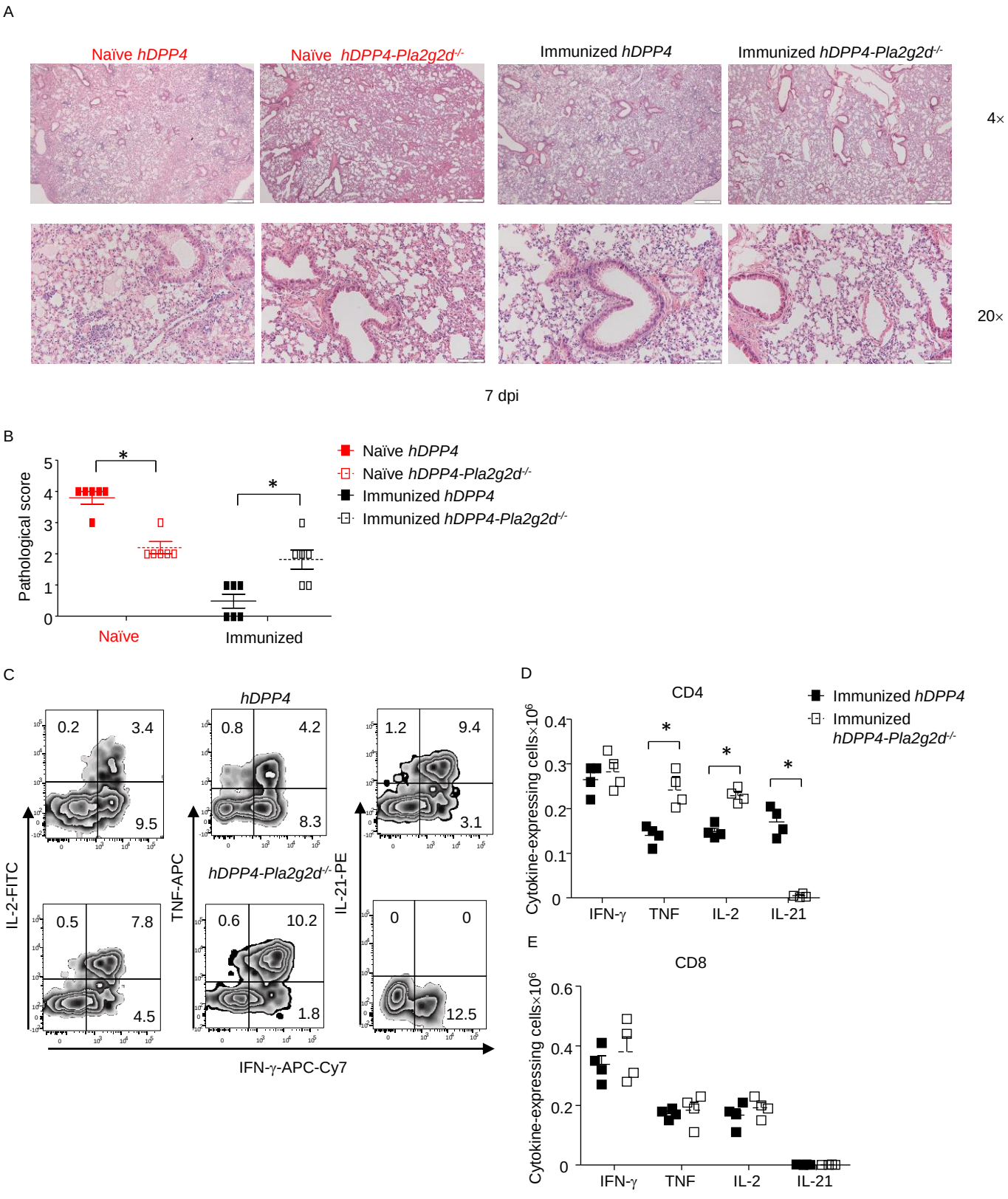
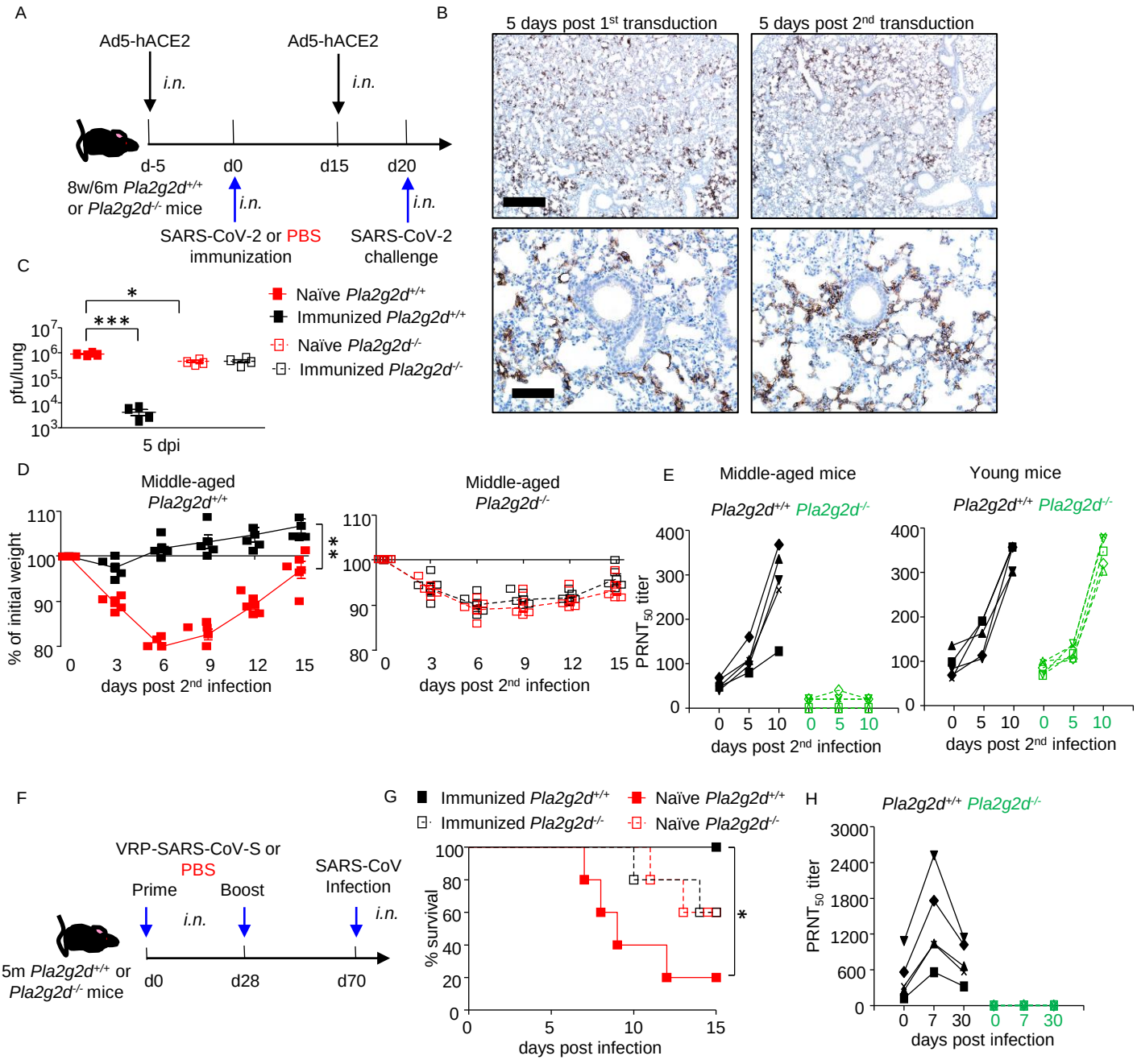
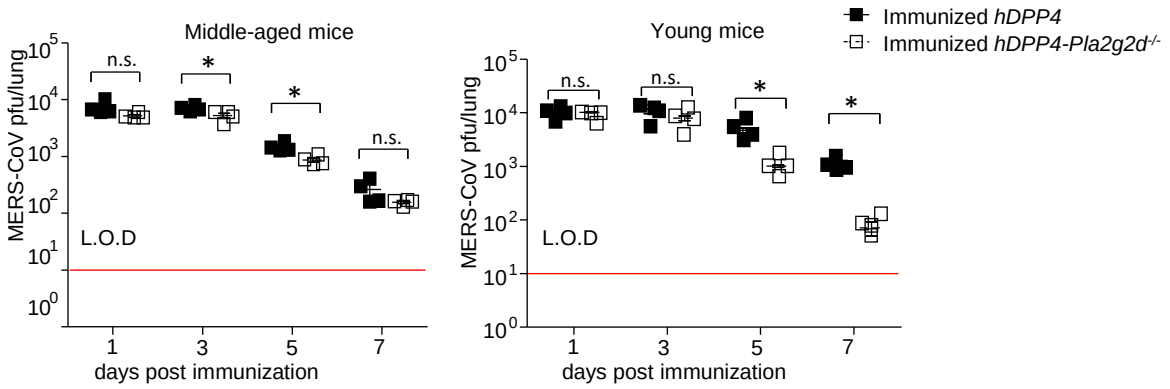


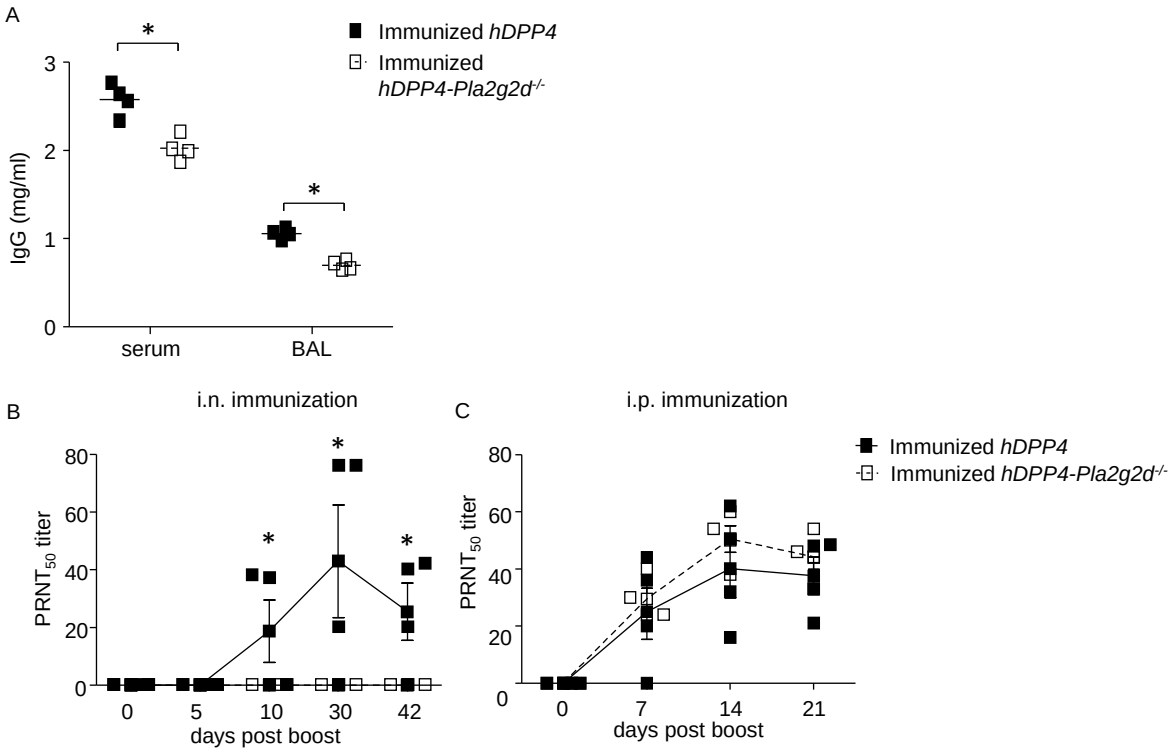
Supplementary Figure 1. Histopathological changes and T cell responses in naïve and VRP-MERS-S immunized middle-aged mice infected with lethal MERS-CoV. (**A**, **B**) Representative histological lung sections from mice sacrificed at 7dpi (**A**) and scoring (**B**) are shown. n=6/group. (**C-E**) CD4 (**C** and **D**) and CD8 (**E**) T cells were purified from lungs and DLNs of infected mice on 7dpi and re-stimulated with a MERS-CoV S protein peptide pool for 6 hours at 37℃. BFA was added at the start of culture. IFN-γ, TNF, IL-2, and IL-21 