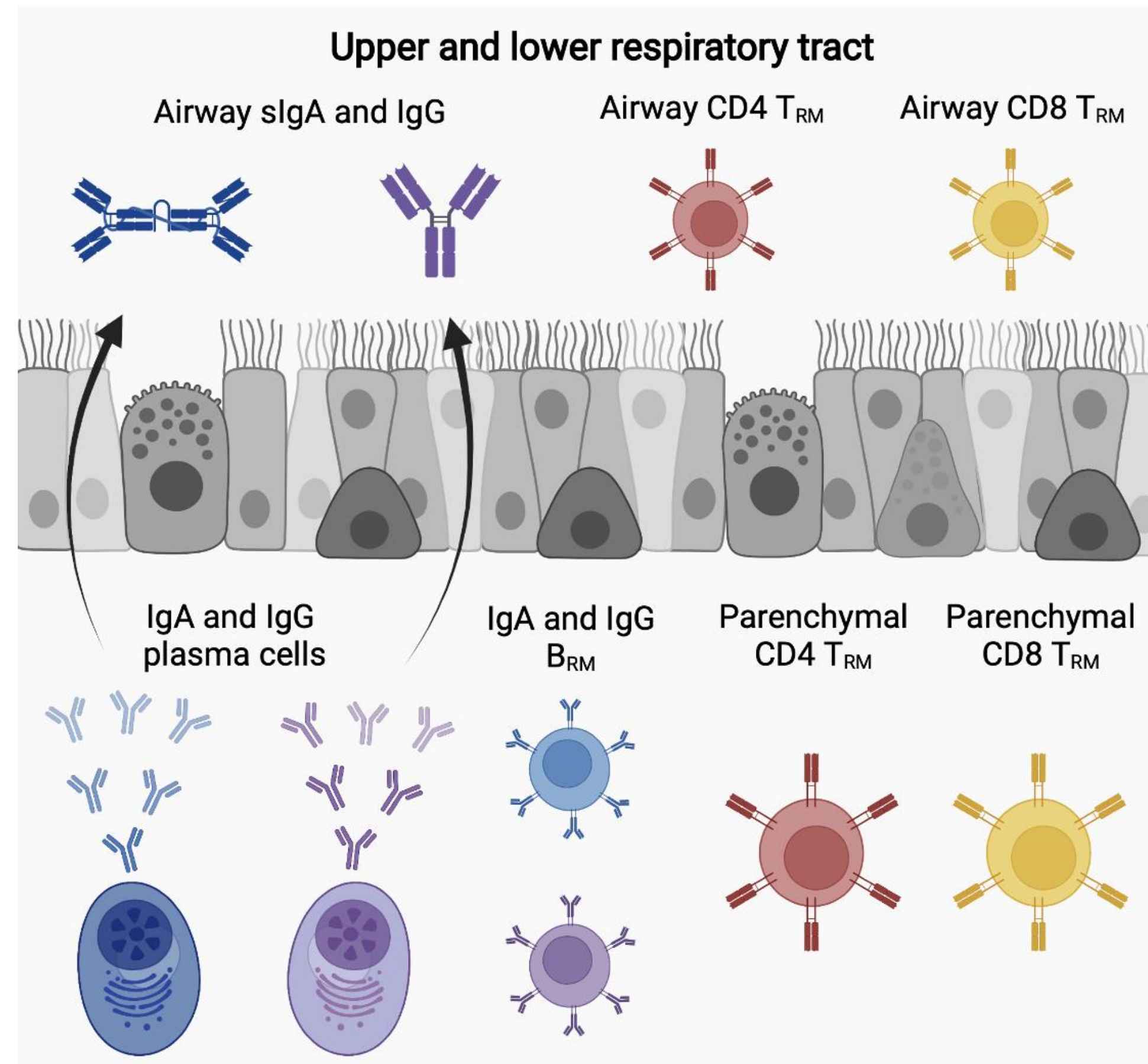


B cell



T cell

Mucosal immunity: sterilizing protection and rapid recall responses



Problems and solutions to nasal vaccines

Current status on mucosal vaccines

- Only a handful of licensed mucosal vaccines
- Live attenuated vaccines require significant R&D for safety and are not usable in immunocompromised
- Only one is available for respiratory pathogens (FluMist)
- FluMist only approved for 2-49 yo and not in pregnancy due to adverse events

Vibrio cholerae

Inactivated

Dukoral Oral — aqueous
 Composition: heat and formaldehyde-inactivated O1 serogroups (Inaba + Ogawa) + CTB

Euvichol, Shanchol Oral — aqueous
 Composition: heat and formaldehyde-inactivated O1 serogroups (Inaba + Ogawa) + 0139

Live attenuated

Vaxchora Oral — aqueous
 Composition: heat and formaldehyde-inactivated O1 serogroup (Inaba) – ctxA attenuation

Influenza A and influenza B viruses

Live attenuated/reassortant

FluMist/Fluenz Nasal — spray
 Composition: quadrivalent antigens from circulating strains incorporated into live attenuated, cold adapted donor influenza vector

Salmonella typhimurium

Live attenuated/reassortant

Typhi Vivotif Oral — capsule
 Composition:
 • Live attenuated Ty21a strain
 • Mutagenesis in LPS synthesis and Vi polysaccharide genes

Poliovirus

Live attenuated

Biopolio (bOPV) Oral — aqueous
 Composition: culture passage attenuated polioviruses 1 and 3 serotypes (5' non-coding region attenuation)

mOPV and tOPV Oral — aqueous
 Composition: culture passage attenuated polioviruses 1, 2 and 3 serotypes (5' non-coding region attenuation)

Rotavirus

Live reassortant

Rotateq Oral — aqueous
 Composition: pentavalent — five human-bovine reassortant rotaviruses (expression of G1, G2, G3, G4, G5 with P7 and G6 with P1A)

Live attenuated

Rotarix Oral — aqueous
 Composition: monovalent — culture passage attenuated (G1 with P1A expression)

Cautionary tale of adjuvanted nasal vaccines

ORIGINAL ARTICLE

Use of the Inactivated Intranasal Influenza Vaccine and the Risk of Bell's Palsy in Switzerland

Margot Mutsch, Ph.D., M.P.H., Weigong Zhou, M.D., Ph.D., Philip Rhodes, Ph.D., Matthias Bopp, Ph.D., Robert T. Chen, M.D., Thomas Linder, M.D., Christian Spyr, Ph.D., and Robert Steffen, M.D.

-1996-1999: 1218 volunteers during four winter seasons
in clinical trial: no AE

-In 2000, the first licensed inactivated intranasal IAV
vaccine approved for use in Switzerland

-Between Oct 2000 and April 2001: 46 cases of Bell's
palsy reported in vaccinees

-Retrospective Case control of Bell's palsy cases in
Switzerland Oct 2000 to April 2001
-773 cases identified->250 with 722 controls

