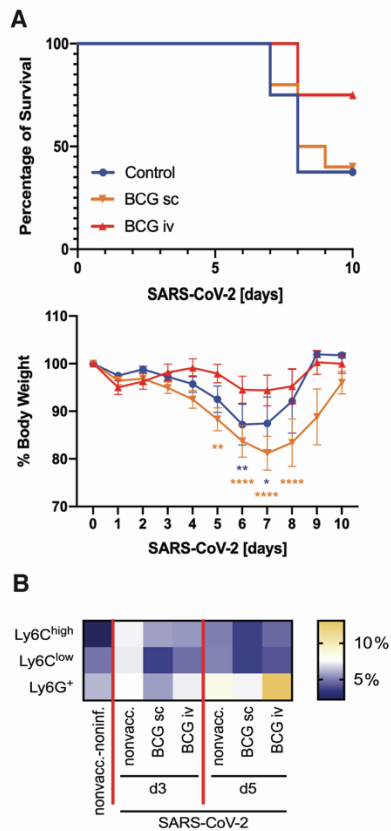


**Supplemental information**

**BCG vaccination provides protection  
against IAV but not SARS-CoV-2**

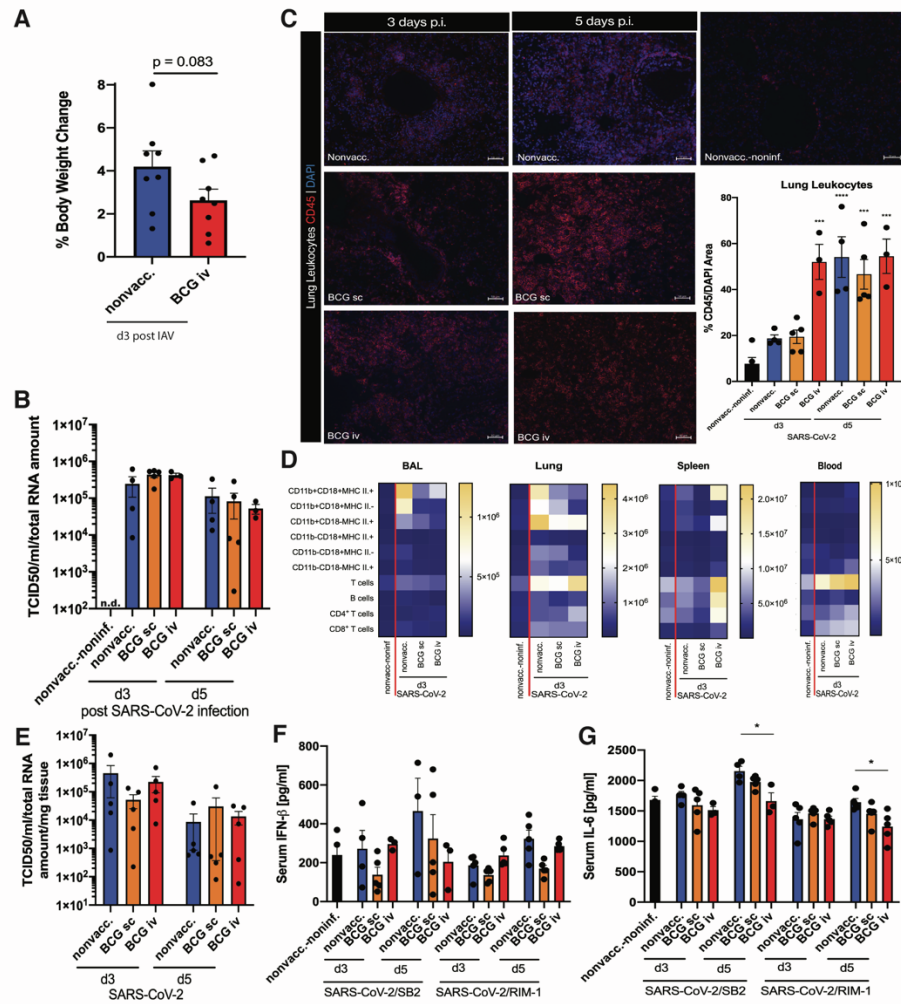
**Eva Kaufmann, Nargis Khan, Kim A. Tran, Antigona Ulndreaj, Erwan Pernet, Ghislaine Fontes, Andréanne Lupien, Patrice Desmeules, Fiona McIntosh, Amina Abow, Simone J.C.F.M. Moorlag, Priya Debisarun, Karen Mossman, Arinjay Banerjee, Danielle Karo-Atar, Mina Sadeghi, Samira Mubareka, Donald C. Vinh, Irah L. King, Clinton S. Robbins, Marcel A. Behr, Mihai G. Netea, Philippe Joubert, and Maziar Divangahi**

