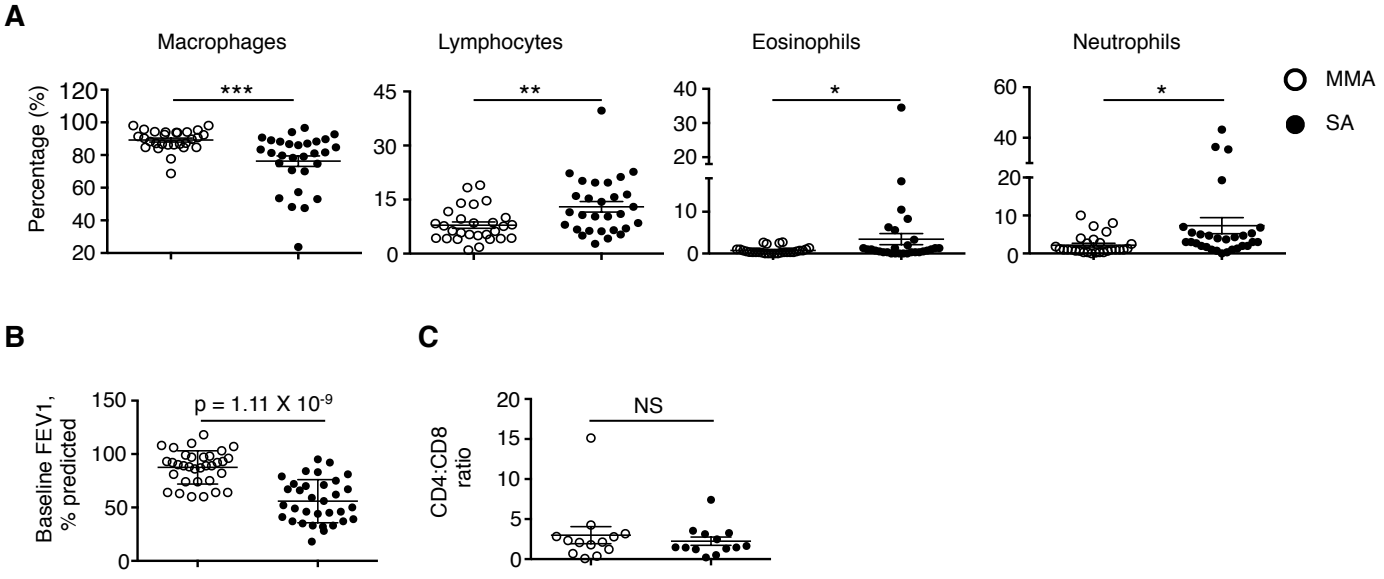
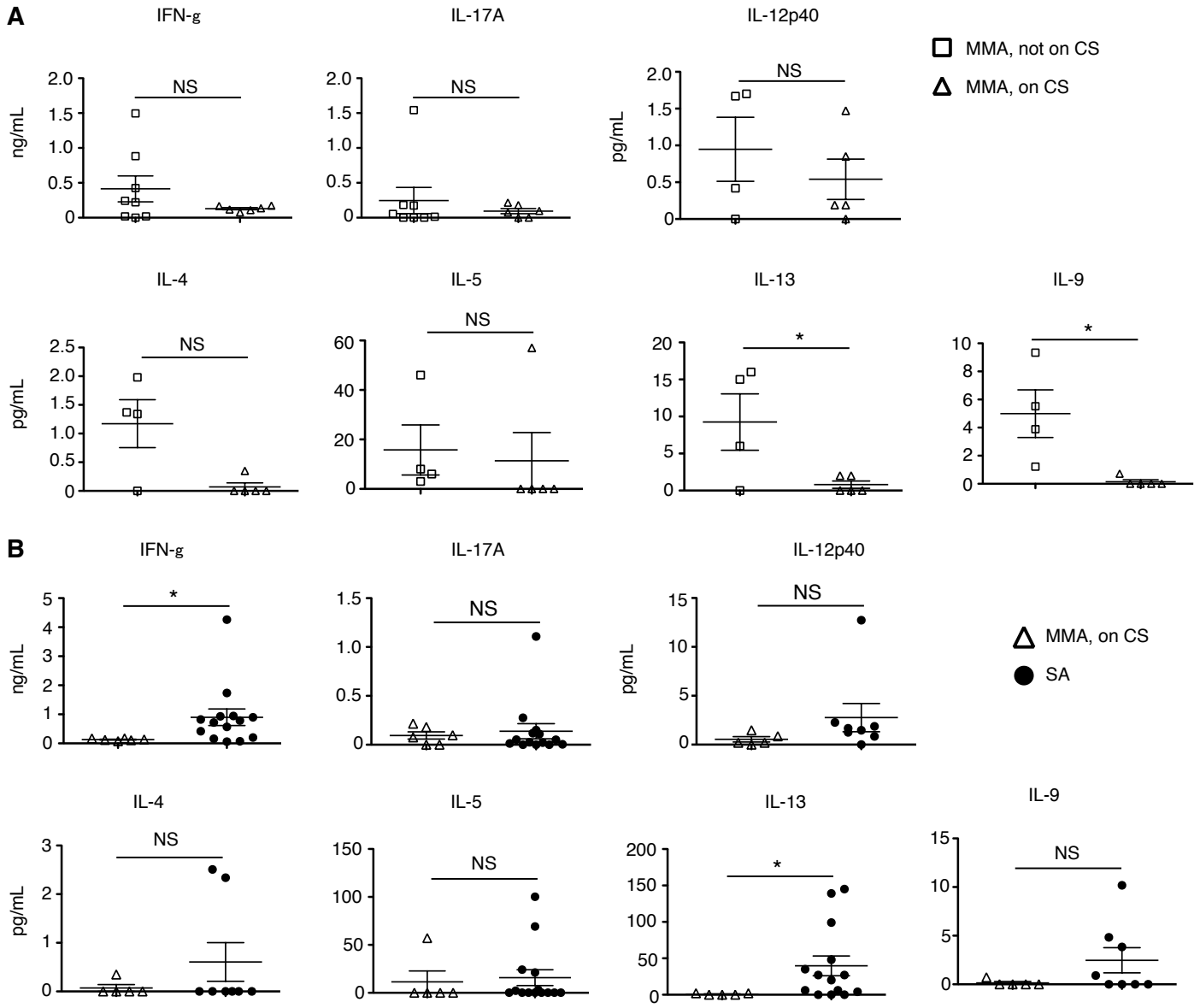
