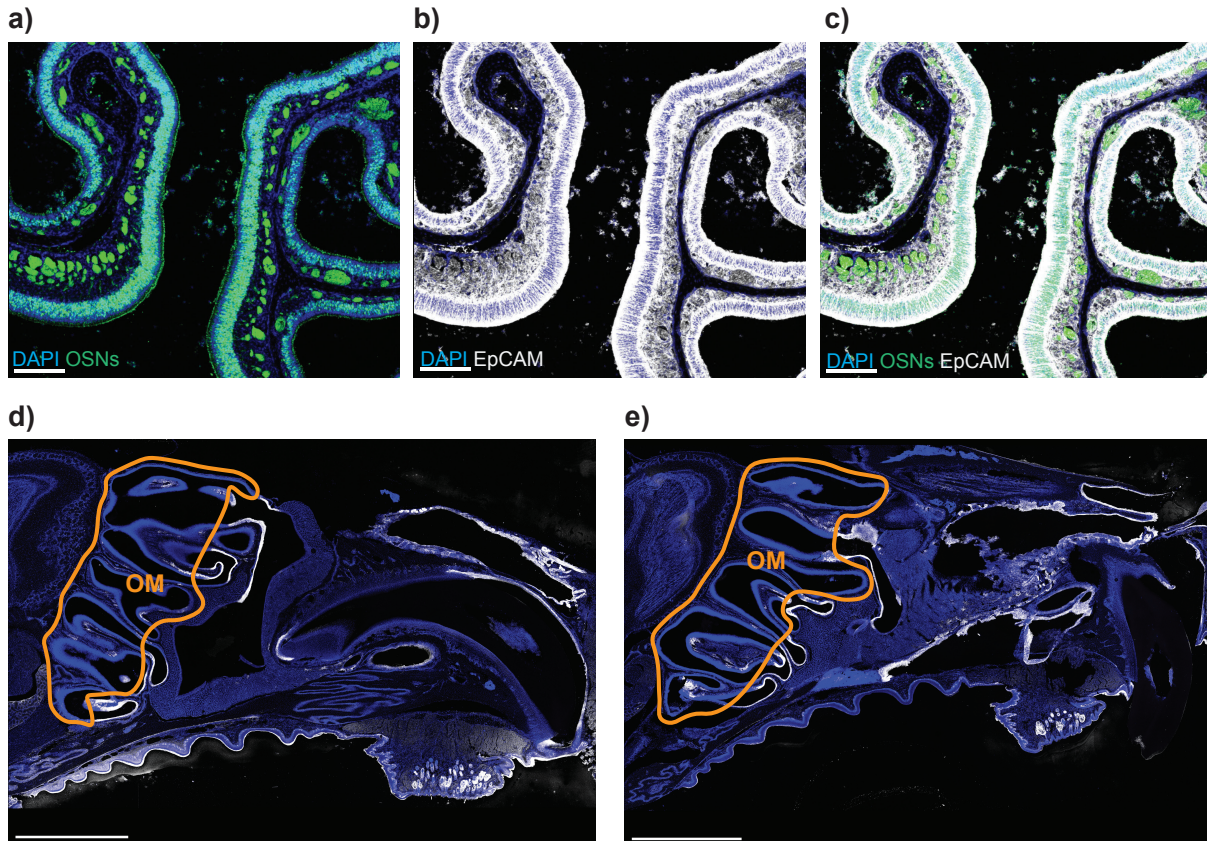


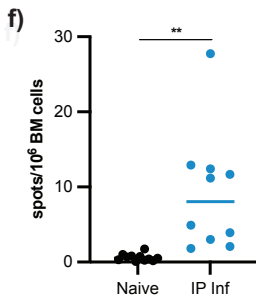
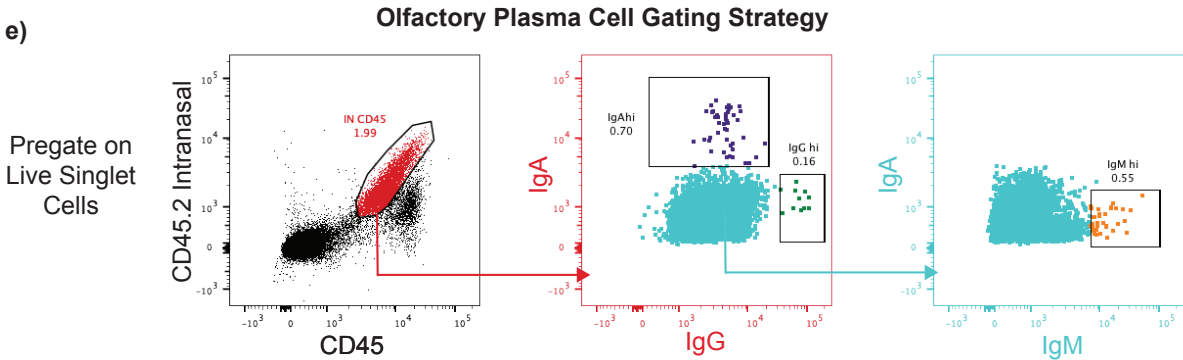
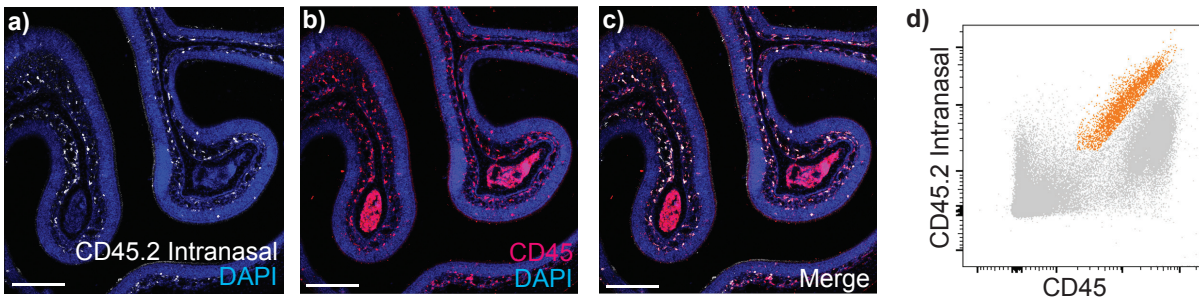
**Figure S1 - Serum Ab Levels Fail to Correlate with Protection of the OM from Infection, related to Fig. 1**

**(a)** Plasma nAb titers