expression by T cells was determined by flow cytometry. n=4 mice/group. (**B**, **C**, **E**) Representative data of 3 independent experiments are shown as means±SEM and are analyzed by Student's t test. n=4/group, * $p<0.05$.



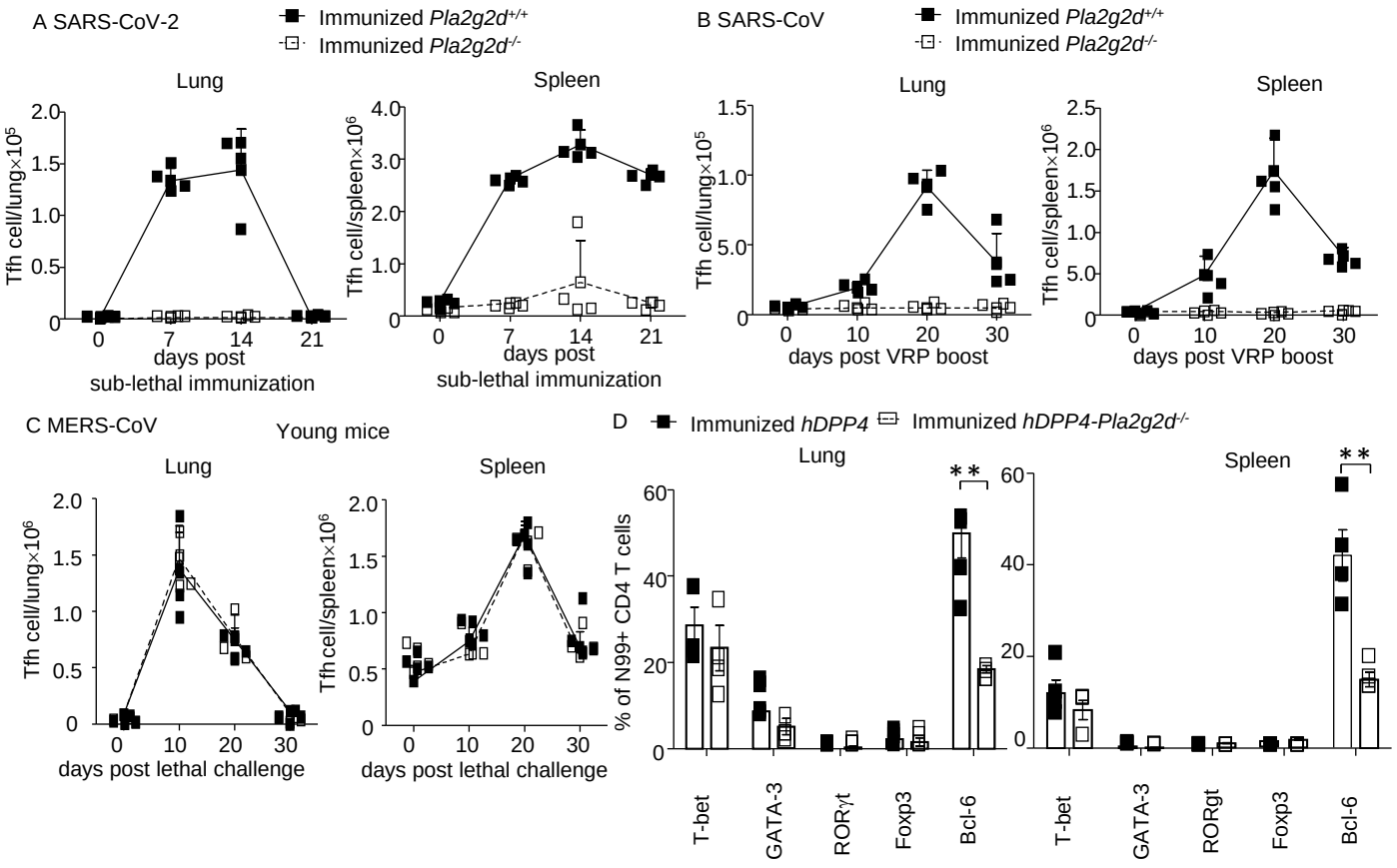
Supplementary Figure 2. Immunization fails to protect middle-aged *Pla2g2d*$^{-/-}$ mice from SARS-CoV-2 or lethal SARS-CoV infection. (**A**) Protocol for SARS-CoV-2 infection and re-challenge. 8-week (young) or 6-month (middle-aged) *Pla2g2d*$^{+/+}$ or *Pla2g2d*$^{-/-}$ mice were transduced with Ad5-hACE2, followed by 10^5 pfu infection with SARS-CoV-2 or PBS i.n. 5 days later (day 0). At 20 dpi, mice were challenged with 10^5 pfu