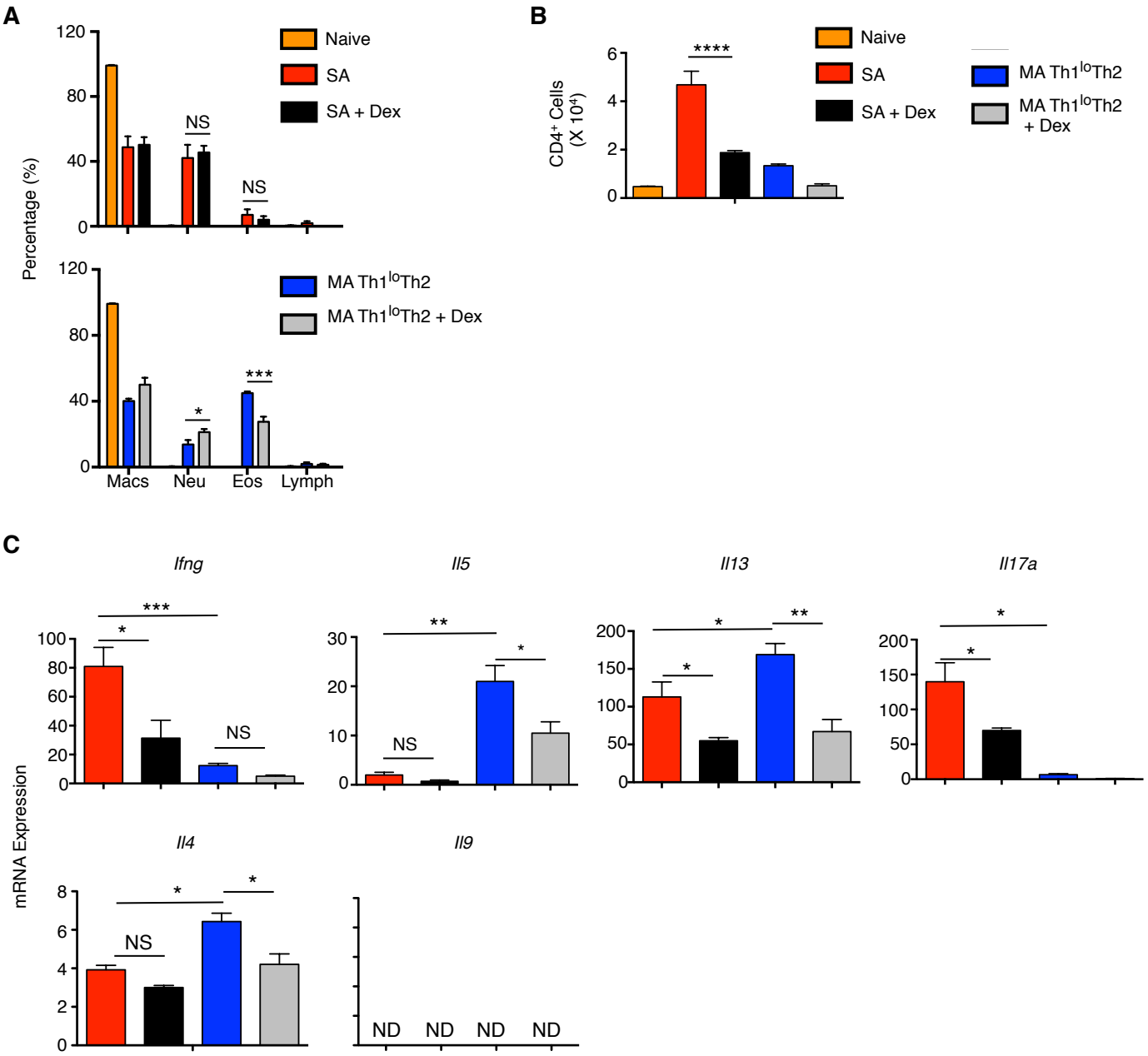