corresponding to Figure 1b-c. **(b)** D4 OM viral titers from WT mice IP infected with VSV ( $n = 5$ ). **(c)** Plasma neutralizing antibody titers corresponding to Figure 1j.



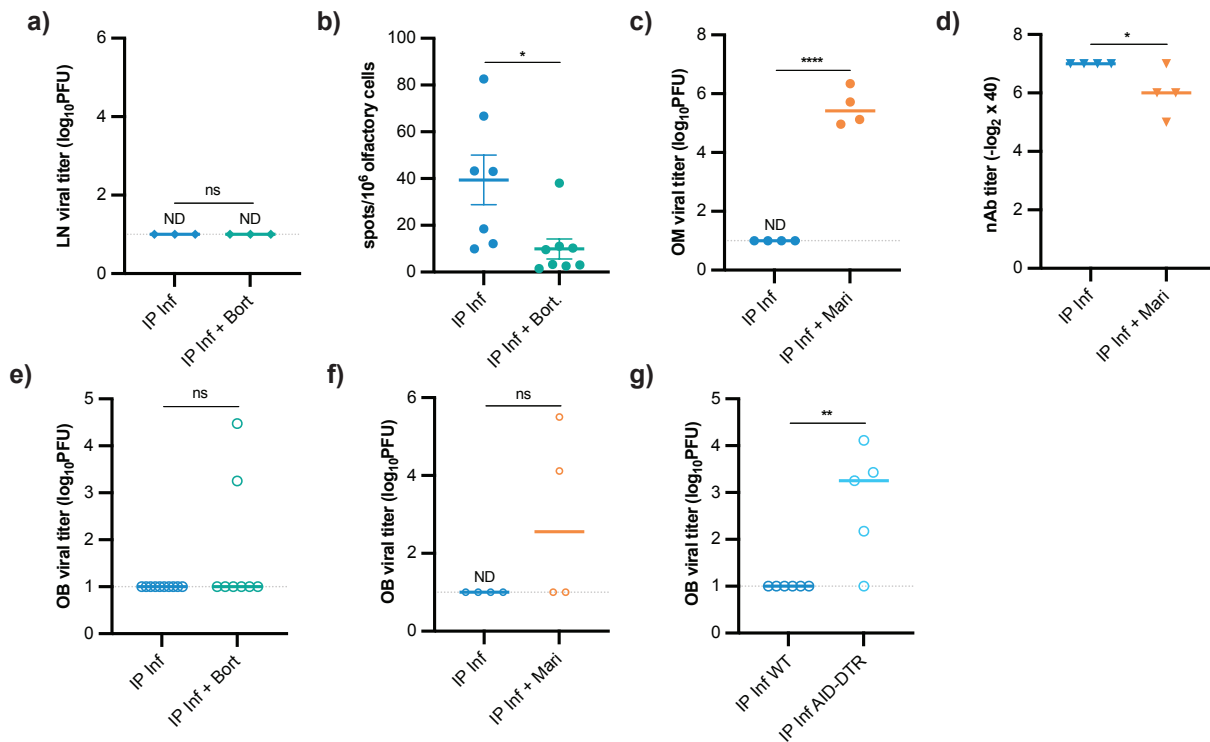
**Figure S2 - Antibody Moves Freely Within the Olfactory Mucosa, related to Fig. 3**