SARS-CoV-2, i.n. (**B**) Expression of hACE2 in transduced mice lungs. Bar=467 and 94 μm, top and bottom panels respectively. (**C**, **D**) Virus titers in lungs at 5 days post challenge (**C**) and weights (**D**) of naïve and immunized middle-aged mice are shown, n=5/group. (**E**) The titer of serum virus-specific neutralizing antibody from SARS-CoV-2-infected middle-aged and young mice at indicated days post challenge was determined by $PRNT_{50}$ assay as described in Methods, n=5/group. Antibody titers from individual mice are shown. (**F**) Protocol for VRP-SARS-S immunization and SARS-CoV infection. 5-month *Pla2g2d*$^{+/+}$ or *Pla2g2d*$^{-/-}$ mice were treated with VRP-SARS-S or PBS i.n. on days 0 and 28, followed by lethal infection with SARS-CoV (10^5 pfu) on day 70, i.n. (**G**) Survival of immunized and infected mice is shown and compared using Kaplan-Meier log-rank survival tests, n=5/group. (**H**) The titer of serum virus-specific neutralizing antibody from SARS-CoV-infected mice at indicated days post challenge was determined by $PRNT_{50}$ assay as described in Methods, n=5/group. Antibody titers from individual mice are shown. (**C**, **D**) Data are shown as means±SEM and are representative of 3 independent experiments. Each pair of data shown in **C** was compared using 1-way ANOVA, while data shown in **D** were analyzed using Multiple regression analysis.* p<0.05, *** p<0.001.



