Supplemental Information

Supplemental Figure Legends:

Supplemental Figure 1: (A) Pro-inflammatory cytokines and chemokines were measured in C57BL/6J mice 48 hours post-infection in BALF by ELISA. **(B)** RAG2$^{-/-}$ mice were infected and treated with either vehicle or CYM-5442 as done in Figure 1 and pro-inflammatory cytokines and chemokines were measured in BALF by ELISA 48-hours post-influenza infection. **(C)** Pro-inflammatory cytokines and chemokines were measured in BALF 48 hours post-infection by ELISA in mice treated with vehicle, CYM-5442 or CYM-5442 + rmCCL2. **(D)** Pro-inflammatory cytokines and chemokines were measured 48 hours post-infection by ELISA in BALF in mice treated with vehicle or CYM-5442 in the presence of either anti-CD11b or isotype control antibody (M7/80) (0.5mg/mouse) 0 and 24 hours post-infection. **(E)** C57BL/6J or IFN- α/β receptor-deficient mice were infected with 1 x 10^4 PFU of influenza virus and treated with either vehicle or CYM-5442 and pro-inflammatory cytokines and chemokines were measured 48 hours post-infection by ELISA in BALF fluid. Data represent average ± SEM from 5 mice/group. *, $p < 0.05$; **, $p < 0.005$; ***, $p < 0.0005$. Results are representative of 2 or more independent experiments.

Supplemental Figure 2: AAL-R or CYM-5442 treatment did not alter viral titers in the lung following influenza virus infection. Mice were infected with 1 x 10^4 PFU WSN influenza virus and either Vehicle (water), AAL-R (0.2mg/kg) (1 hour post-infection) or CYM5442 (2mg/kg) (1,13, 25 and 37 hours-post-infection) were administered i.t. to

mice. Viral titers were determined at the indicated times post-infection by plaque assay on MDCK cells.

Supplemental Figure 3: RP-002 treatment does not alter viral titers in the lung following human pathogenic influenza virus infection. Mice were infected with 1×10^5 PFU A/Wisconsin/WSLH34939/09 influenza virus and either Vehicle (water) or RP-002 (2mg/kg on 1 and 25 hours post-infection) were administered i.t. to mice. Viral titers were determined at the indicated times post-infection by plaque assay on MDCK cells.

Supplemental Figure 4: (A) Western blot of FACS purified lung cell populations from uninfected and 48 hours post-influenza virus infected S1P1-eGFP mice. **(B)** $S1P_1$ receptor expression is not altered after CYM-5442 treatment. Flow cytometry histograms showing eGFP fluorescence on lung endothelial, epithelial cells, CD4, CD8 T cells and B cells in $S1P_1$-eGFP mice infected with influenza virus and treated with or without CYM-5442.

Supplemental Figure 5: Mean fluorescence intensity of CD69 expression was quantified on vehicle or CYM-5442 treated macrophages/monocytes or NK cells in *Rag2*$^{-/-}$ mice 48 hours post-influenza virus infection by flow cytometry staining. Data represent average $\pm$ SEM representing 5 mice/group. *, $p < 0.05$; and ***, $p < 0.0005$. Results are representative of two independent experiments.

Supplemental Figure 6: Expression of cellular adhesion molecules on pulmonary endothelial cells 48 hours post influenza virus infection in C57BL/6J mice treated with either vehicle or CYM-5442. Data represent average ± SEM from 5 mice/group and represents 2 independent experiments.

Supplemental Figure 7: Inhibition of inflammatory macrophage/monocyte recruitment does not alter cytokine/chemokine responses following influenza virus infection. C57BL/6J or CCR2 receptor deficient mice were infected with 1 x 10^4 PFU of influenza virus and treated with either vehicle or CYM-5442 (2mg/kg 1, 13, 25, and 36 hours post infection. **(A)** Total numbers of innate immune cells were quantified from lung digests by flow cytometry at 48 hours post-influenza virus infection and **(B)** Pro-inflammatory cytokines and chemokines were measured 48 hours post-infection by ELISA in BALF fluid. Data represent average ± SEM from 5 mice/group. *, $p < 0.05$; **, $p < 0.005$; ***, $p < 0.0005$. Results are representative of two independent experiments.