**(a-c)** 5  $\mu\text{g}$  of  $\alpha\text{-EpCAM}$  antibody was administered IN into an OMP-GFP mouse 5 minutes prior to sacrifice. Coronal OM sections were stained with DAPI and  $\alpha\text{-rat}$  Alexa Fluor 647. DAPI = blue, OMP-GFP = green, EpCAM = white. Scale bars = 50  $\mu\text{m}$ . **(d-e)** 20  $\mu\text{g}$  of  $\alpha\text{-EpCAM}$  antibody injected IP into WT mice 12h before sacrifice. Mice were previously infected with VSV 2 days prior **(d)** or 21 days prior **(e)**. Sagittal head sections stained with  $\alpha\text{-rat}$  Alexa Fluor 647 and DAPI to reveal *in vivo* antibody distribution. Blue = DAPI, Green = OMP-GFP, White =  $\alpha\text{-EpCAM}$ . Scale bar = 2 mm. Olfactory regions in orange.



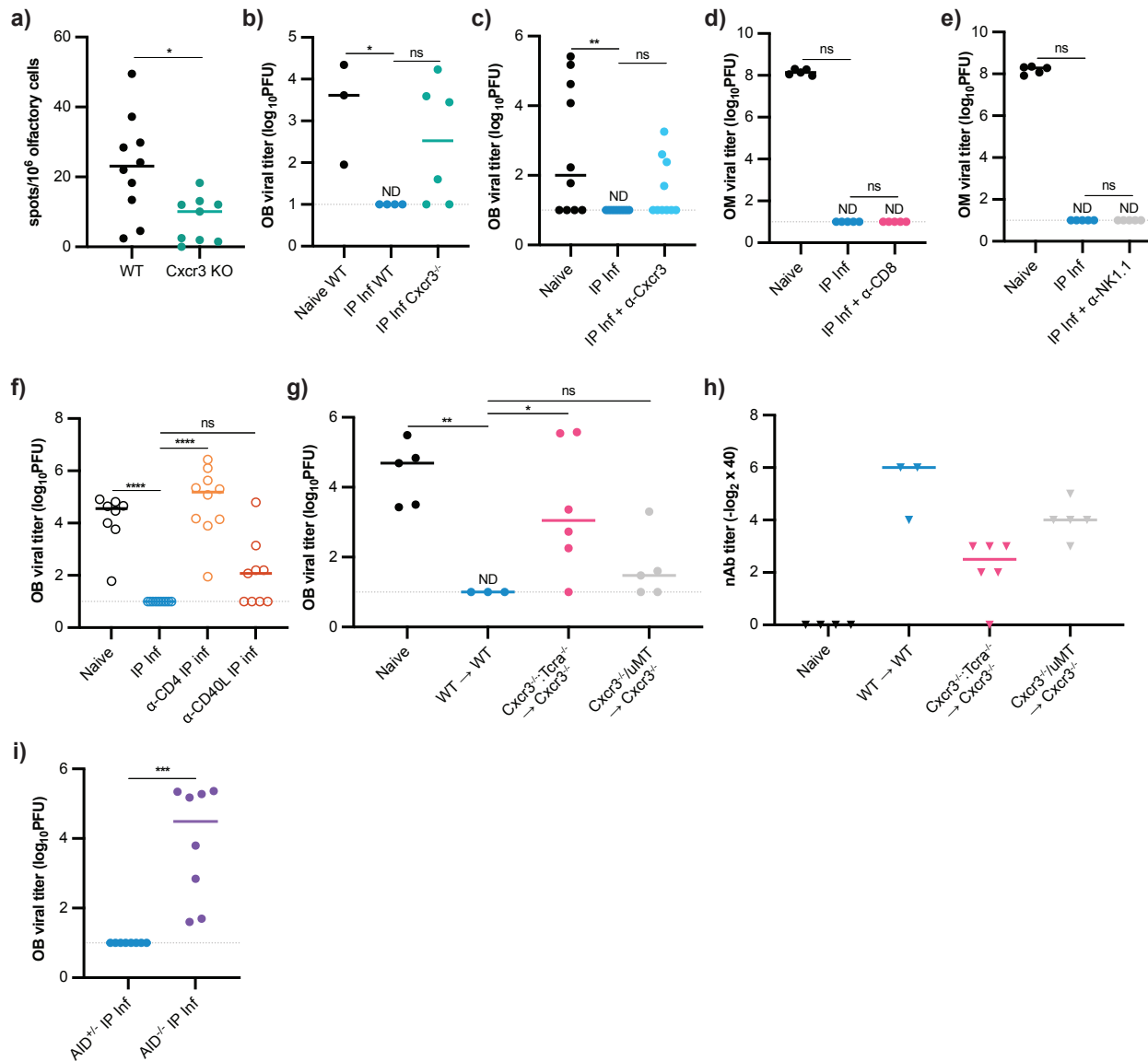
**Figure S3 - Plasma Cells are Detected in Mice, related to Fig. 4**