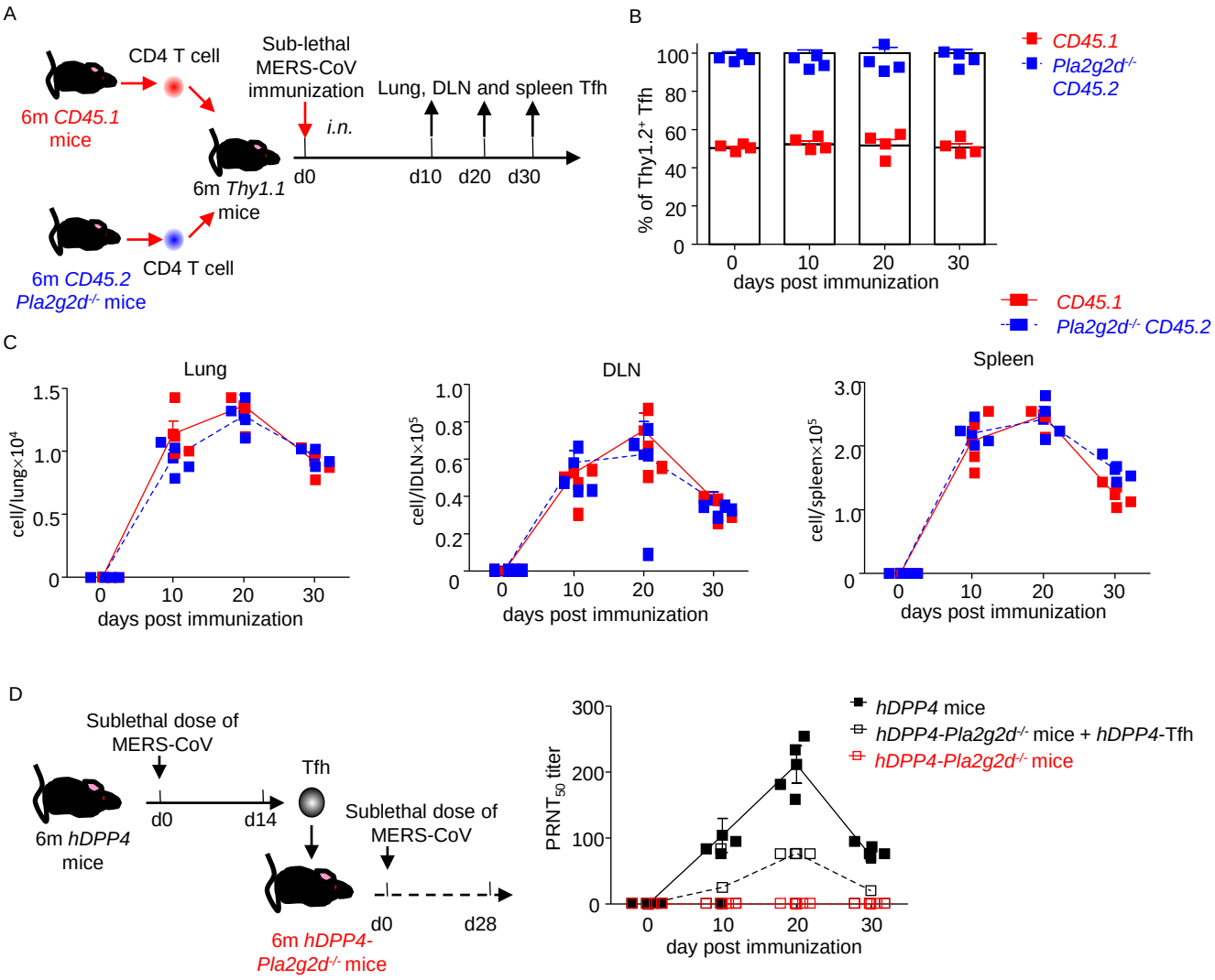
Supplementary Figure 3. Virus clearance in naïve mice immunized with a sublethal dose of MERS-CoV. 8-week (young) or 6-month (middle-aged) *hDPP4* or *hDPP4-Pla2g2d*$^{-/-}$ mice were treated with a sublethal dose (100pfu) of MERS-CoV. Lung virus titers of MERS-CoV at indicated time points are shown, n=4/group. Representative data of 3 independent experiments are shown as mean±SEM and analyzed by Student's t test. *, $P < 0.05$.



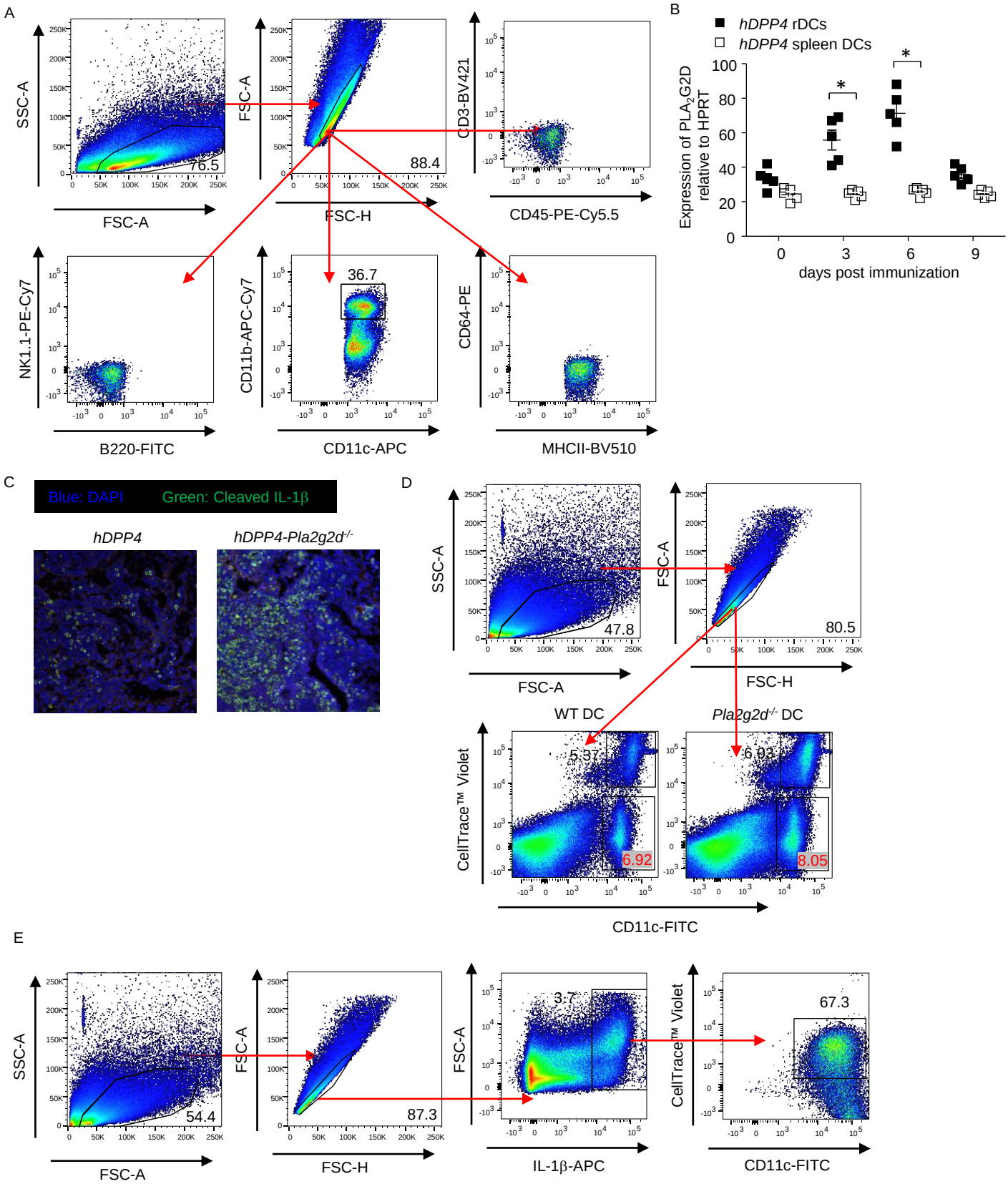
Supplementary Figure 4. Antibody production in immunized middle-aged *hDPP4* and *hDPP4-Pla2g2d*$^{-/-}$ mice. 5-month *hDPP4* or *hDPP4-Pla2g2d*$^{-/-}$ mice were immunized with VRP-MERS-S/VRP-MERS-N, or PBS i.n. on days 0 and 28. (**A**) Sera and BAL IgG were harvested at 15 dpi and quantitated by ELISA using mouse IgG standard as described in Methods, n=6/group. (**B**, **C**) Serum MERS-CoV-specific $PRNT_{50}$ antibody titers at indicated days post i.n. (**B**) and i.p. (**C**) immunization with VRP-MERS-S, n=4/group. Data are shown as mean±SEM and are representative of 3 independent experiments. Data shown in **A** and **B** were compared using Student's t test.* $p<0.05$.



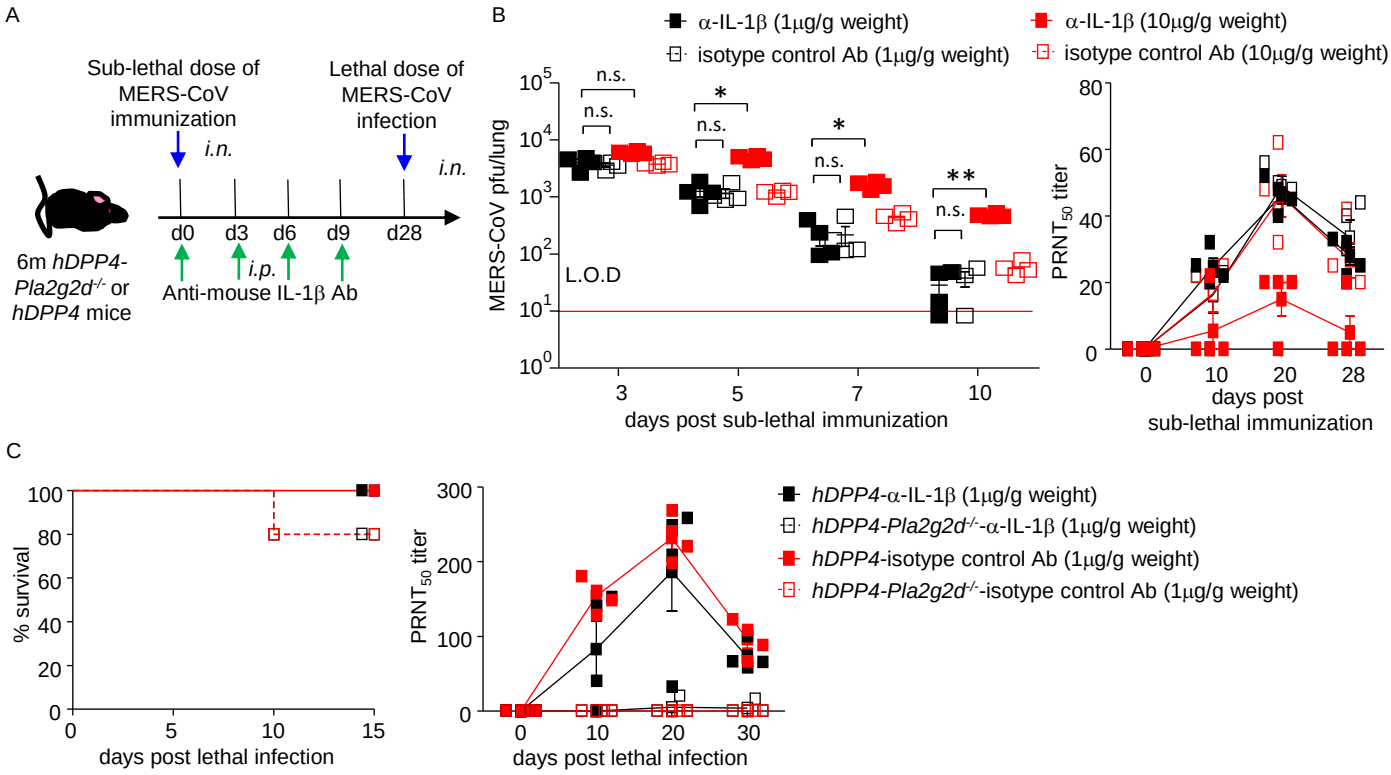