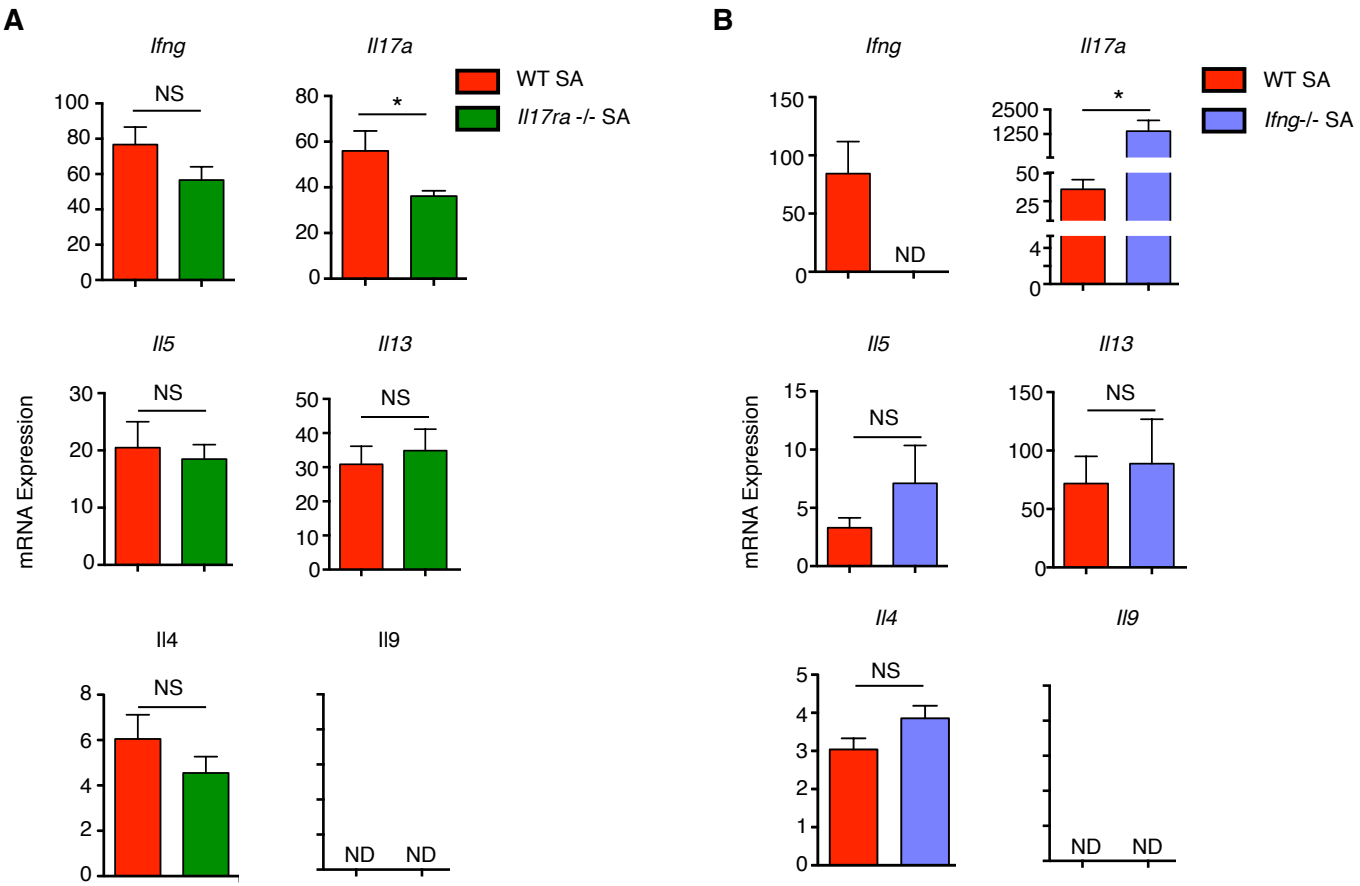

**Supplemental Figure 1.** Cellular infiltrate in the airway lumen, FEV1 and IFN-g mRNA expression in human asthma subjects. (**A**) Differential cell counts in BAL fluid of subjects with MMA and SA; n = 28 and 29 for MMA and SA, respectively. (**B**) Baseline FEV1% predicted for MM and SA subjects; n = 33 each for MMA and SA. (**C**) Ratio of CD4+ and CD8+ T cell percentages in the BAL fluid of MMA and SA subjects; n = 13 each for MMA and SA. For (**A-C**), * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, NS – not significant by Mann-Whitney test.




**Supplemental Figure 2. (A)** Concentration of indicated cytokines in culture supernatants of BAL cells from MMA subjects treated with or without corticosteroid therapy.; n = 6 and 8 for MMA with or without CS therapy, respectively, for IFN-g and IL-17A and n = 5 and 4 for MMA with or without CS therapy, respectively for IL-4, IL-5, IL-9, IL-12p40 and IL-13. **(B)** Concentration of indicated cytokines in supernatants of *ex vivo* cultured BAL cells from MMA patients on CS therapy and severe asthma patients. n = 5-6 and 14 for MMA + CS and SA, respectively, for IFN-g, IL-17A, IL-5 and IL-13 estimation, n = 5 and 8 for MMA + CS and SA, respectively, for IL-4, IL-9 and IL-12p40 estimation. For (**A-B**), * p ≤ 0.05, NS – non-significant using Mann-Whitney test.




**Supplemental Figure 3.** Cellular infiltrate in the airway lumen and cytokine mRNA expression in mouse asthma models.(**A**) Percentages of cell types in BAL fluid of mice sensitized and challenged in SA and MA Th1$^{lo}$Th2 models ± Dex. * $p \leq 0.05$, *** $p \leq 0.001$, NS – non-significant using Student's unpaired t-test (**B**) Total lung CD4$^+$ T cell numbers in mice sensitized and challenged in SA and MA Th1$^{lo}$Th2 models ± Dex quantified by flow cytometry. **** $p \leq 0.0001$ using One-way ANOVA with Tukey's post-hoc test. (**C**) Cytokine mRNA expression in whole lungs of mice sensitized and challenged in SA and MA Th1$^{lo}$Th2 models ± Dex. ND – not detected. * $p \leq 0.05$, ** $p \leq 0.01$, *** $p \leq 0.001$, NS – not significant using One-way ANOVA with Tukey's post-hoc test. Data shown are mean ± s.e.m and representative of 2-3 independent experiments with n = 3-4 mice per group.