Table 2. Risk of Bell's Palsy among Participants in the Case–Control Study.*

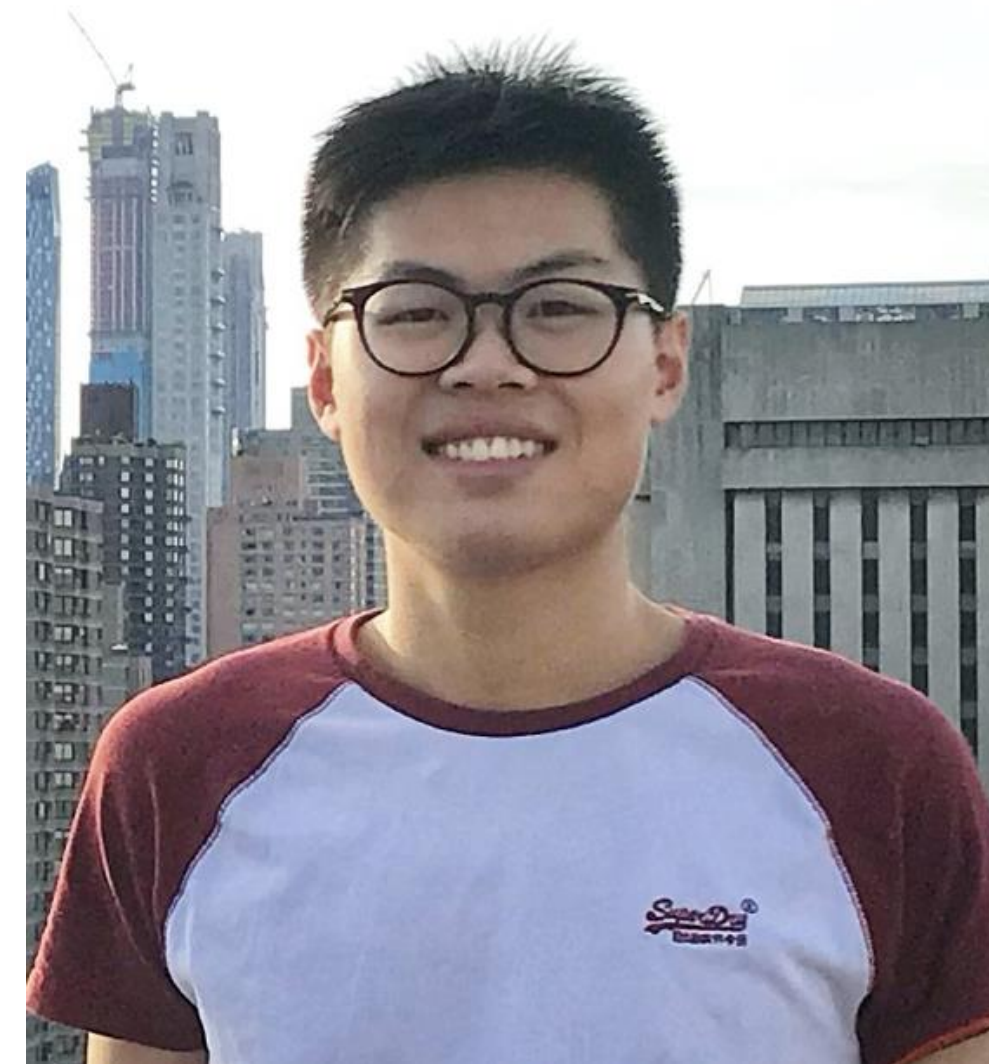
Vaccine and Bell's Palsy Onset Interval	Case Patients (N=250) no. (%)	Controls (N=722) no. (%)	Adjusted Odds Ratio (95% CI)
Intranasal vaccine†			
Onset interval ≤91 days	63 (25.2)	7 (1.0)	84.0 (20.1–351.9)
Onset interval >91 days	5 (2.0)	1 (0.1)	
Parenteral vaccine			
Onset interval ≤91 days	10 (4.0)	41 (5.7)	1.1 (0.6–2.0)
Onset interval >91 days	17 (6.8)	49 (6.8)	

Solution: Prime and Spike

We found a way to safely and robustly induce protective immunity in the respiratory mucosa with a nasal booster



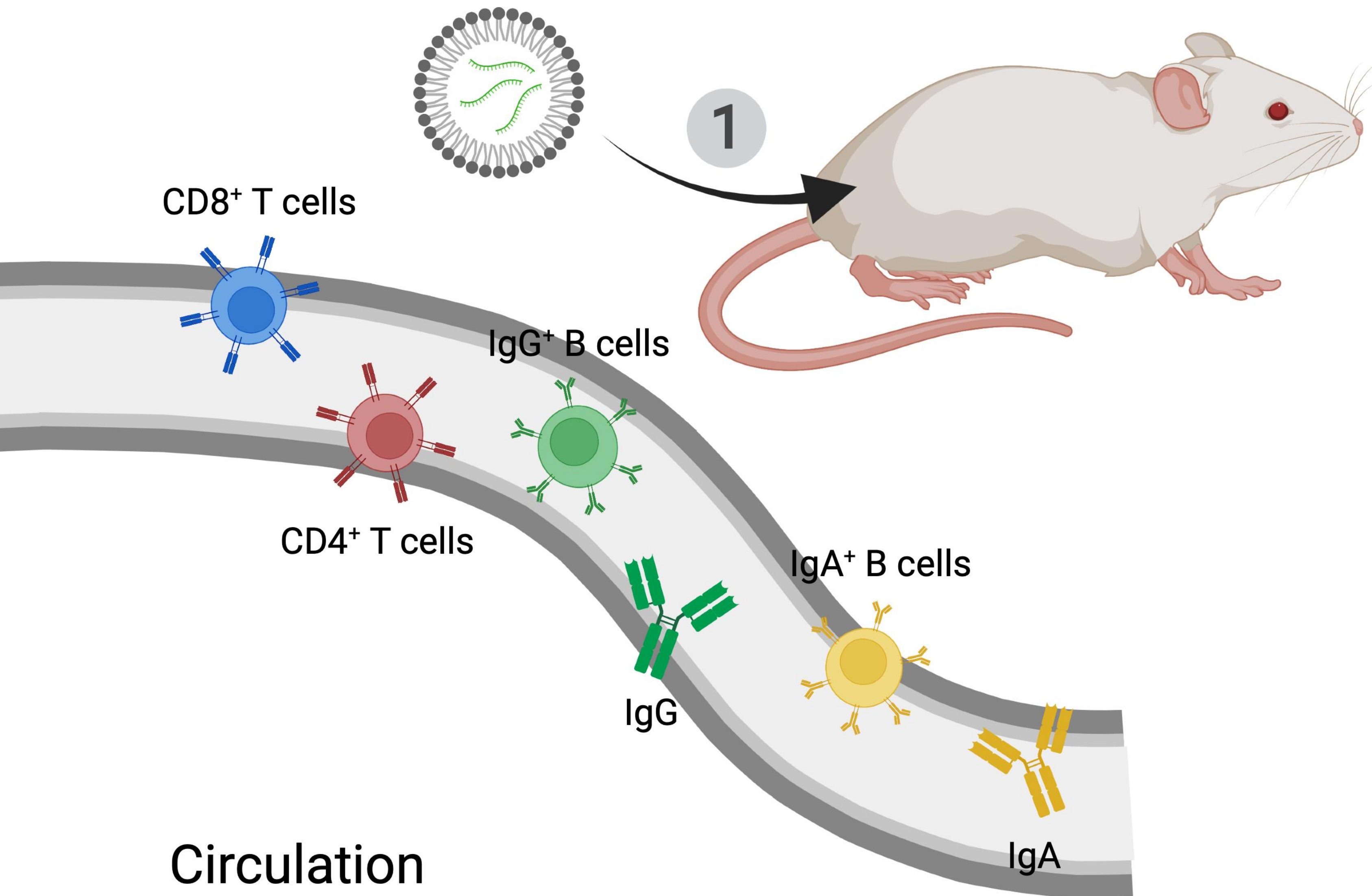
Ben Israelow



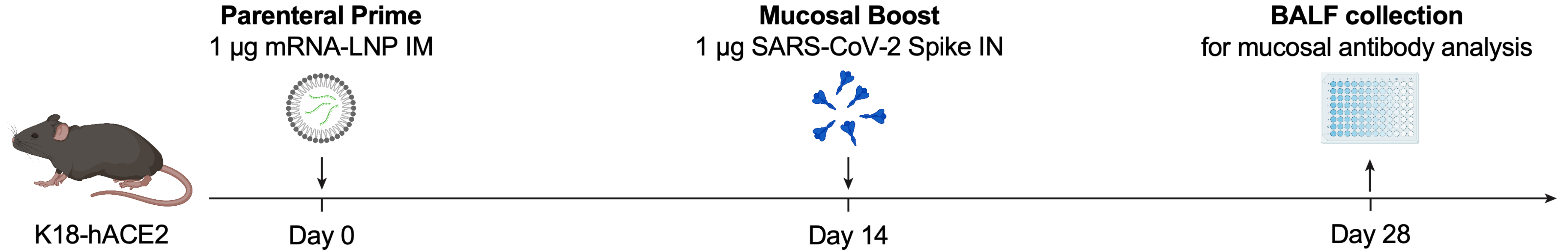
Tianyang Mao

“Spiking” respiratory immunity via intranasal boosting of prime-induced systemic immunity

