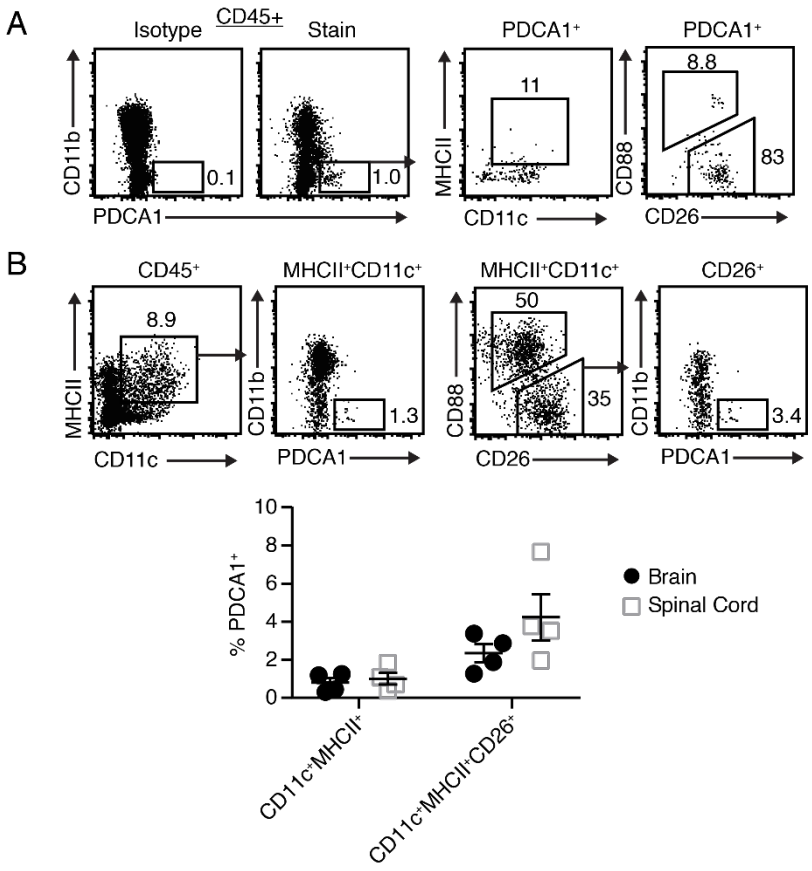
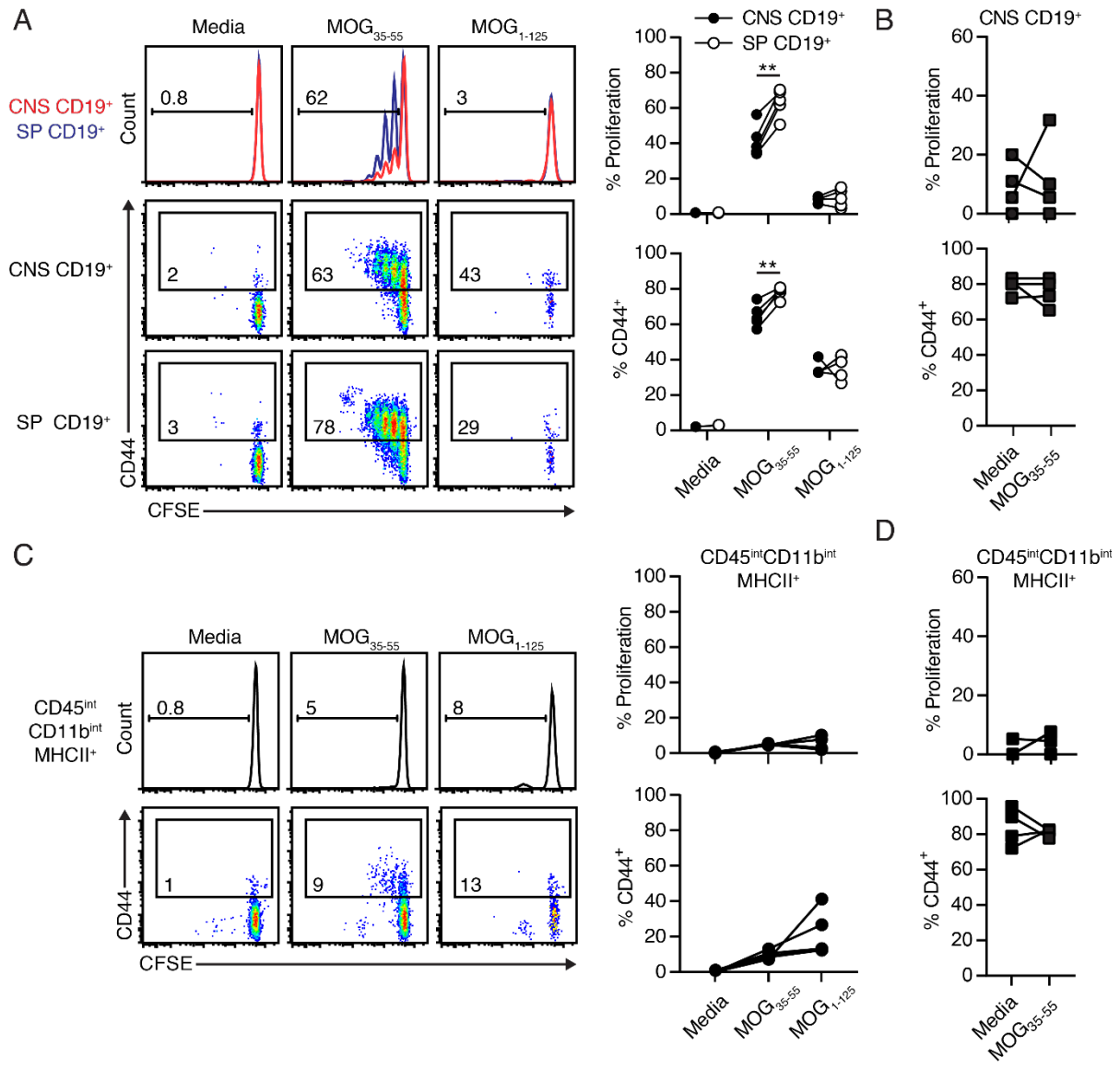
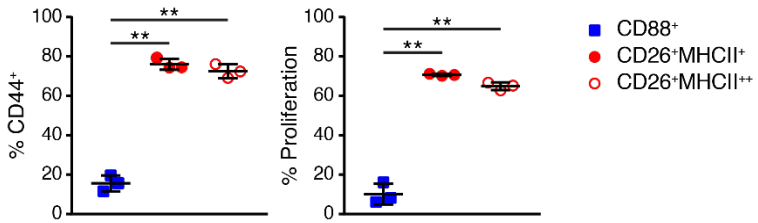