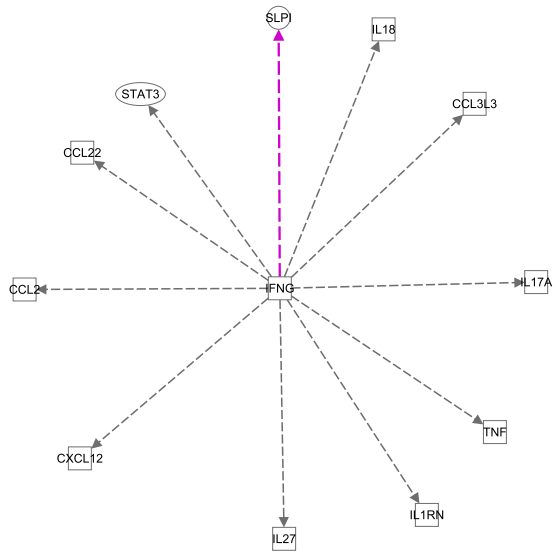



**Supplemental Figure 4.** Cytokine mRNA expression in WT, *Il17ra*-/- and *Ifng* -/- mice subjected to the SA model. Mice were subjected to the SA Model and analyzed 24 h after the final allergen challenge. (**A**) Cytokine mRNA expression in whole lungs of WT and *Il17ra*-/- mice. (**B**) Cytokine mRNA expression in whole lungs of WT and *Ifng*-/- mice.
For (**A-B**), * $p \leq 0.05$, NS – not significant by Student's unpaired t-test. Data shown are mean ± s.e.m and representative of 2-3 independent experiments with n = 3-4 mice per group.

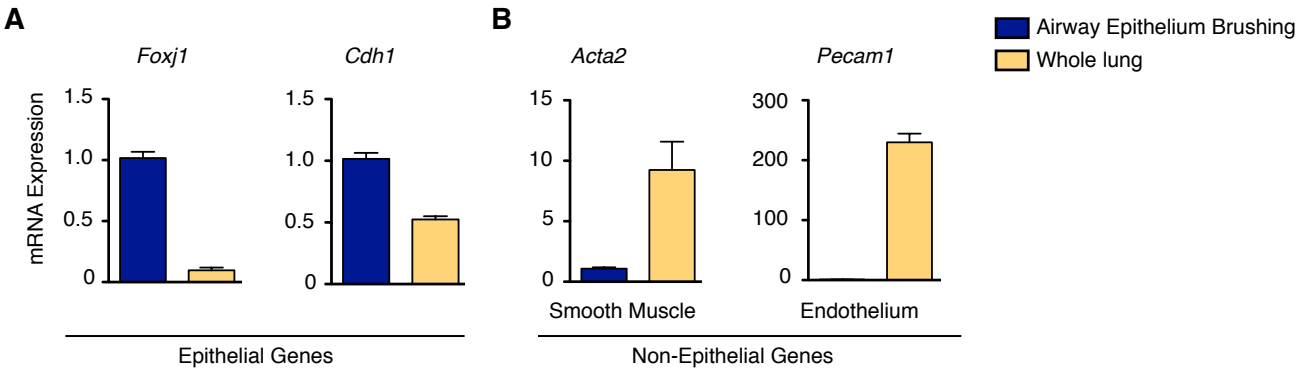
**Table 1: Airway hyperresponsiveness-related genes (IPA output)**