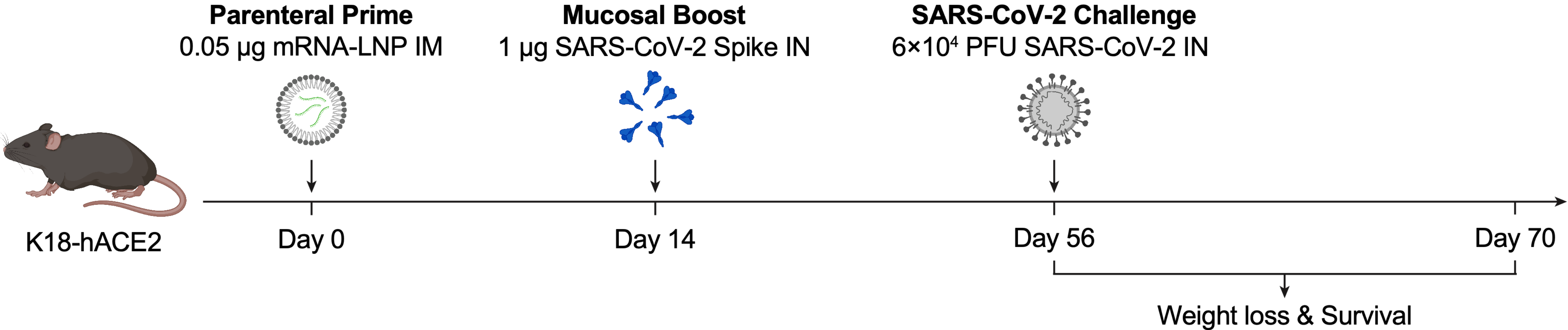
Parenteral mRNA-LNP prime



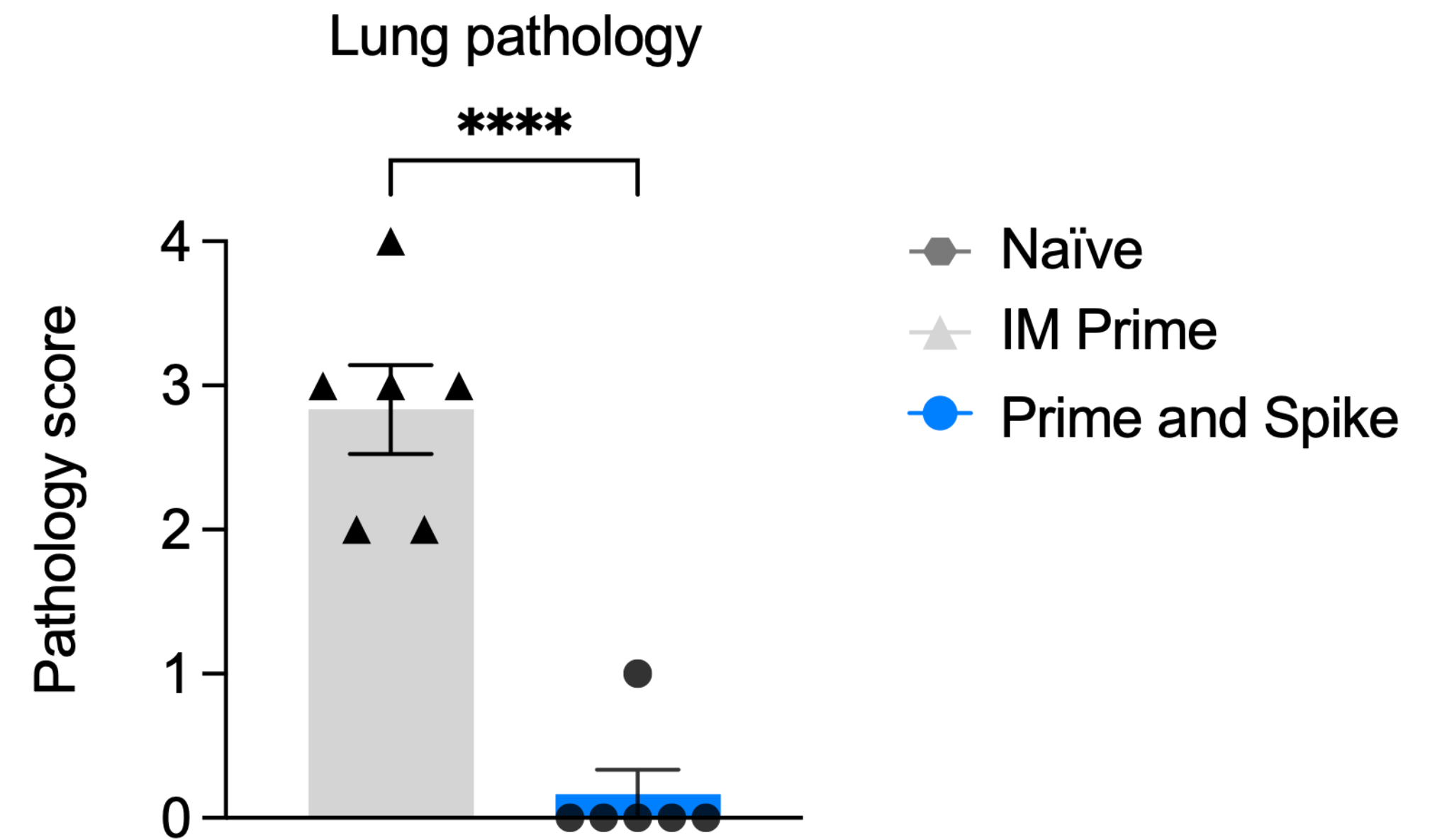
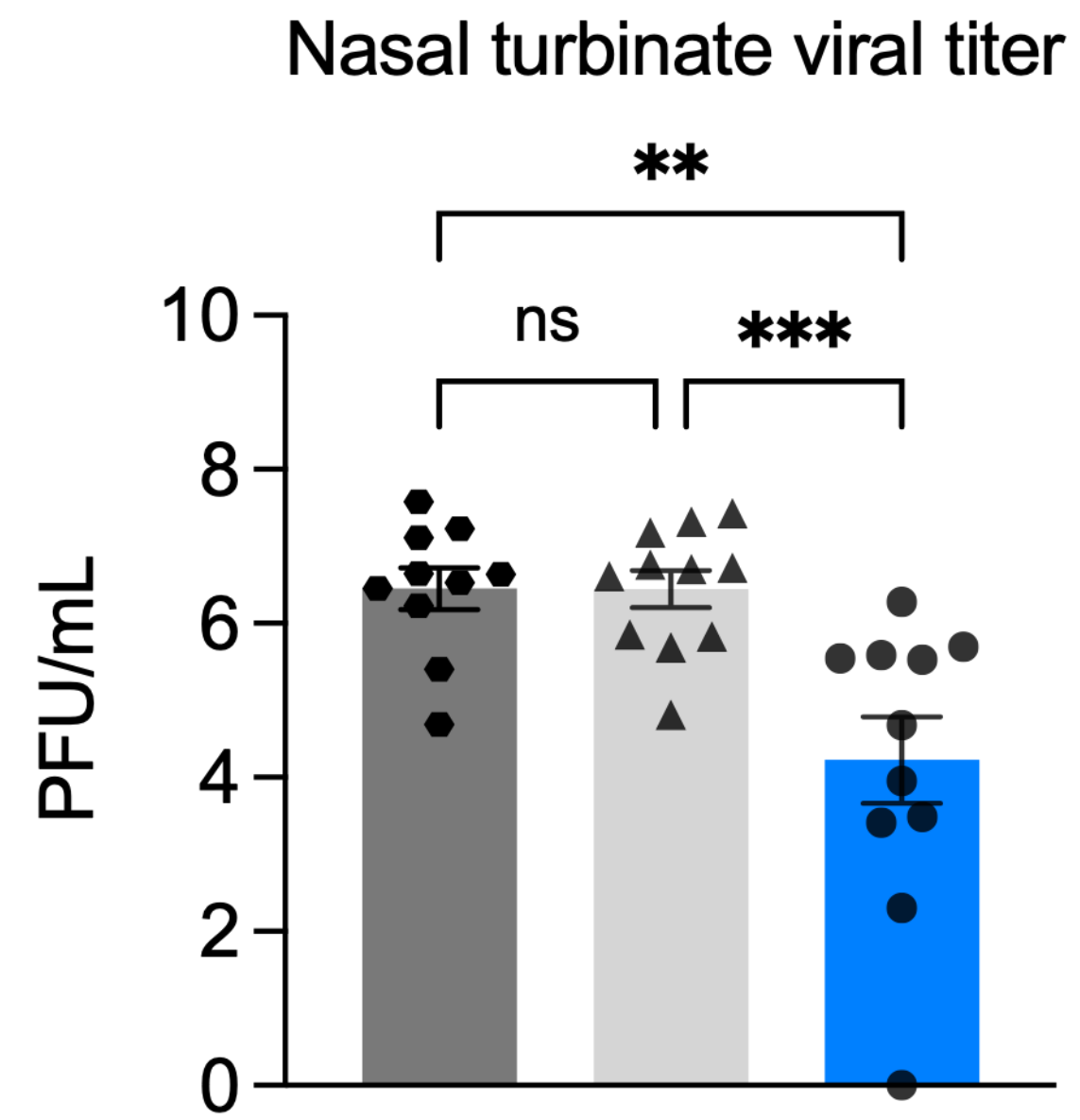
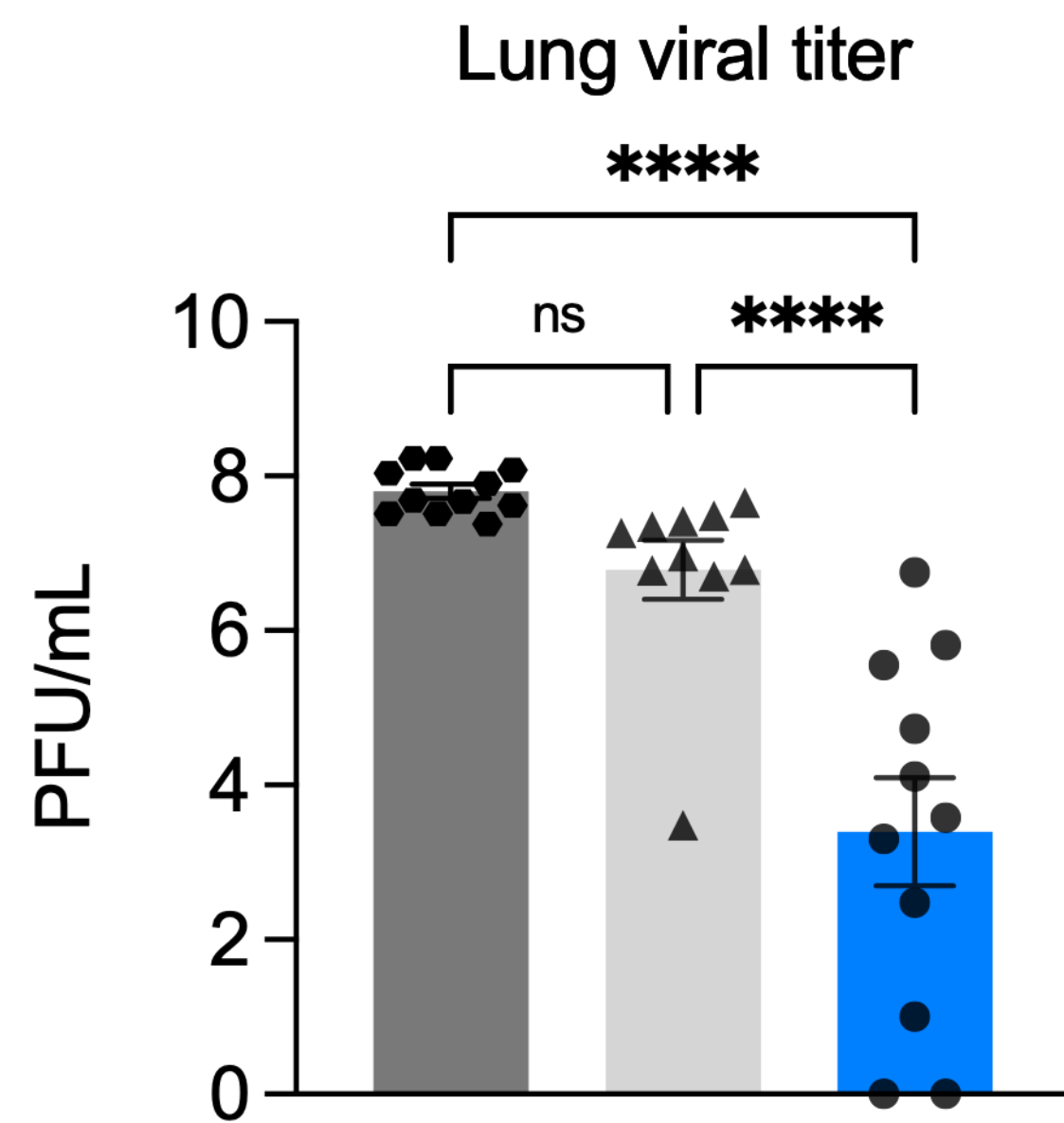