**(a-c)** Intranasal CD45.2 antibody labeling. 2  $\mu\text{g}$  of  $\alpha\text{-CD45.2-AlexaFluor-647}$  antibody was administered IN into an OMP-GFP mouse 5 minutes prior to sacrifice and fixation. Coronal sections of the decalcified olfactory mucosa were stained with DAPI and  $\alpha\text{-CD45-PE}$ . DAPI = blue, Intranasal CD45.2 = white, CD45 = red. Scale bars = 200  $\mu\text{m}$ . **(d)** Example of CD45.2 IN antibody labeling on flow cytometer. Orange indicates “IN+” cells, positive for both IN-administered CD45.2 and conventional CD45 staining. **(e)** Gating strategy for plasma cells identified in Figure 4 b-c. **(f)** ELISPOT was performed to detect VSV-specific antibody secreting cells in the bone marrow of naïve (n = 10) and d35 IP VSV infected (n = 10) mice, corresponding to data in Figure 4f.



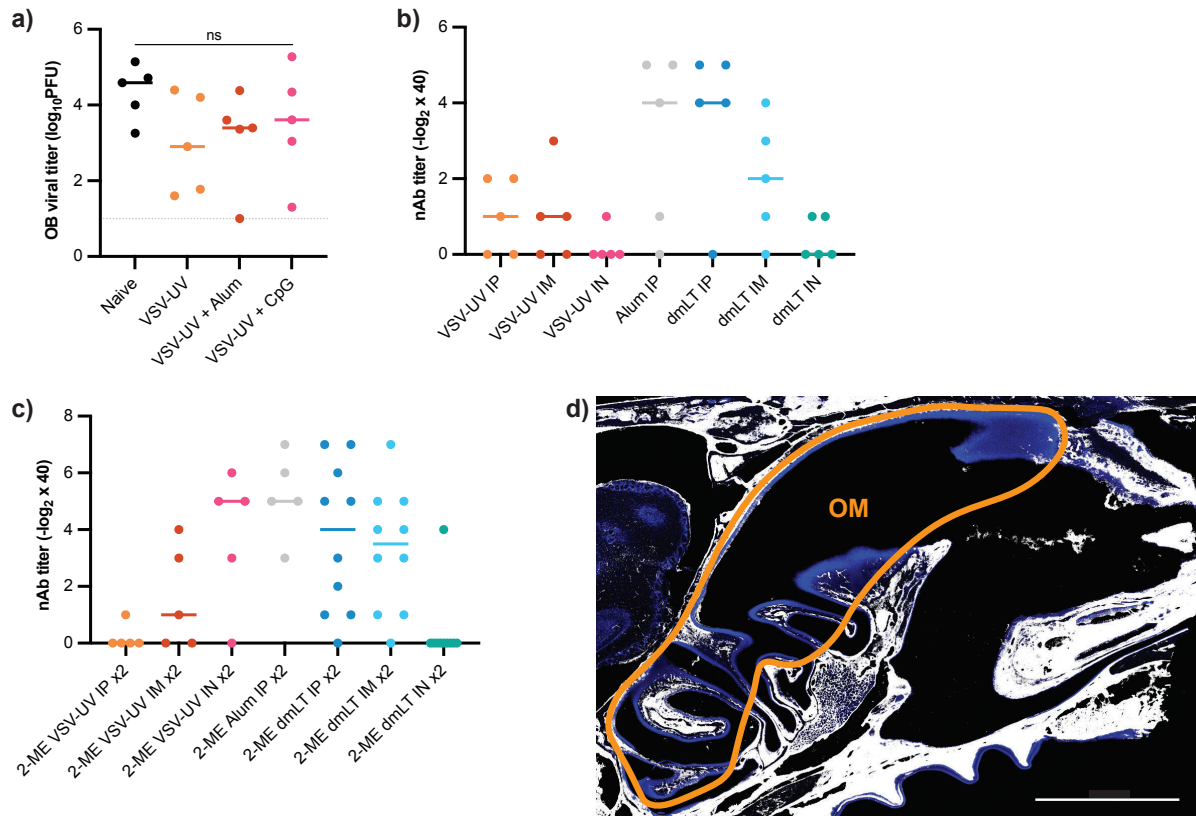
**Figure S4 - Olfactory Plasma Cells Protect the Brain from Infection, related to Fig. 5**

