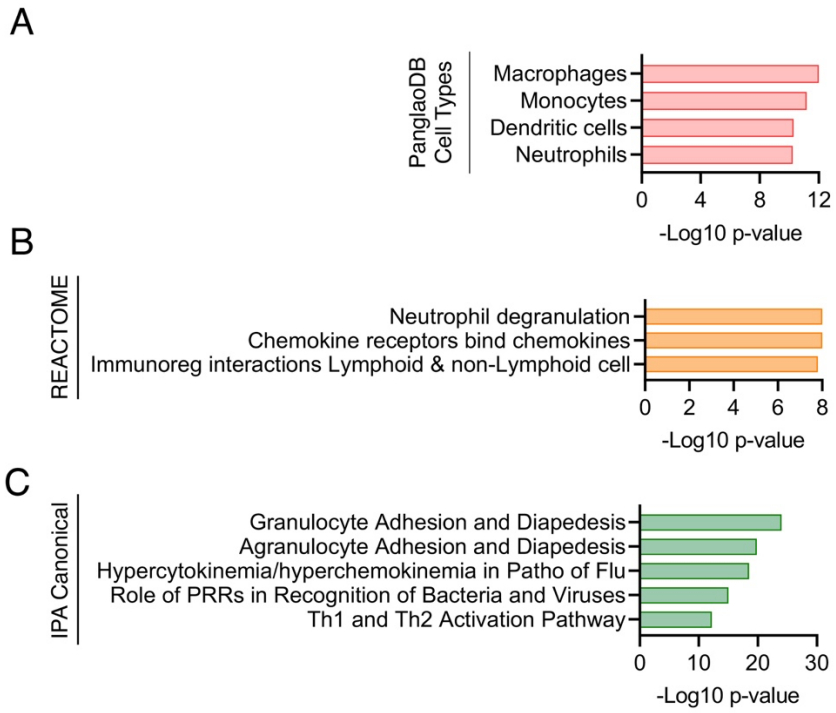
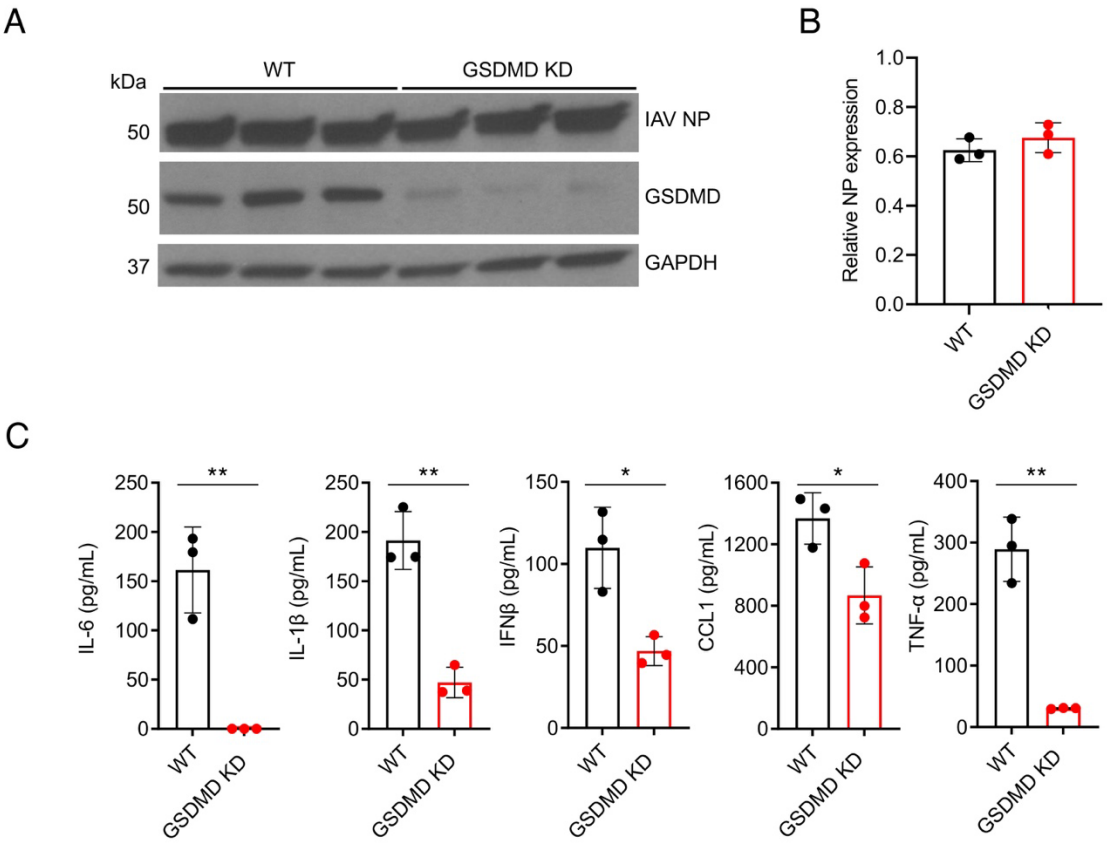
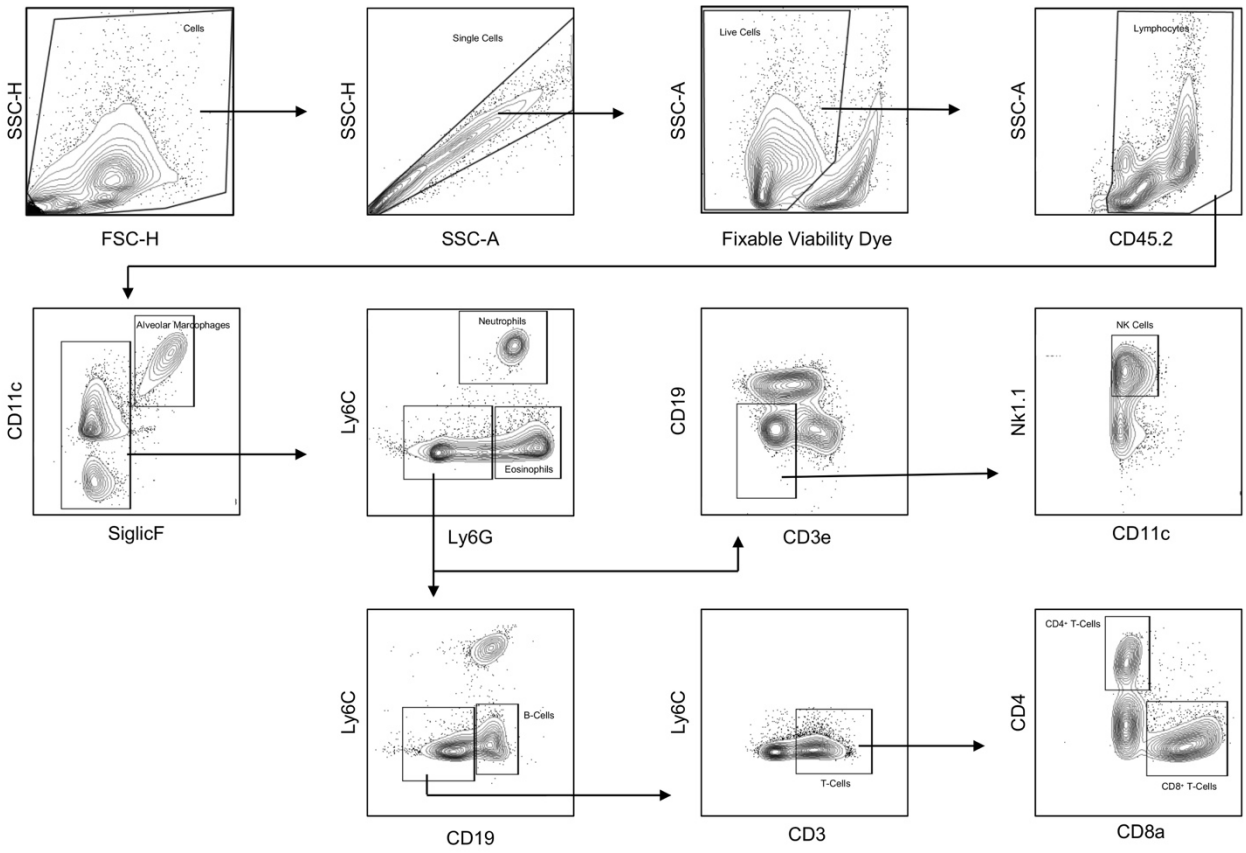


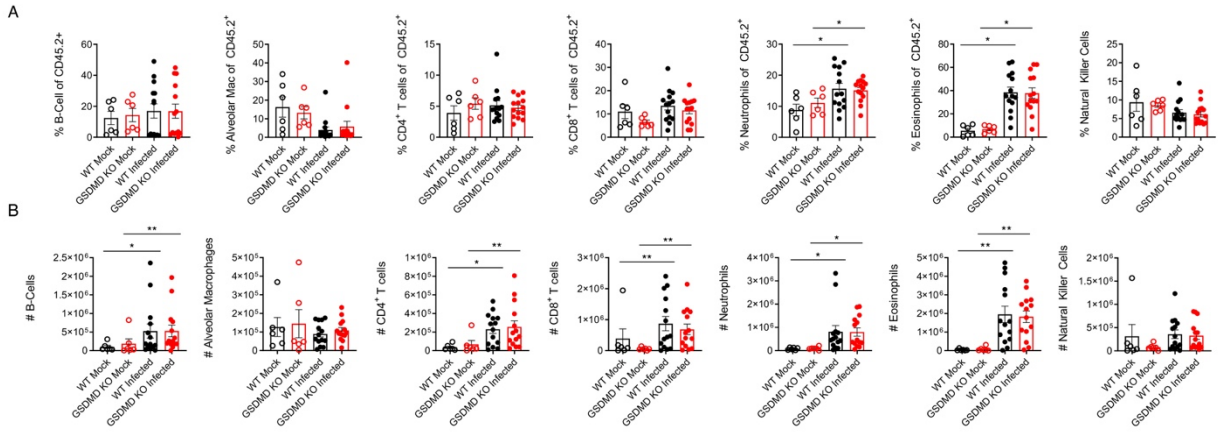

**Supplementary Figure 1: Pathway analysis of gene signatures downregulated in GSDMD KO mice. A-C** Differentially expressed genes in day 7 post infection GSDMD KO lungs versus WT were subjected to pathway and cell type analysis. **A** Downregualted genes in GSDMD KO versus WT lungs were subjected to PanglaoDB analysis and all significant associations with specific cell types are shown. **B** Significant REACTOME gene set enrichments ($p<0.05$) for all downregulated genes in GSDMD KO versus WT lungs. **C** All differentially expressed genes were examined using Ingenuity Pathway Analysis and the top five most significant Canonical Pathways are shown.