| | | |
|---|---|---|
| 2210013O21Rik | ICOS | PIK3R1 |
| ADAM12 | **IFNG** | PLAT |
| ADIPOQ | IgG | platelet activating factor |
| ALOX5 | IGHG1 | PRG2 |
| AMBP | IL4 | PRMT2 |
| arginase | IL5 | PTAFR |
| C3 | IL6 | PTEN |
| C5 | IL9 | RAC1 |
| C3AR1 | IL10 | Ras |
| C5AR1 | IL13 | RIPK2 |
| C5AR2 | IL18 | RORC |
| CARD11 | IL22 | RUNX3 |
| CAT | IL25 | **SLPI** |
| CCL2 | IL27 | SMAD3 |
| Ccl2 | IL13RA2 | SOCS3 |
| CCL11 | IL15RA | SPI1 |
| CCL17 | IL17A | SPON2 |
| CCL22 | IL17B | SPRED1 |
| CCL28 | IL17RA | STAT3 |
| CCL3L3 | IL1RL1 | STAT4 |
| CCR3 | IL1RN | STAT6 |
| CD44 | IL27RA | TACR1 |
| CD86 | IL2RB | TBX21 |
| CD1D | IL4R | Tgf beta |
| CD300LF | IL6R | TICAM1 |
| CDH13 | ITK | TLR4 |
| CHD4 | KIT | TNF |
| CLCA1 | LAMA2 | TNFAIP6 |
| CMA1 | LGALS3 | TNFRSF4 |
| CX3CR1 | LTA | TNFRSF9 |
| CXCL12 | LTB4R | TNFRSF1A |
| CXCR4 | LTC4S | TPSG1 |
| DLL4 | MAPK3 | TRAF3IP2 |
| F2RL1 | MGAT5 | Traj18 |
| FLT3LG | mir-1 | TSLP |
| GATA3 | MYD88 | U0126 |
| GGT5 | NFE2L2 | VDR |
| HAS2 | Nos | VEGFA |
| HGF | NRTN | |
| HRAS | PIK3CD | |

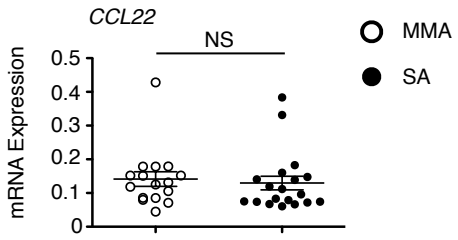
**Table 1.** List of AHR-related genes identified using Ingenuity Knowledge Base (IKB) Diseases and Functions search bar from the IPA software.



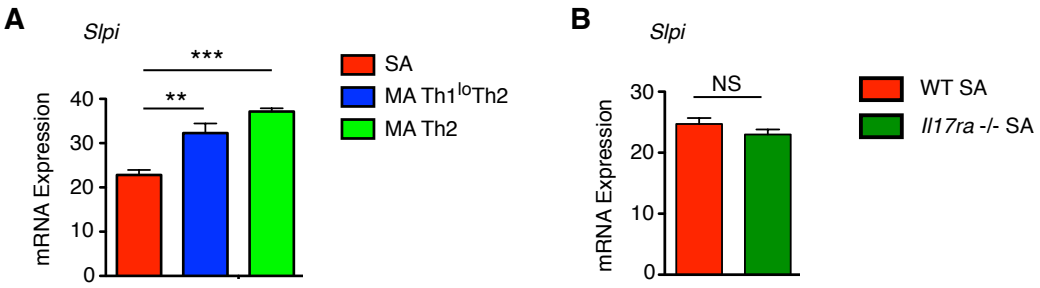

**Supplemental Figure 5.** IFN-γ-regulated AHR-related genes expressed in structural cells of the lung identified using IPKB. Using IPA's Build function, AHR-related genes shown in Table 1 were specifically selected for genes expressed in the lung, epithelial cells and smooth muscle cells. Genes from this reduced set were further tested for regulation by IFN-g in the lung using Path Explorer function.