(a) LN VSV titers from mice IP infected and treated with ( $n = 3$ ) or without ( $n = 3$ ) bortezomib 21 dpi or given no treatment ( $n = 3$ ). At 35 dpi, mice were challenged with VSV SC (hock), and 8h later lymph nodes were harvested for viral titer assay. (b) VSV-specific ELISPOT from olfactory peels in mice either 28 dpi or 28 and treated with bortezomib at d21, d22. (c-d) OM viral titers (c) and plasma nAb titers (d) from mice VSV IP infected and treated with ( $n = 4$ ) or without ( $n = 4$ ) marizomib beginning 21 days after infection and VSV IN rechallenge 35 dpi. In (e), OB viral titers corresponding to bortezomib treatments in Figure 5a-b are given. (f) OB viral titers from marizomib treatment in Figure S4b-c. (g) OB viral titers from AID<sup>Cre/+</sup> x iDTR mice in Figure 5c-d. For (a-g), parametric unpaired t-test was used for significance. ND (not detected), ns (not significant), \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ , \*\*\*\*  $P < 0.0001$ .



**Figure S5 - CXCR3 and T cell help are Indispensable to Protect the Brain from Olfactory Infection, related to Fig. 6**

**(a)** VSV-specific ELISPOT performed on the olfactory peels of *Cxcr3*<sup>-/-</sup> mice and WT mice 21 dpi. **(b)** OB VSV titers from mice in Fig. 6a, b. **(c)** OB VSV titers from mice in Fig. 6c, d. **(d)** OM VSV titer in mice rechallenged IN with VSV. Experimental groups: naïve mice (n =5), mice previously infected IP with VSV (21 dpi), and previously IP infected mice (21 dpi) given  $\alpha$ -CD8 depleting Ab at 1, 4, and 7 dpi. **(e)** OM VSV titer in mice rechallenged IN with VSV. Experimental groups: naïve mice (n =5), mice previously infected IP with VSV (21 dpi), and previously IP infected mice (21 dpi) given  $\alpha$ -NK1.1 depleting Ab at 1, 4, and 7 dpi. **(f)** OB VSV titers from mice in Fig. 6i, j. **(g-h)** OB VSV titers from mice in Fig. 6k shown in **(g)**, and corresponding plasma nAb titers shown in **(h)**. **(i)** OB VSV titers from mice in Fig. 6l, m. For (b-g), Ordinary One-Way ANOVA with multiple comparisons was performed. For (a, i), parametric unpaired t-test was used for significance. ND (not detected), ns (not significant), \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ , \*\*\*\*  $P < 0.0001$ .



**Figure S6 - Robust Vaccine-induced nAb Titers do not Guarantee Protection of the Olfactory Mucosa and Brain, related to Fig. 7**

(a) OB viral titers from data in Fig. 7a,c. (b) Plasma neutralizing Ab titers from Fig. 7d are quantified. (c) Plasma from Fig. 7e-g were treated with 2-ME and nAb titers are plotted. (d) 20  $\mu$ g of  $\alpha$ -EpCAM antibody injected IP into WT mice 12h before sacrifice. Mice were previously immunized with VSV-UV + dmLT 23d and 2d prior. Sagittal head sections stained with  $\alpha$ -rat Alexa Fluor 647 and DAPI to reveal *in vivo* antibody distribution. Blue = DAPI, Green = OMP-GFP, White =  $\alpha$ -EpCAM. Scale bar = 2 mm. Olfactory regions in orange. For (a-b), statistical significance was determined using Ordinary One-Way ANOVA with multiple comparisons. ND (not detected), ns (not significant)  $P > 0.05$ , \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ .