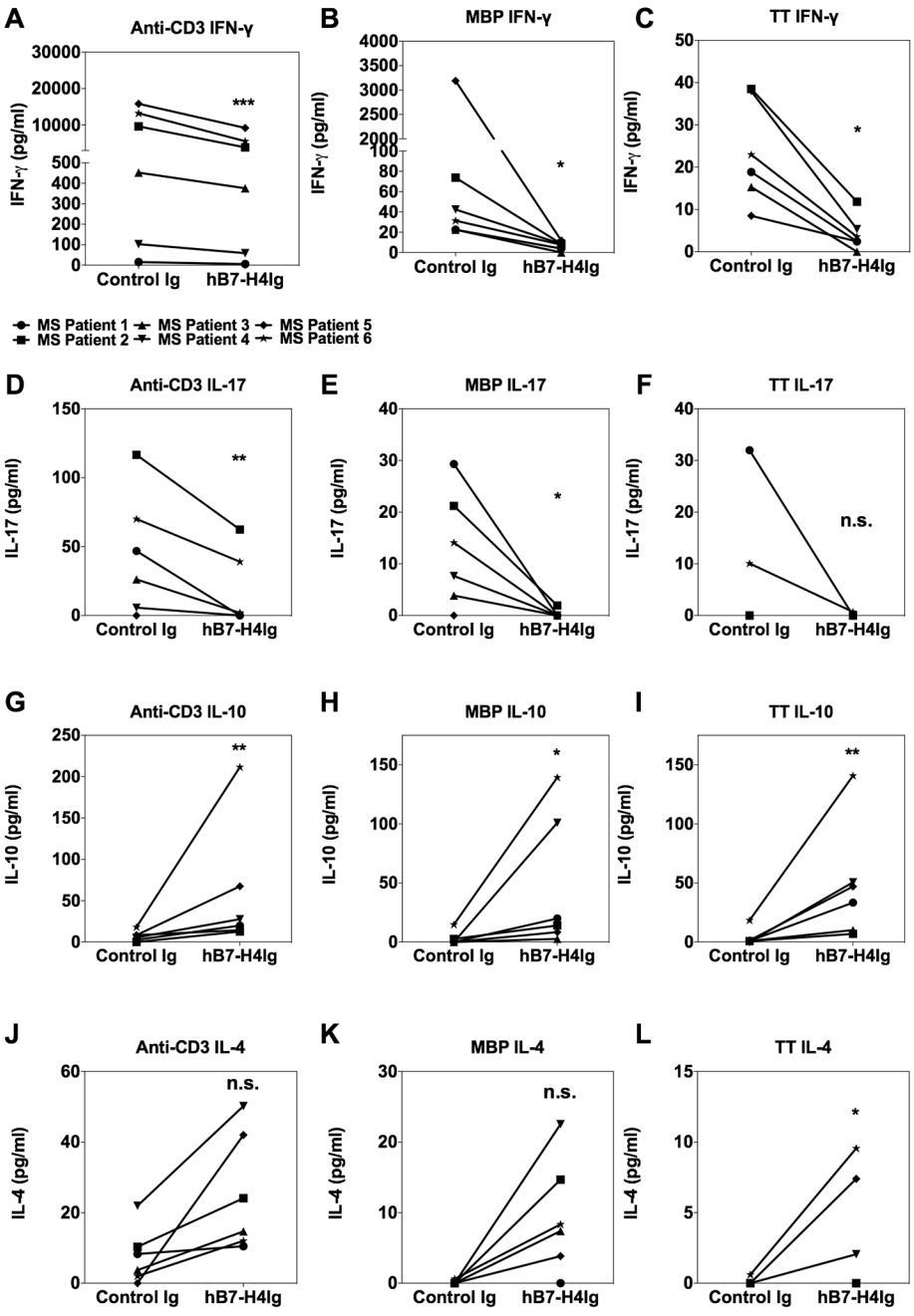
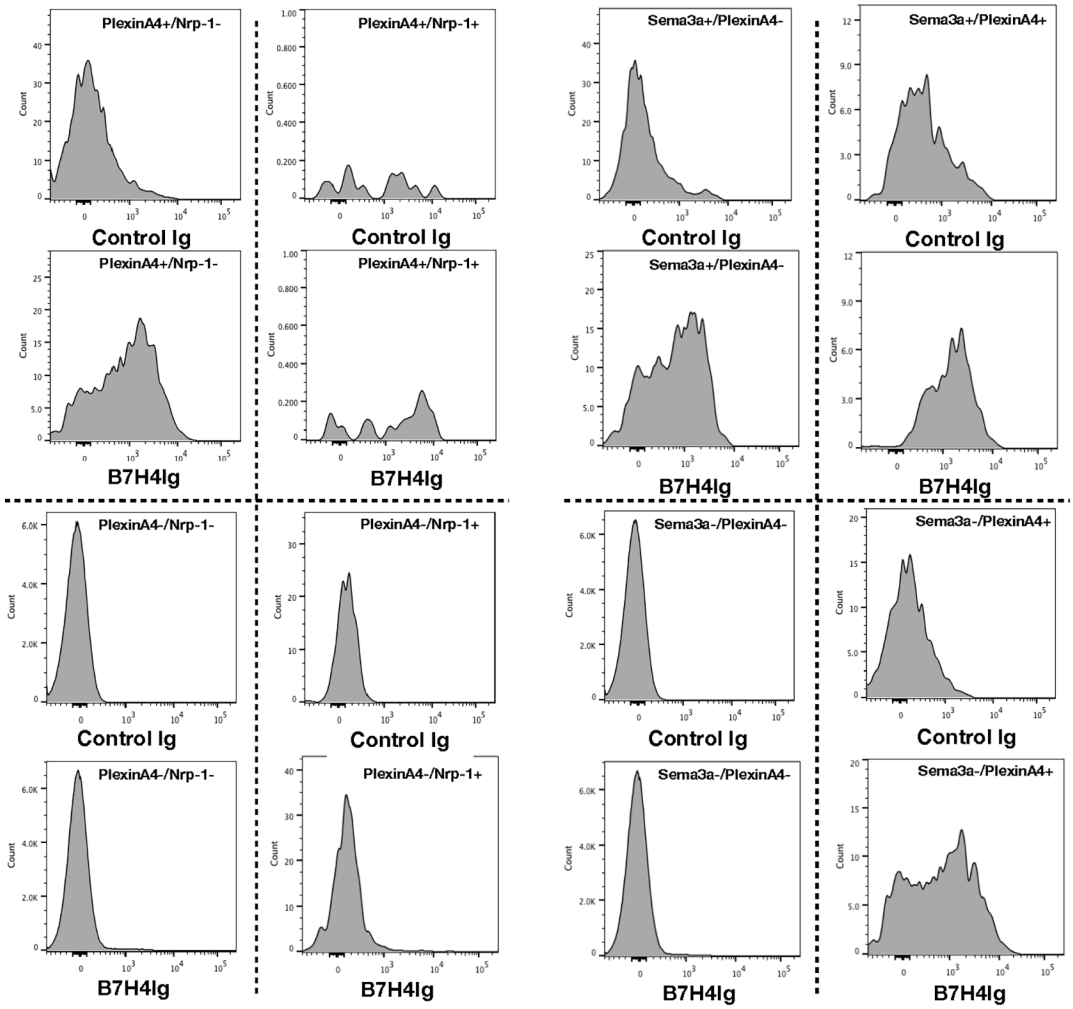