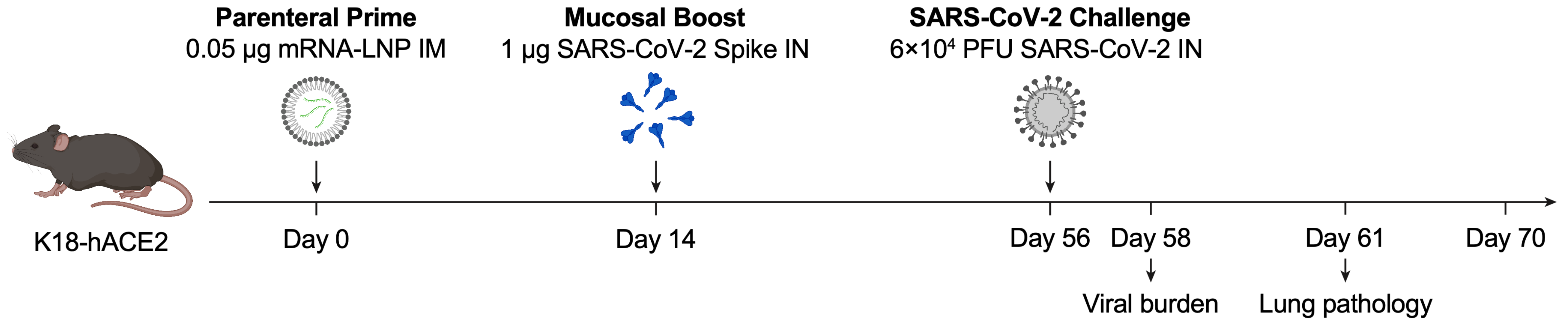
IN Spike boosting elicits mucosal spike-specific IgA and IgG production in the airway



IN Spike boosting confers complete mucosal protection against lethal SARS-CoV-2 infection