Supplemental Figure 1 – pDC are present in the CNS during EAE but express low levels of MHCII.

EAE was induced by adoptive transfer of WT myelin-primed Th17 cells into naïve syngeneic hosts. Mononuclear cells were isolated from the brain and spinal cord at peak clinical disease and analyzed by flow cytometry. (A) pDC were identified by expression of PDCA1. Expression of MHCII and CD11c (middle panel) and CD88 and CD26 (right panel) was assessed gating on $PDCA1^+$ cells. (B) Quantification of pDC as a percentage of total $CD11c^+MHCII^+$ DC or $CD11c^+MHCII^+CD26^+$ DC. The dot plots show representative results obtained with brain mononuclear cells. Gating is indicated above each plot. Error bars represented as mean ± SEM.

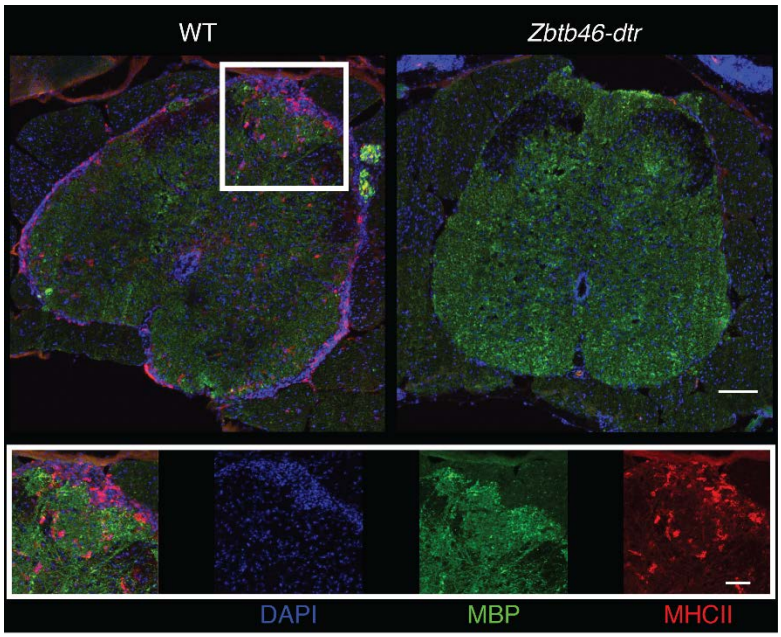


Supplemental Figure 2 – B cells are able to present MOG_{35-55} peptide, but not MOG_{1-125} protein, to MOG-reactive $CD4^+$ T cells; microglia are incompetent as antigen presenting cells.
EAE was induced by active immunization with MOG peptide, and immune cells were isolated from the CNS and spleen (SP) at peak disease. B cells ($MHCII^+CD45^+CD11b^-CD11c^-CD19^+$) and microglia ($MHCII^+CD45^{int}CD11b^{int}$) were FAC sorted and co-cultured with MOG-reactive T cells in the presence of myelin peptide (MOG_{35-55}) or myelin protein (MOG_{1-125}). B cells (A) or microglia (C) were co-cultured with $CD44^-CD62L^+CD4^+$ T cells from naïve 2D2 TCR transgenic mice. B cells (B) or microglia (D) were co-cultured with $CD4^+$ T cells isolated from the CNS of actively immunized WT mice at the peak of EAE. T cell proliferation was measured by CFSE dilution. Activation was measured as the percentage of $CD44^+$ cells among total $CD4^+$ T cells. Each circle represents a data point generated from a single mouse. Connected circles indicate paired samples from the same mouse. *$p<0.05$, **$p<0.01$ by paired, 2-tailed Student's t test. Data are representative of at least 2 experiments. N=3-5 mice per group.



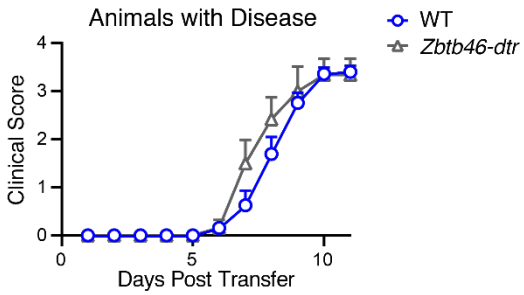
Supplemental Figure 3 – MHCII^{+} and MHCII^{++} CNS cDC demonstrate comparable efficacy as APC when activating MOG-specific CD4^{+} T cells.

