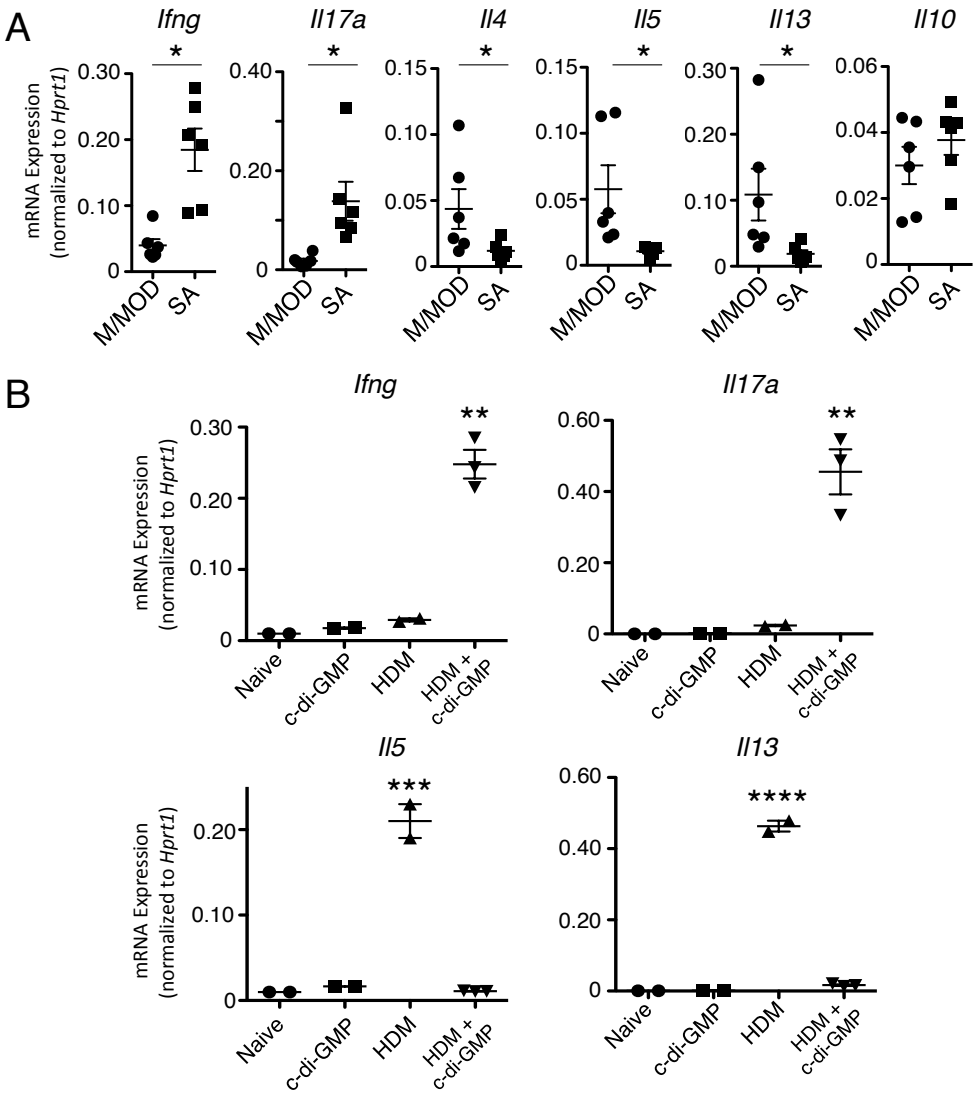
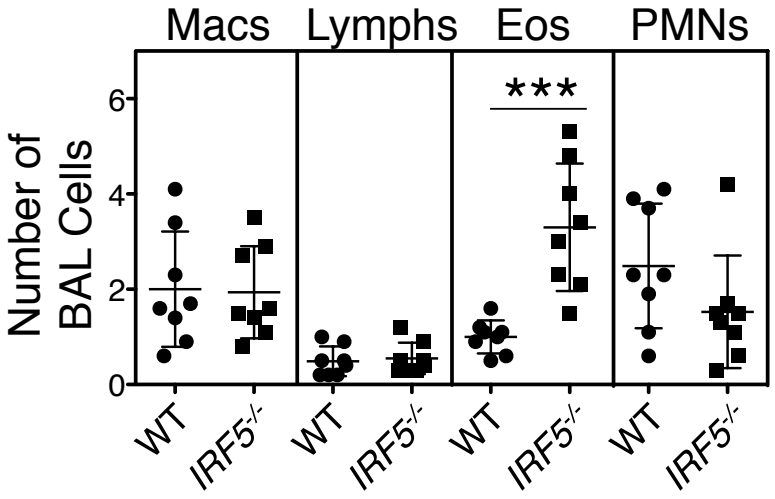
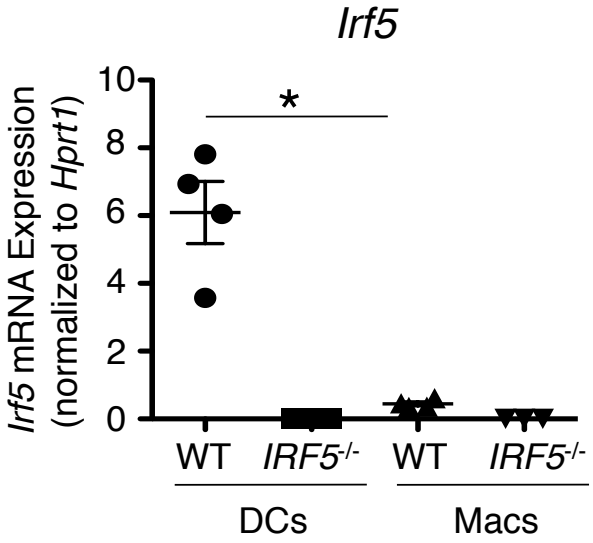


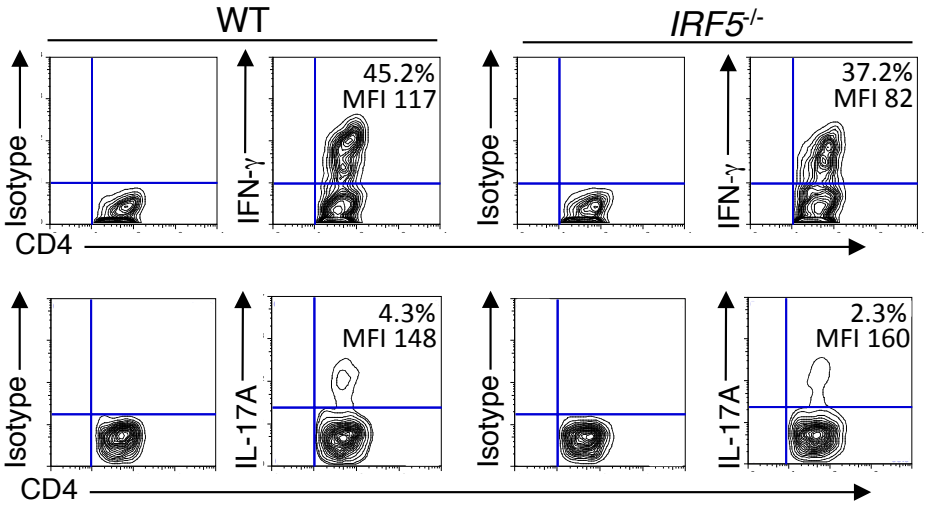
Supplemental Figure 1 Lung cytokine expression in the mild/moderate and severe asthma models. WT mice were subjected to the full 28-day mild/moderate (M/MOD) or severe asthma (SA) models. **(A)** Cytokine mRNA levels in whole lung homogenates measured by qRT-PCR. **(B)** Cytokine mRNA levels in an experiment similar to **(A)** but including comparison to naïve, untreated mice and demonstrating that c-di-GMP alone does not result in induction of cytokine expression in the lung. The data also demonstrate that house dust mite antigen (HDM) alone generates a Type 2 cytokine response whereas HDM + c-di-GMP induces Type 1 and Type 17 cytokine (**A,** n = 6 mice per group; **B**, n = 2-3 mice per group). Data are mean ± SEM and each experiment was performed at least twice. *P ≤ 0.05, using Mann-Whitney U test in **(A)** and **P ≤ 0.01, ***P ≤ 0.001, ****P ≤ 0.0001 compared to all other conditions using one way ANOVA with Bonferroni's multiple comparison test in **(B).**



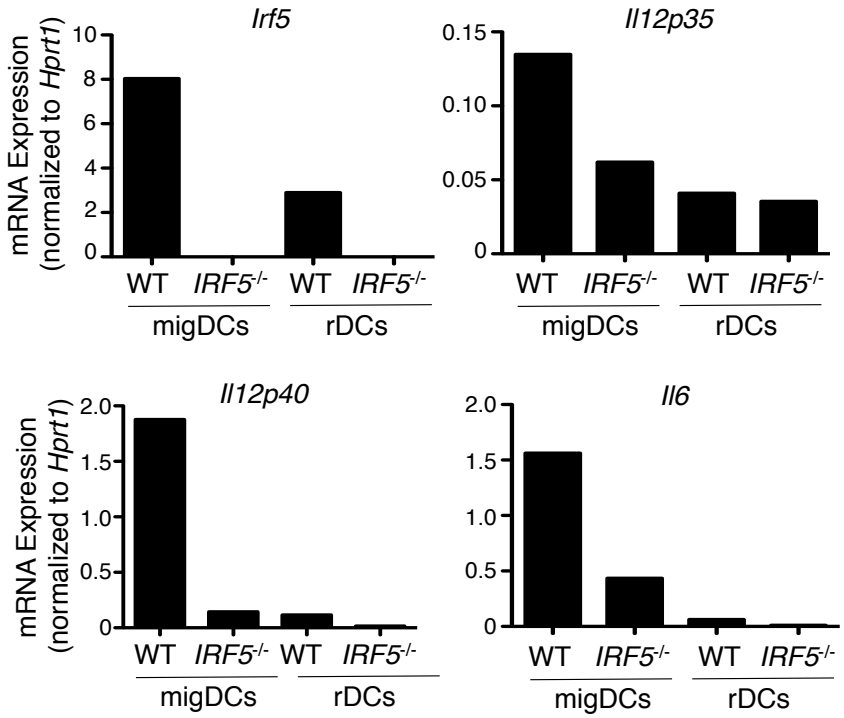