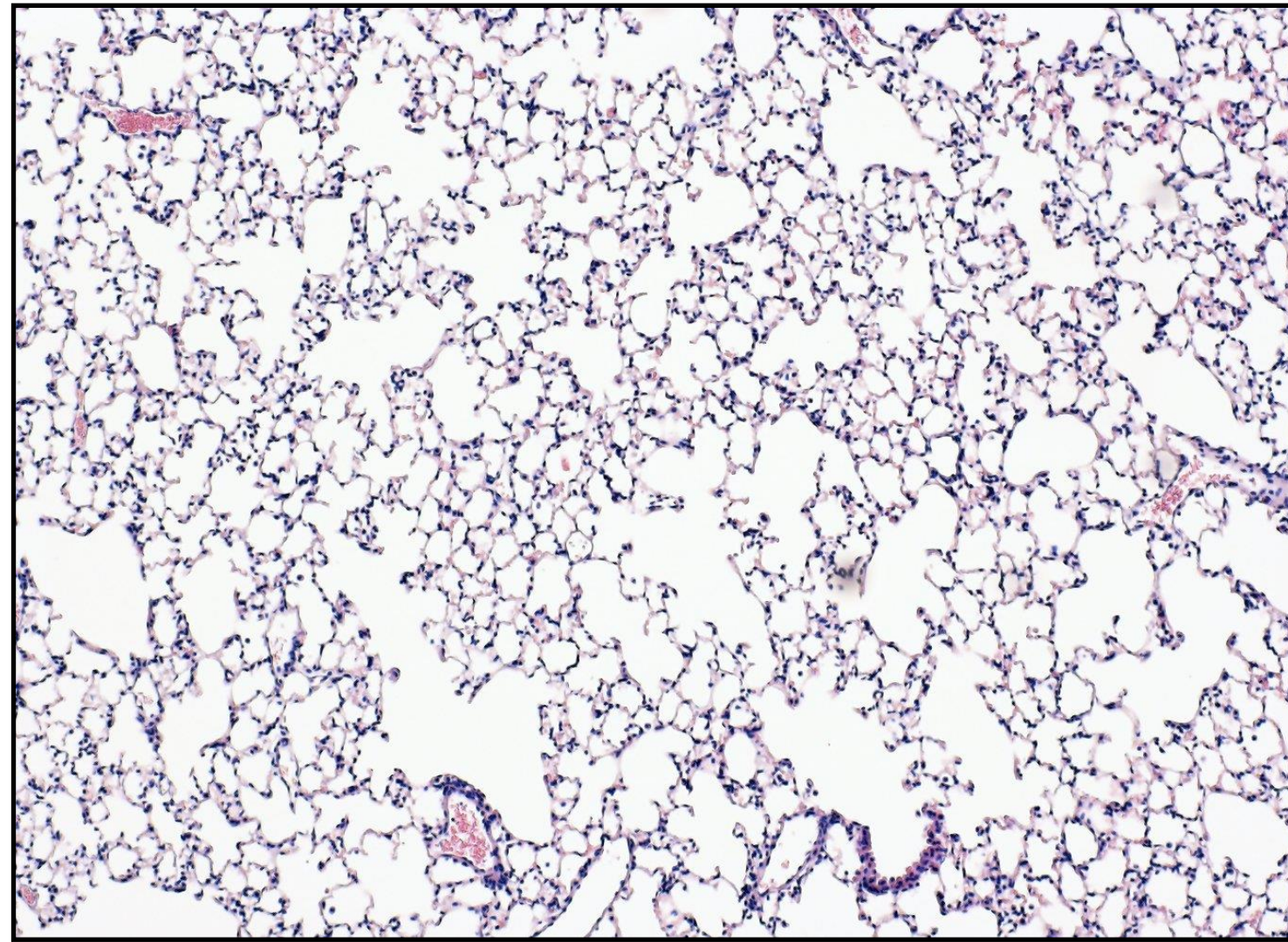
IN Spike boosting reduces viral titer and alleviates lung pathology in the respiratory tract



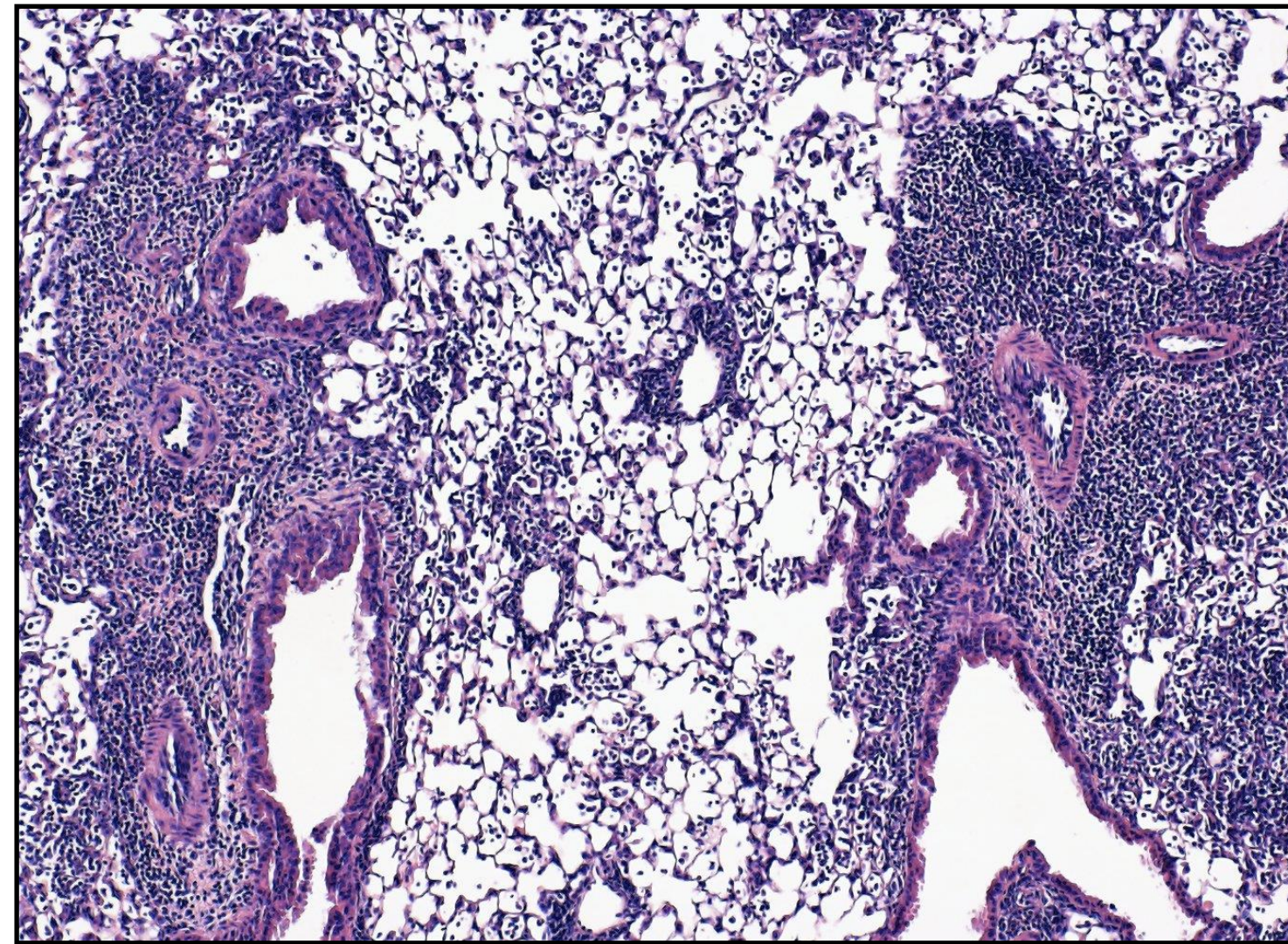
- Naïve
- ▲ IM Prime
- Prime and Spike

IN Spike boosting prevents severe inflammatory infiltration in the lower respiratory tract

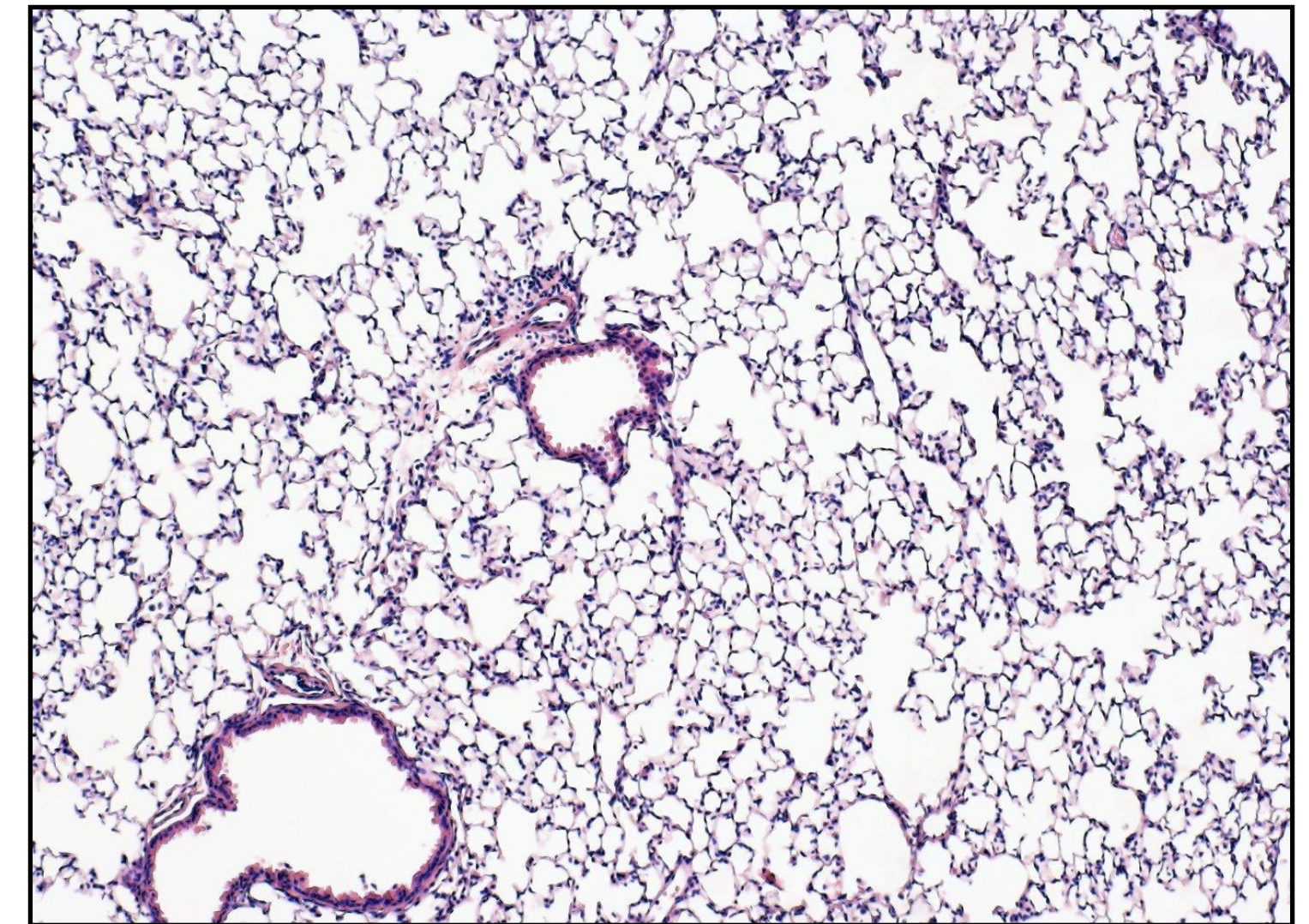
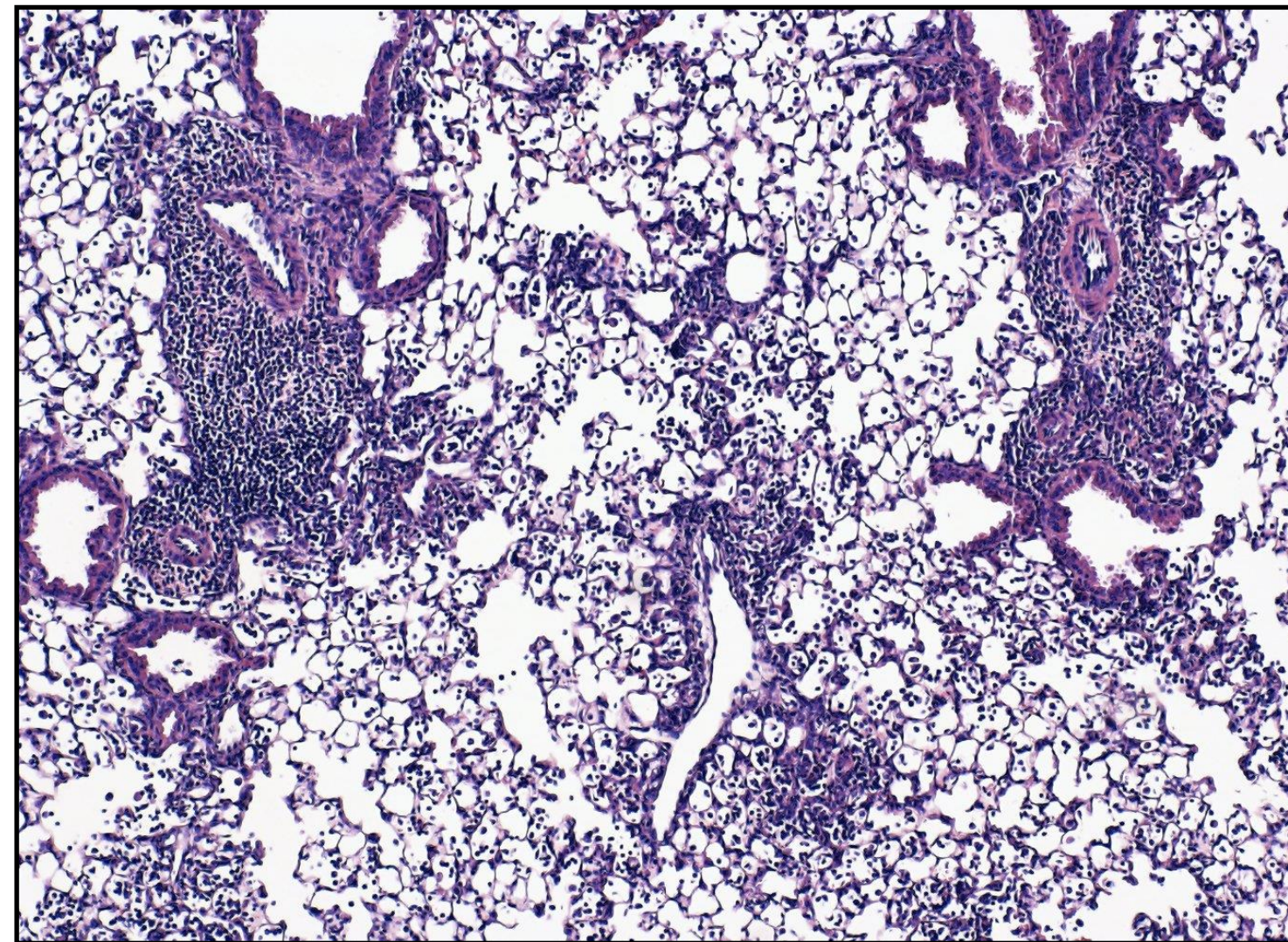