Supplementary Figure 5. PLA_2G2D deficiency specifically impairs the development of Tfh subpopulation. (**A**-**C**) Dynamics of Tfh development in lungs and spleens of middle-aged mice immunized with SARS-CoV-2 (**A**) or VRP-SARS-S (**B**), or young mice immunized with a sublethal dose of MERS-CoV (**C**) at indicated days post immunization, n=5/group. (**D**) 5-month *hDPP4-Pla2g2d*$^{-/-}$ mice and hDPP4 mice were immunized with VRP-MERS-N as described above. Lungs and spleens were harvested on day 70 post priming. Expression of T-bet (Th1), GATA-3 (Th2), RORγt (Th17), Foxp3 (regulatory T cells, Treg) and Bcl-6 (Tfh) by lung and spleen CD4 T cells was determined by flow cytometry. Data are shown as means±SEM and are representative of 3 independent experiments. n=5/group, (**D**) Data were analyzed using Student's t test. ** $p<0.01$.



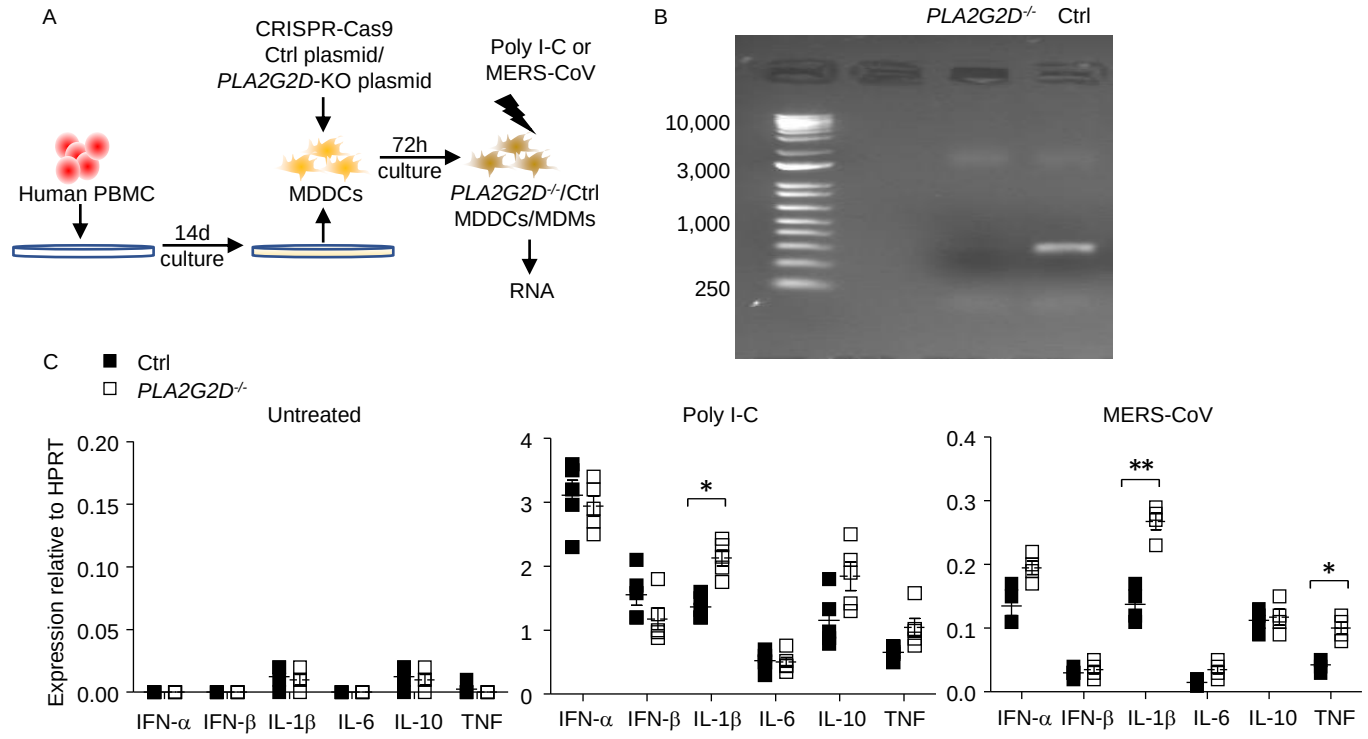
Supplementary Figure 6. Impaired Tfh development in immunized middle-aged mice is mediated by T cell-extrinsic factors. (**A**) Protocol for CD4 T cell adoptive transfer. (**B**, **C**) The relative percentage (**B**) and absolute numbers (**C**) of PD-1$^+$CXCR5$^+$Thy1.1$^-$CD45.1$^+$ and PD-1$^+$CXCR5$^+$Thy1.1$^-$CD45.1$^-$ cells in lungs, DLNs and spleens of recipient Thy1.1$^+$ mice at indicated days post infection are shown. (**D**) Protocol for CD4 Tfh cell adoptive transfer (left) and neutralizing antibody production by recipient mice (right) after lethal challenge. Data are shown as means±SEM and are representative of 3 independent experiments. n=4/group/time point.