Supplemental Figure 2 Differential BAL cell numbers collected from WT and *IRF5*$^{-/-}$ mice subjected to the severe asthma model. WT and *IRF5*$^{-/-}$ mice were subjected to the full 28-day severe asthma (SA) model. Differential bronchoalveolar lavage (BAL) cell percentages were determined from at least 300 cells counted per Giemsa-stained cytospin slide. The number of each cell type was then calculated based upon the total BAL cell recovery for each mouse. (Macs, macrophages; Lymphs, lymphocytes, Eos, eosinophils, PMNs, neutrophils). ***$P \leq 0.001$ one way ANOVA with Bonferroni's multiple comparison test. n = 6-8 mice per group. Data are mean $\pm$ SEM and are representative of 3 independent experiments.



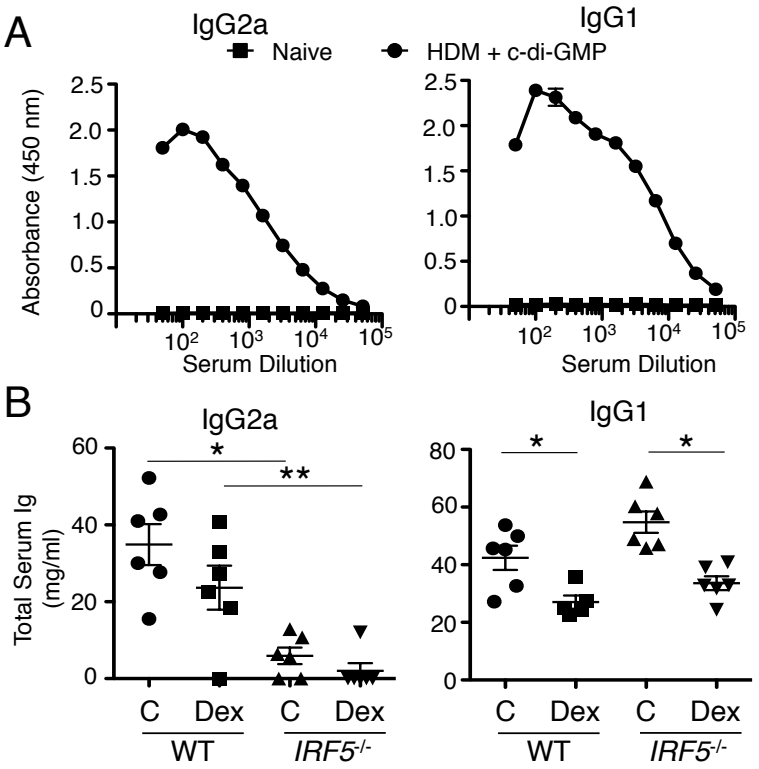
Supplemental Figure 3 Significantly higher IRF5 expression in lung DCs versus macrophages in mice treated with HDM + c-di-GMP. Lungs from WT and *IRF5*$^{-/-}$ mice were harvested 24 h following immunization with house dust mite (HDM) + c-di-GMP on d 1, 3, and 5. DCs and macrophages (Macs) were enriched from collagenase/DNAse-digested tissue using CD11c magnetic bead separation (Miltenyi Biotec). These two cell populations were then purified by cell sorting using a FACSAria cell sorter (BD Immunocytometry Systems) based upon autofluorescence and MHC Class II staining: lung macrophages are autofluorescence^{high}/MHC ClassII^{low}, and DCs are autofluorescence^{low}/MHC Class II^{high}. mRNA was prepared from the purified cells and qRT-PCR was performed for *Irf5* expression relative to *Hprt1*. *P $\leq$ 0.05, **P $\leq$ 0.05 using Mann-Whitney U test. The experiment was performed twice independently.