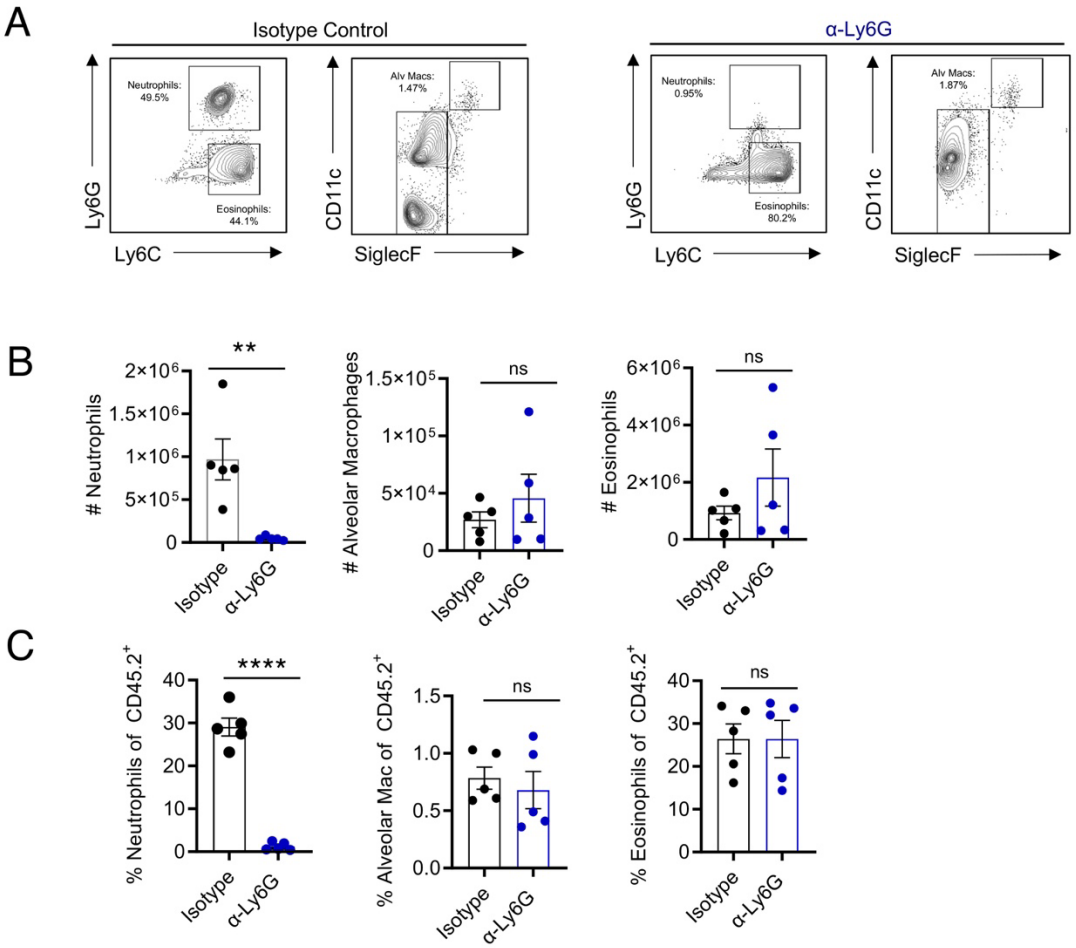

**Supplemental Figure 2: Human GSDMD promotes secretion of pro-inflammatory cytokines *in vitro*. A** Western blotting for PMA-differentiated WT and GSDMD knockdown (KD) human THP1 macrophages 48 hours post infection with PR8 at an MOI of 10 (NP = influenza virus nucleoprotein). Three technical replicates from one experiment were probed. **B** Densitometry quantifaction of NP levels relative to GAPDH in **A**. **C** ELISA quantification of IL-6, IFNβ, IL-1β, CCL1, or TNF-α levels in supernatants from cells infected as in **A** (*p < 0.05, **p < 0.01, t-test).



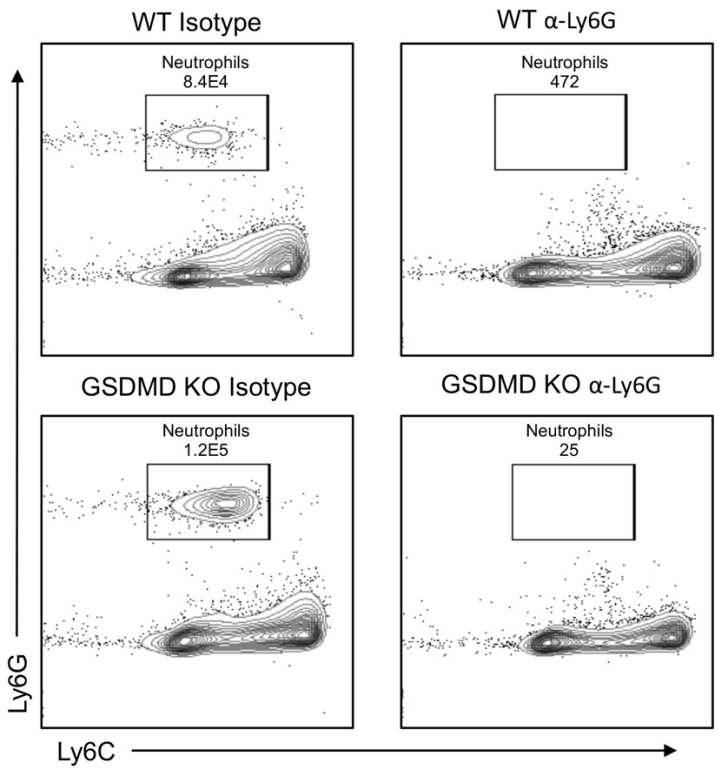

**Supplementary Figure 3: Gating strategy for quantifying immune cell recruitment to mouse lungs during IAV infection.**




**Supplementary Figure 4: GSDMD does not affect immune cell recruitment to the lung during IAV infection. A-B** WT and GSDMD KO mice were infected with 50 TCID50 of PR8. Analysis was done on day 7 post infection using the flow cytometry gating strategy show in Supplementary Figure 3. **A** Percentage of indicated cell type relative to all CD45.2$^{+}$ immune cells (*p < 0.05, two-way ANOVA and Tukey multiple comparisons test). **B** Number (#) of infiltrating immune cells into the lungs of mock and infected mice (*p < 0.05, **p < 0.01, two-way ANOVA and Tukey multiple comparisons test). Neutrophil # data is repeated from **Fig 4E** in main text.




**Supplementary Figure 5: Ly6G antibody treatment depletes neutrophils but not other innate immune cells. A-C** WT and GSDMD KO mice as infected in **Fig 5A**. **A** Representative flow cytometryt plots showing neutrophil, eosinophil, and alveolar macrophage gating rom lungs on day 5 post infection. Upstream gating performed as in Supplementary Figure 3. **B** Neutrophil, eosinophil, and alveolar macrophage total number (#) in the lung on day 5 post infection (**p < 0.01, ns, not significant, t-test). Neutrophil # data is repeated from **Fig 5B** in main text. **C** Neutrophil, eosinophil, and alveolar macrophage percentage of all CD45.2$^+$ cells in the lung on day 5 post infection (****p < 0.0001, ns, not significant, t-test).




**Supplementary Figure 6: Ly6G antibody treatment depletes neutrophils in GSDMD KO mice as epected.** Representative flow cytometry dot plots showing neutrophil gating of single-cell suspensions from the lungs of mice on day 5 post infection as in **Fig 5G**. These plots represent data from mice randomly chosen to be sacrificed to confirm neutrophil depletion.