Fig. S1



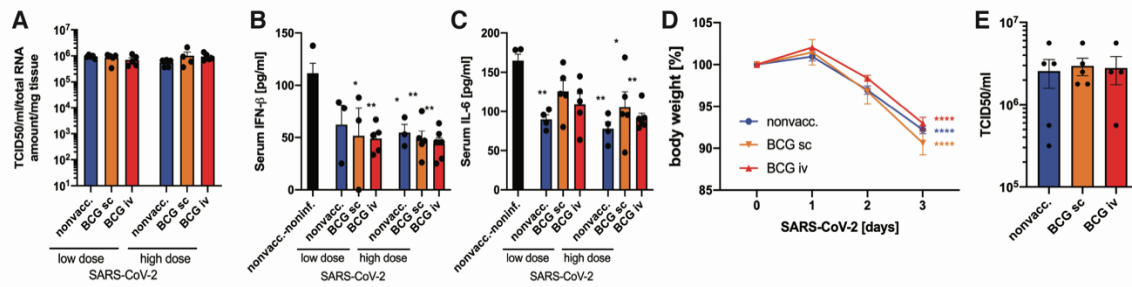
**Fig. S1: SARS-CoV-2 infection in the mouse model. Related to Figure 1.** (A) Mortality and morbidity of BCG-vaccinated and control K18-hACE2/J mice after intratracheal infection with  $1 \times 10^4$  TCID<sub>50</sub>/ml SARS-CoV-2/SB2 ( $n=8-10$ /group). (B) Frequencies of myeloid cells in the blood of K18-hACE2/J mice at day 3 and 5 post intratracheal SARS-CoV-2 infection (4000 TCID<sub>50</sub>/ml),  $n=3-10$ /group, refer to Table S1. Data are displayed as mean  $\pm$  SEM. \*  $p < 0.05$ , \*\*  $p \leq 0.01$ , \*\*\*  $p \leq 0.001$ , \*\*\*\*  $p \leq 0.0001$  (Survival analyses and 2way ANOVA).

Fig. S2



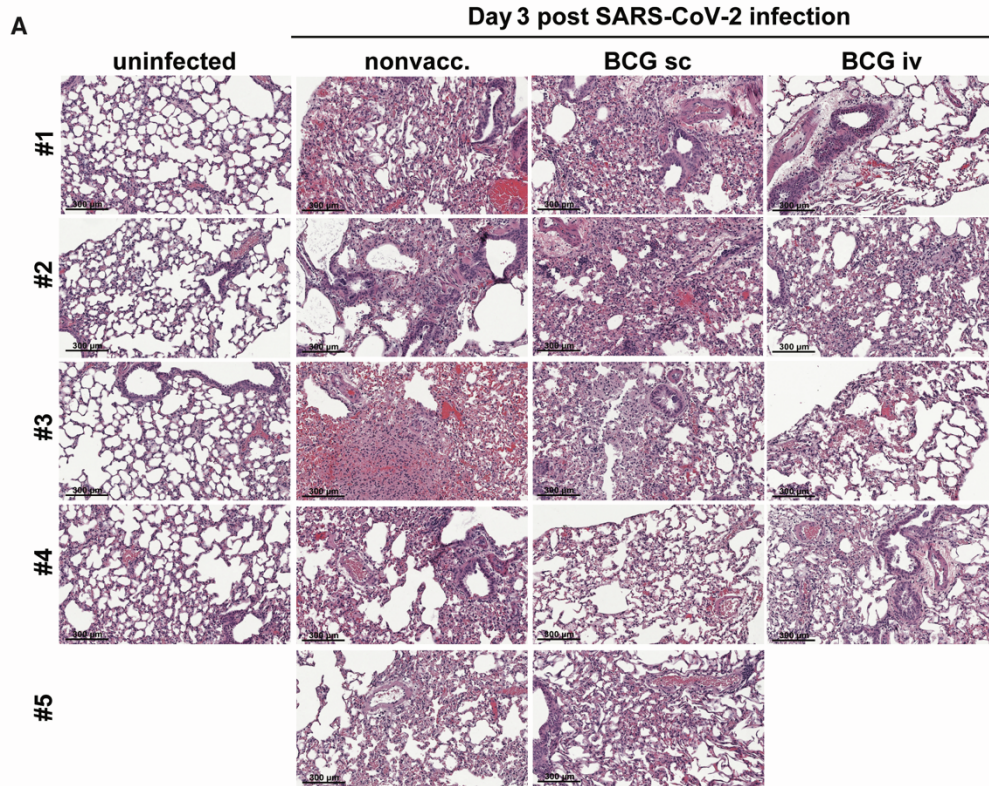
**Fig. S2: IAV and SARS-CoV-2 infection in the Syrian Golden Hamster model. Related to Figure 2.** Syrian Golden Hamsters were BCG-vaccinated and intranasally infected with IAV-H3N2 or SARS-CoV-2/SB2 or /RIM-1. (A) Percent Body Weight change at day 3 post infection with  $1 \times 10^5$  PFU IAV-H3N2 in BCG-iv vaccinated and nonvaccinated control Golden Hamsters,  $n=8$ /group. (B) Lung viral load in Syrian Golden Hamsters after SARS-CoV-2/SB2 ( $1 \times 10^5$  PFU) infection, determined by qPCR,  $n=3-5$ /group. (C) Total lung leukocytes at day 3 and 5 post-SARS-CoV-2/SB2 infection in Syrian Golden Hamsters,  $n=3-5$ /group. (D) Flowcytometric analysis of cell populations in BAL, lung, spleen, and blood at day 3 post SARS-CoV-2/SB2 infection in Syrian Golden Hamsters,  $n=3-6$ /group, refer to Table S1. (E) Lung viral load in Syrian Golden Hamsters after SARS-CoV-2/RIM-1 infection, determined by qPCR,  $n=5$ /group. (F and G). Serum IFN- $\beta$  and IL-6 levels in Syrian Golden Hamsters post SARS-CoV-2 infection,  $n=3-5$ /group. Data are displayed as mean  $\pm$  SEM. \*  $p < 0.05$ , \*\*  $p \leq 0.01$ , \*\*\*  $p \leq 0.001$ , \*\*\*\*  $p \leq 0.0001$  (ONEway ANOVA).