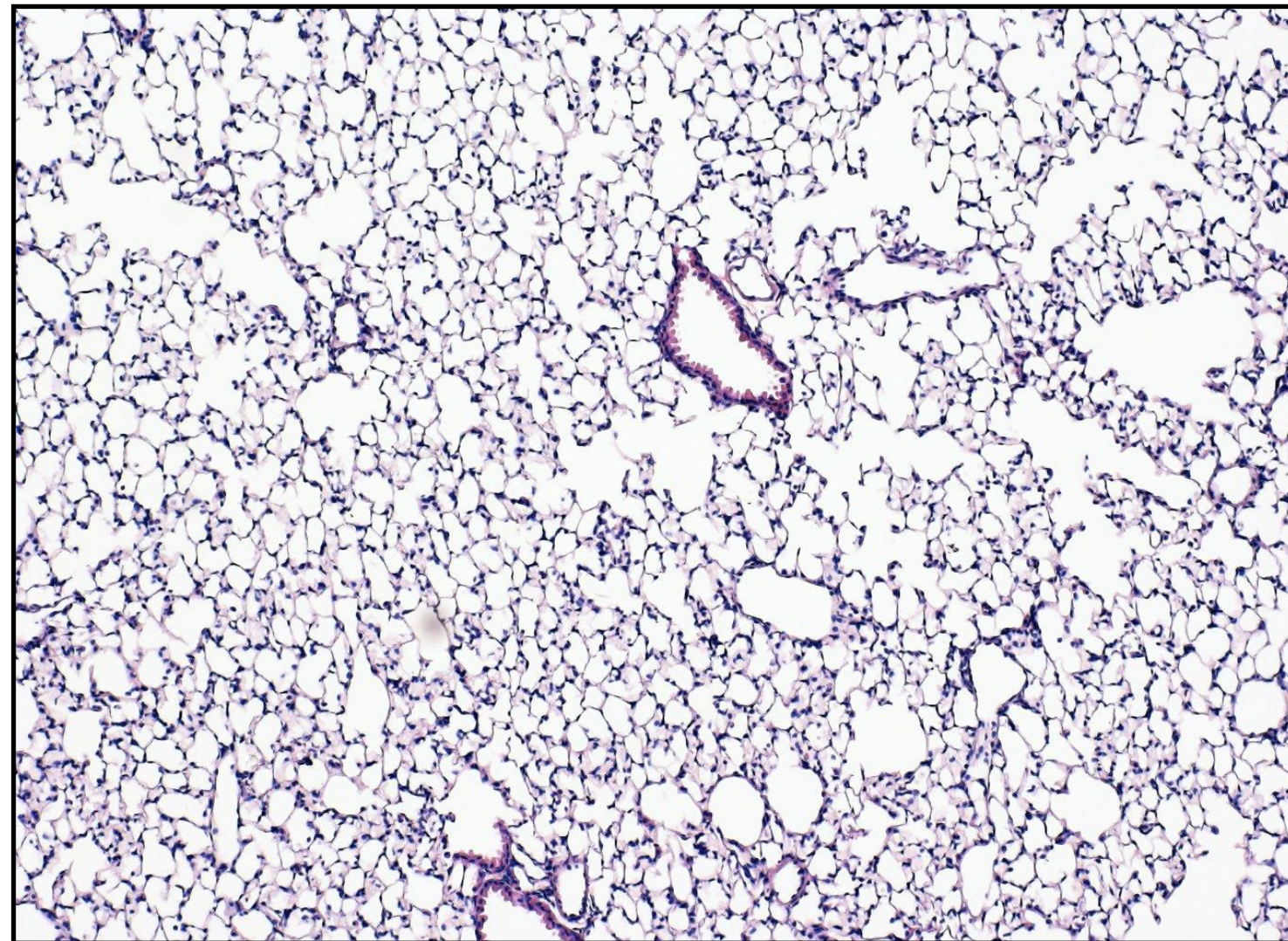
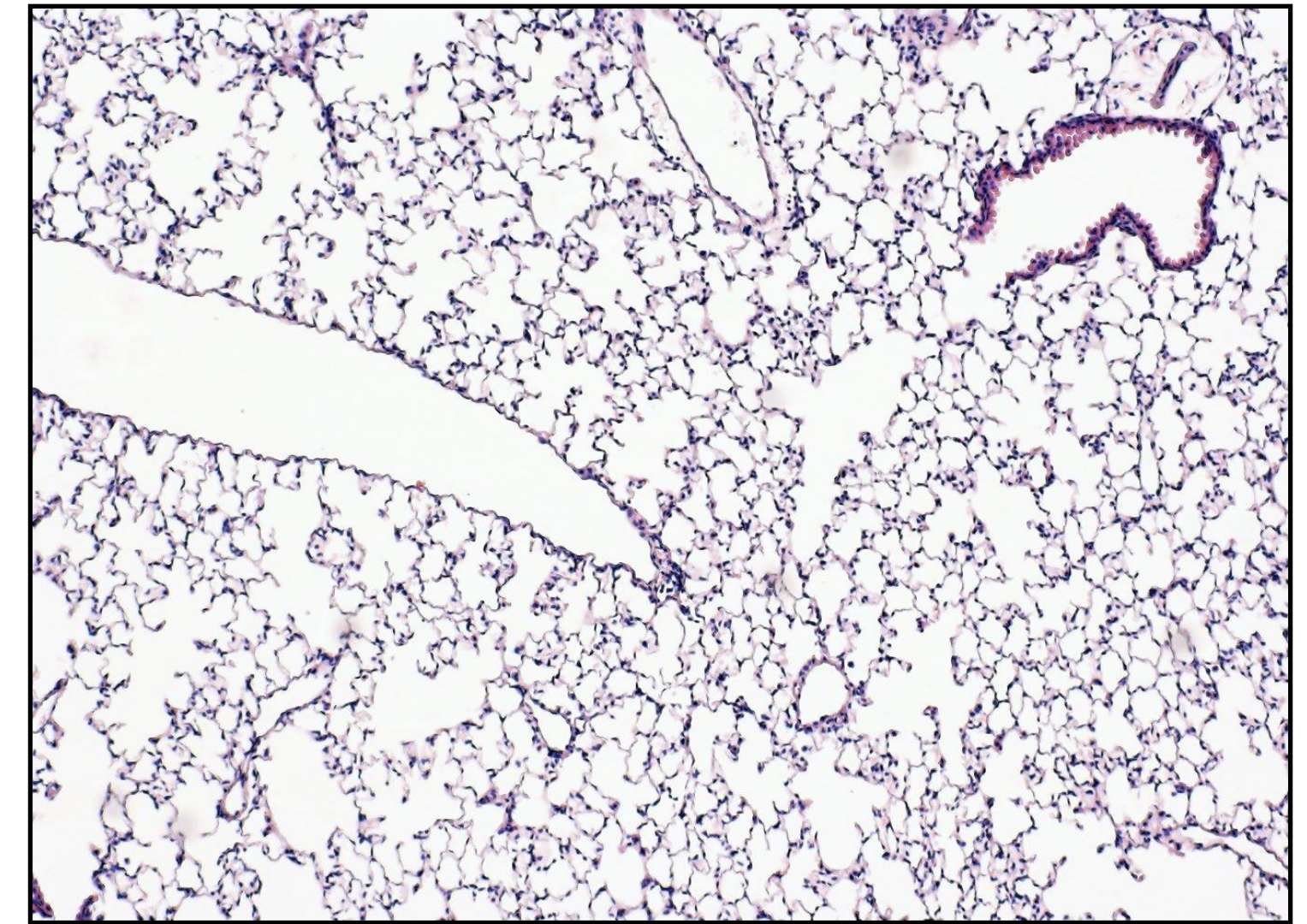
Uninfected