Supplementary Figure 7. Lung compared to spleen DCs express high levels of PLA_2G2D and IL-1β. 5-month *hDPP4* and *hDPP4-Pla2g2d*$^{-/-}$ mice were treated with VRP-MERS-S or PBS i.n. on day 0 and 28, followed by a lethal dose (750pfu) of MERS-CoV on day 70, i.n. Mice were treated intranasally with CFSE at day 0 post infection to track the migration of rDCs. (**A**) Phenotype of purified rDCs ($CD3^-CD19^-CD56^-MHC\text{-}II^+CD64^-$). (**B**) Expression of *Pla2g2d* by rDCs and spleen DCs harvested from immunized hDPP4 mice is shown. Data are shown as means±SEM and analyzed using Student's t test. n=5/group, * $p<0.05$. (**C**) Expression of cleaved IL-1β by purified $CD11c^+$ rDCs from *hDPP4* or *hDPP4-Pla2g2d*$^{-/-}$ mice determined by fluorescent microscopy. (**D**) CellTrace dye (Violet)-labelled $CD11c^+$ rDCs from *hDPP4* or *hDPP4-Pla2g2d*$^{-/-}$ mice were adoptively transferred into *hDPP4-Pla2g2d*$^{-/-}$ mice as described in Fig. 5C. Transferred $CD11c^+$ rDCs in DLN of recipients at 5 days post transfer were detected by flow cytometry. (**E**) CellTrace dye (Violet) and CD11c expression of IL-1β-expressing cells in DLN were determined by flow cytometry. (**C-E**) Data are representative of 3 independent experiments.