Supplemental Figure 4 Decreased numbers of IFN-γ– and IL-17A-expressing CD4$^+$ T cells in the lymph nodes of *IRF5*$^{-/-}$ mice in the sensitization phase of the severe asthms model. Lymph nodes were harvested 24 h following immunization with house dust mite (HDM) + c-di-GMP on d 1, 3, and 5. Total lymph node cells were re-stimulated in vitro for 72 h with HDM. For intracellular IFN-γ (APC, clone XMG1.2; BD Biosciences catalog 554413; 1:100) and IL-17A (PE, clone TC11-18H10; BD Biosciences catalog 559502; 1:100) staining, in vitro-stimulated cells were treated with PMA (50 ng/ml) and ionomycin (500 ng/ml) for 5 h with brefeldin A (GolgiPlug; BD Biosciences) added during the final 3 h. The cells were fixed in 4% paraformaldehyde for 20 min at RT, followed by permeabilization (CytoPerm; BD Biosciences) for 30 min at 0^{o}C, then optimally diluted antibody also for 30 min at 0^{o}C. Plots shown are gated on CD4$^+$ T cells.



Supplemental Figure 5 Lymph node resident DCs express less IRF5 and inflammatory cytokines than migratory DCs. Lymph nodes were harvested 24 h following immunization with house dust mite (HDM) + c-di-GMP on d 1, 3, and 5. Lymph node resident DCs (rDCs) and migratory DCs (migDCs) were purified by cell sorting using the gating strategy shown in Figure 3A. mRNA was isolated and qRT-PCR was performed on the purified cells for *Irf5, Il12p35, Il12p40 and Il6*. Expression levels for cells pooled from 4-5 mice are shown relative to *Hprt1*.



Supplemental Figure 6 Specificity of HDM-specific ELISAs, and total serum IgGs in the SA model. (A) As described in detail in the Methods, an antigen-specific ELISA was developed incorporating plates coated with house dust mite (HDM), incubation with diluted sera from naïve or mice treated with HDM + c-di-GMP, then detection with labeled antibodies specific for mouse IgG2a or IgG1. Shown is absorbance at 450 nm with correction measured at 570 nm. **(B)** Total serum IgG2a and IgG1 was measured in sera obtained from WT and *IRF5*$^{-/-}$ mice that had been subjected to the full SA model. These values were compared to absorbance values in the HDM-specific assays above in order to generate an arbitrary combined value for individual mice. The data plotted using these arbitrary values are shown in Figure 6C. Total serum and HDM-specific Igs were below the level of detection in serum from naïve, untreated animals. *P $\leq$ 0.05, **P $\leq$ 0.05using Mann-Whitney U test. n = 5-6 mice per group and the experiment was performed twice independently.