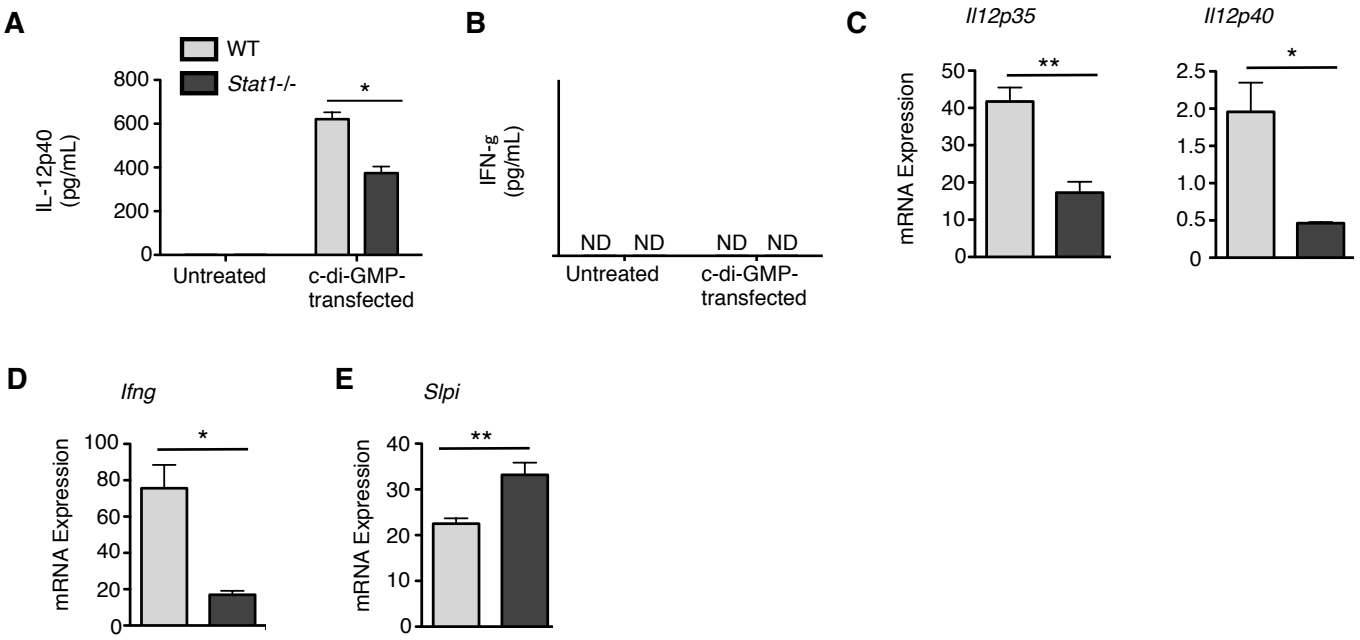

**Supplemental Figure 6.** Characterization of mouse airway epithelial cell brushings. qRT-PCR analysis of expression of **(A)** Epithelial-specific genes and **(B)** non-epithelial genes in whole lung and brush-harvested samples. Data shown are mean ± s.e.m and representative of 3 independent experiments with n = 3-4 mice per group.




**Supplemental Figure 7.***Ccl22* mRNA expression analyzed by qRT-PCR in epithelial brushings of MMA and SA subjects; n = 16 and 19 for MMA and SA, respectively. NS – non-significant, Mann-Whitney test.




**Supplemental Figure 8.** SLPI mRNA expression in different models of asthma. **(A)** SLPI mRNA expression in airway epithelial brushings from mice subjected to the SA, MA Th1$^{lo}$Th2 and MA Th2 asthma models. ** $p \leq 0.01$, *** $p \leq 0.001$ using One-way ANOVA with Tukey's post-hoc test. **(B)** SLPI mRNA expression in airway epithelial brushings of WT and *Il17ra*-.- mice subjected to the severe asthma model. NS – not significant by Student's unpaired t-test. For (**A-B**), data shown are mean ± s.e.m and representative of 2-3 independent experiments with n = 3-4 mice per group.




**Supplemental Figure 9.** c-di-GMP regulation of IFN-g production via IL-12 induction is dependent on STAT1. **(A)** IL-12p40 and **(B)** IFN-g concentrations in culture supernatants of WT and Stat1-/- BMDMs transfected with c-di-GMP. **(C)** *Il12p35* and *Il12p40* mRNA expression in lymph nodes of WT and *Stat1-/-* sensitized in the severe asthma model. **(D)** *Ifng* mRNA expression in whole lungs of WT and *Stat1-/-* mice sensitized and challenged in the severe asthma model. **(E)** *Slpi* mRNA expression in airway epithelial brushings from WT and *Stat1-/-* mice sensitized and challenged in the severe asthma model. For (**A-E**) * $p \leq 0.05$, ** $p \leq 0.01$ using Student's unpaired t-test. Data shown are mean ± s.e.m and representative of 2 independent experiments with n = 3-4 mice per group.