Supplementary Figure 8. IL-1β blockade alone failed to reverse impaired neutralizing antibody production. (**A**) 6-month *hDPP4* or *hDPP4-Pla2g2d*$^{-/-}$ mice were inoculated with a sublethal dose (100pfu) of MERS-CoV i.n. on day 0 and treated with different doses of anti-IL-1β antibody. (**B**) Lung virus titers of MERS-CoV and neutralizing antibody production by hDPP4 mice were determined at the indicated time points. n=4/group. Each pair of data shown in D was compared using 1-way ANOVA, * $p<0.05$; ** $p<0.01$. (**C**) The survival of, and neutralizing antibody production by *hDPP4* or *hDPP4-Pla2g2d*$^{-/-}$ mice after lethal challenge (n=5/group) are shown. Data are shown as means±SEM and are representative of 3 independent experiments.



Supplementary Figure 9. PLA_2G2D deficiency modifies the inflammatory status of human MDMs and MDDCs. (**A**) Protocol for engineering human *PLA2G2D*$^{-/-}$ MDDCs, using CRISPR-Cas9, as described in Methods. (**B**) Efficacy of deletion was monitored by PCR for each donor (shown for one donor). (**C**) RNA expression of inflammation-related molecules (IFN-α, IFN-β, IL-1β, IL-6, IL-10, TNF) in untreated, Poly I-C-treated or MERS-CoV-infected MDDCs as determined by RT-PCR. Data in **C** are from five 50-60 year old human donors and analyzed using Student's t test, * $p<0.05$, ** $p<0.01$.