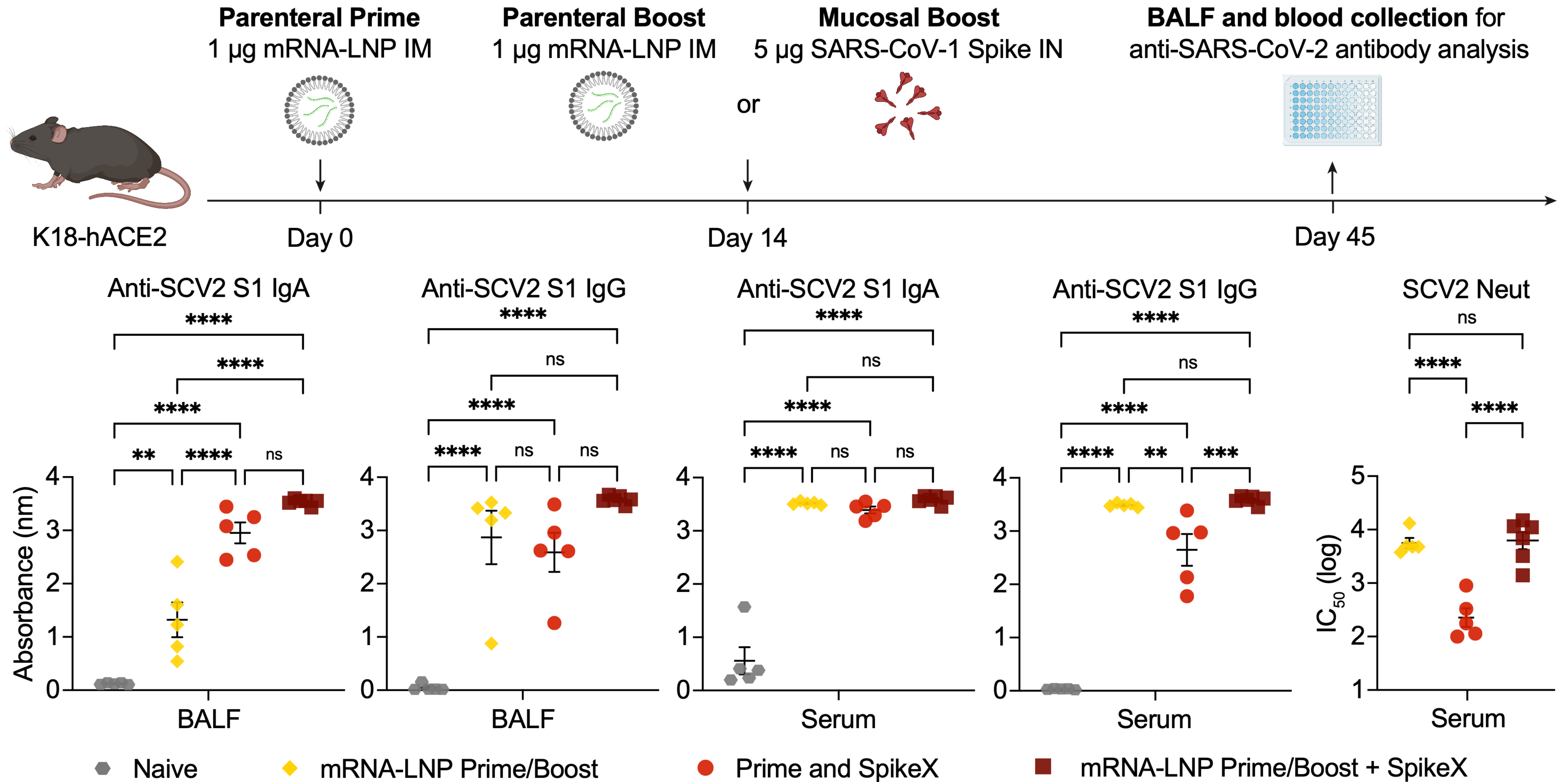
IM Prime



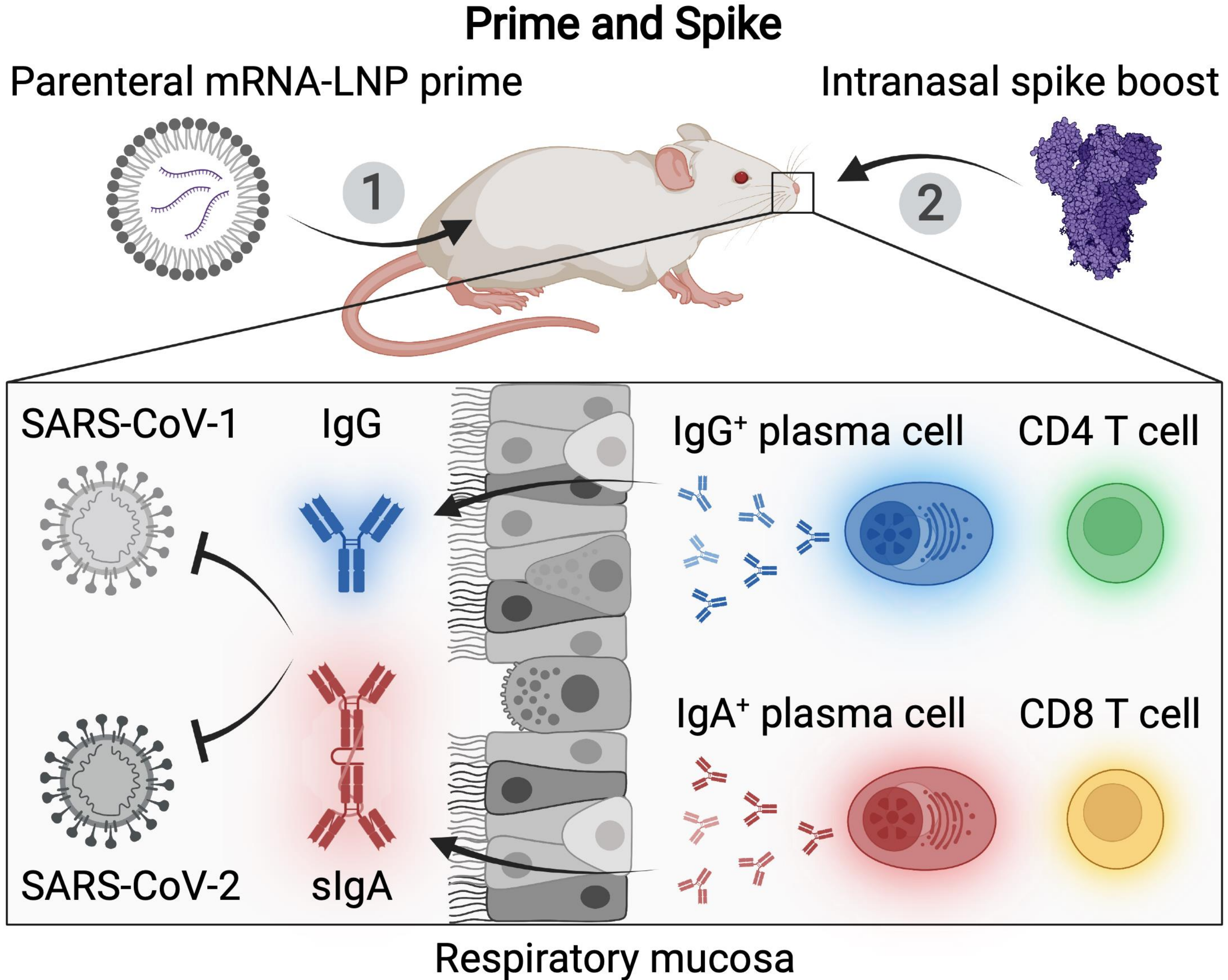
Prime and Spike



IN SCV1 boosting induced mucosal and systemic antibody responses against SARS-CoV-2



Conclusions



- Prime and Spike leverages existing memory cells to stimulate robust mucosal immunity in the upper and lower respiratory tract.
- Prime and Spike induces robust local T and B cell immunity at the respiratory mucosa.
- Prime and Spike protects mice with partial immunity from lethal SARS-CoV-2 infection.
- Intranasal boosting with SARS-CoV-1 spike elicits pan-sarbecovirus immunity without invoking original antigenic sin.