Fig. S3



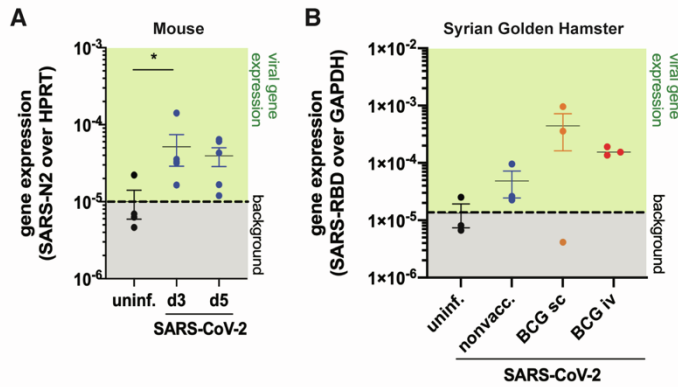
**Fig. S3: SARS-CoV-2 infection in the Roborovski Hamster model. Related to Figure 3.** Roborovski Hamsters were BCG-vaccinated and intranasally infected with SARS-CoV-2/RIM-1. **(A)** Lung viral load in 1-month BCG-vaccinated and nonvaccinated Roborovski Hamsters at day 3 post SARS-CoV-2/RIM-1 infection ( $1.4 \times 10^4$  PFU and  $1 \times 10^5$  PFU), determined by qPCR,  $n=4-5$ /group. **(B and C)** Serum IFN- $\beta$  and IL-6 levels in Roborovski Hamsters post SARS-CoV-2 infection,  $n=3-5$ /group. **(D and E)** Weight loss and lung viral load determined by TCID50/ml assay in 6-month BCG-vaccinated and control Roborovski Hamsters infected with SARS-CoV-2/RIM-1 ( $1.4 \times 10^4$  PFU) for 3 days,  $n=4-5$ /group. Stars in Morbidity curve **(D)** indicate significant weight loss compared to day 0. Data are displayed as mean  $\pm$  SEM. \*  $p < 0.05$ , \*\*  $p \leq 0.01$ , \*\*\*  $p \leq 0.001$ , \*\*\*\*  $p \leq 0.0001$  (2way ANOVA).

Fig. S4



**Fig. S4: Lung histopathology in SARS-CoV-2-infected Roborovski Hamsters. Related to Figure 4. (A)** Lung histopathology (H&E staining, 20x) in 6-month BCG-vaccinated (s.c. and i.v.) Roborovski Hamsters infected with SARS-CoV-2/RIM-1 (low dose,  $1.4 \times 10^4$  PFU, i.n.) for 3 days (n=4-5/group).

Fig. S5



**Fig. S5: SARS-CoV-2 gene expression in the bone marrow of infected mice and Syrian Golden Hamsters.**

**Related to Figure 5.** (A) SARS-CoV-2 viral load in the bone marrow of K18-hACE2/J mice (day 3 and 5 post i.t. infection with 4000 TCID SARS-CoV-2/SB2), n=4/group. (B) SARS-CoV-2 viral load in the bone marrow of BCG-vaccinated and nonvaccinated Syrian Golden Hamsters (d3 post i.n. infection with 1x10<sup>5</sup> PFU SARS-CoV-2/RIM-1), n=3/group. Data are displayed as mean +/- SEM. \* p < 0.05 (2way ANOVA).

	Gene/region	RIM-1
	5'UTR	C241T
ORF1ab	ORF1a_DUF3655	C2772T (Syn)
	ORF1a polyprotein (papain viral protease)	T5157C (Syn)
	ORF1ab polyprotein (Rpol_N)	C14143T (Pro4716Leu)
		C15059T (Syn)
	S	A1841G (Asp614Gly)
	ORF3a	C41T (Thr14Ile)

**Table S2: Mutations identified in SARS-CoV-2 variant RIM-1. Related to Figure 2.** (GenBank accession number MW599736). Mutations are relative to the Severe acute respiratory syndrome coronavirus 2 isolate Wuhan-Hu-1 reference sequence (Genbank accession number NC\_045512.2).