EAE was induced by adoptive transfer of WT myelin-primed Th17 cells into naïve syngeneic hosts. CNS mononuclear cells were isolated at peak clinical severity and FAC sorted to isolate CD88^{+}, CD26^{+}MHCII^{+}, and CD26^{+}MHCII^{++}, DC subsets. Each DC subset was co-cultured with MOG-reactive, CD44^{-}CD62L^{+} CD4^{+} T cells that were isolated from pooled spleens and lymph nodes of naïve 2D2 TCR transgenic mice. T cell proliferation was measured by CFSE dilution. The percent of CD4^{+} T cells that expressed the activation marker CD44 or that underwent 1 or more division is shown for each group. **$p<0.01$ P values were determined using 1-way ANOVA with Tukey's post-hoc test. N=3 mice. Data are representative of 3 experiments. Error bars indicate mean ± SEM.



Supplemental Figure 4 – cDC depleted Zbtb46-dtr→WT adoptive transfer recipients with a clinical score of 0 show no signs of CNS inflammation or tissue damage on histological examination.

Bone marrow chimeric mice were generated by reconstituting lethally irradiated $CD45.1^+$ hosts with $CD45.2^+$ WT or *Zbtb46-dtr* bone marrow cells. EAE was induced by the adoptive transfer of WT myelin-primed Th17 cells into fully reconstituted chimeric mice. DT was administered on a daily basis beginning 3 days prior to adoptive transfer. Mice in all groups were euthanized at the time of peak disease in the WT→WT cohort. CNS samples were subjected to immunohistological analysis. Spinal cord sections from a representative WT→WT mouse (top left panel, score 3) and a *Zbtb46-dtr*→WT (top right panel, score 0) mouse are shown. The inset shows an inflammatory lesion in the WT spinal cord higher magnification of. Scale bars are 100 µm (top) and 50 µm (bottom).



Supplemental Figure 5 – DT treated Zbtb46-dtr→WT adoptive transfer recipients that succumbed to EAE followed a similar clinical course to their WT→WT *counterparts.*
Bone marrow chimeric mice were generated by reconstituting lethally irradiated CD45.1^{+} hosts with CD45.2^{+} WT or *Zbtb46-dtr* bone marrow cells. EAE was induced by the adoptive transfer of WT myelin-primed Th17 cells into fully reconstituted chimeric mice. DT was administered daily, beginning 3 days prior to adoptive transfer. Mice were monitored on a daily basis and rated for degree of neurological disability by an examiner blinded to the identity of the experimental groups. Shown are average disease scores only for animals which developed neurological deficits; WT→WT (13 of 15), and *Zbtb46-dtr*→WT (6 of 15).