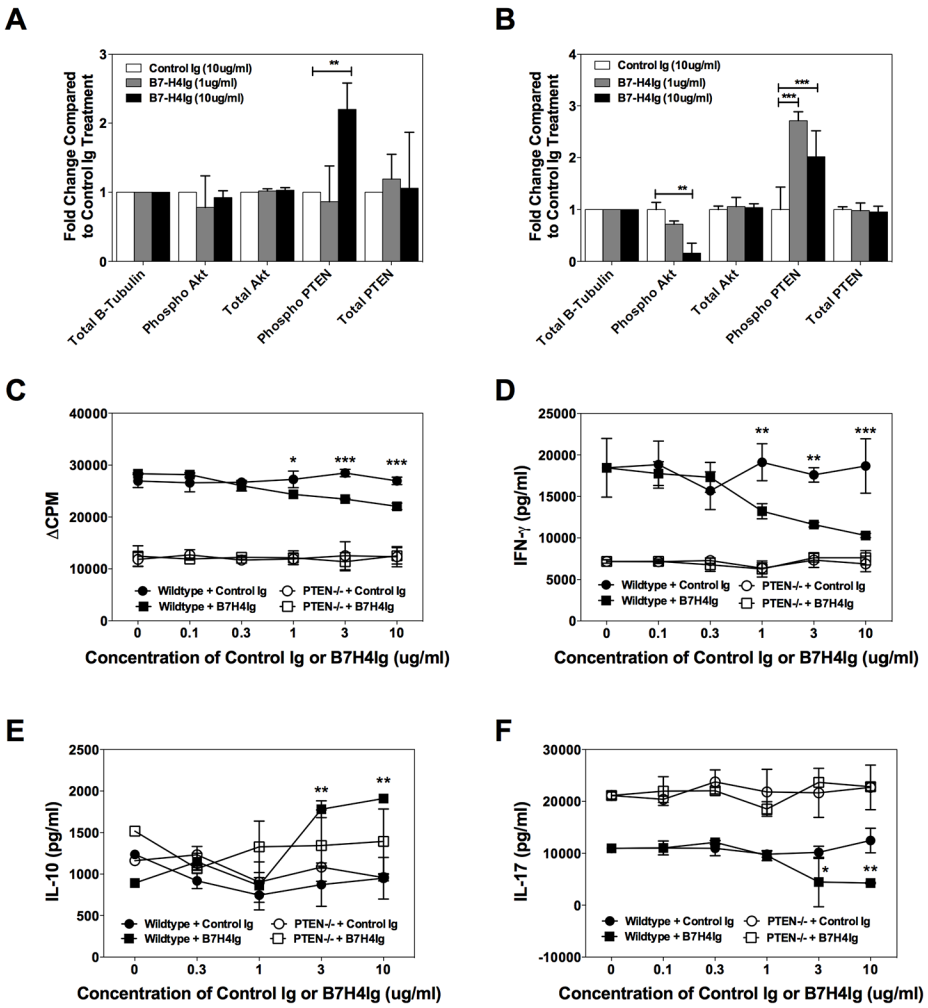


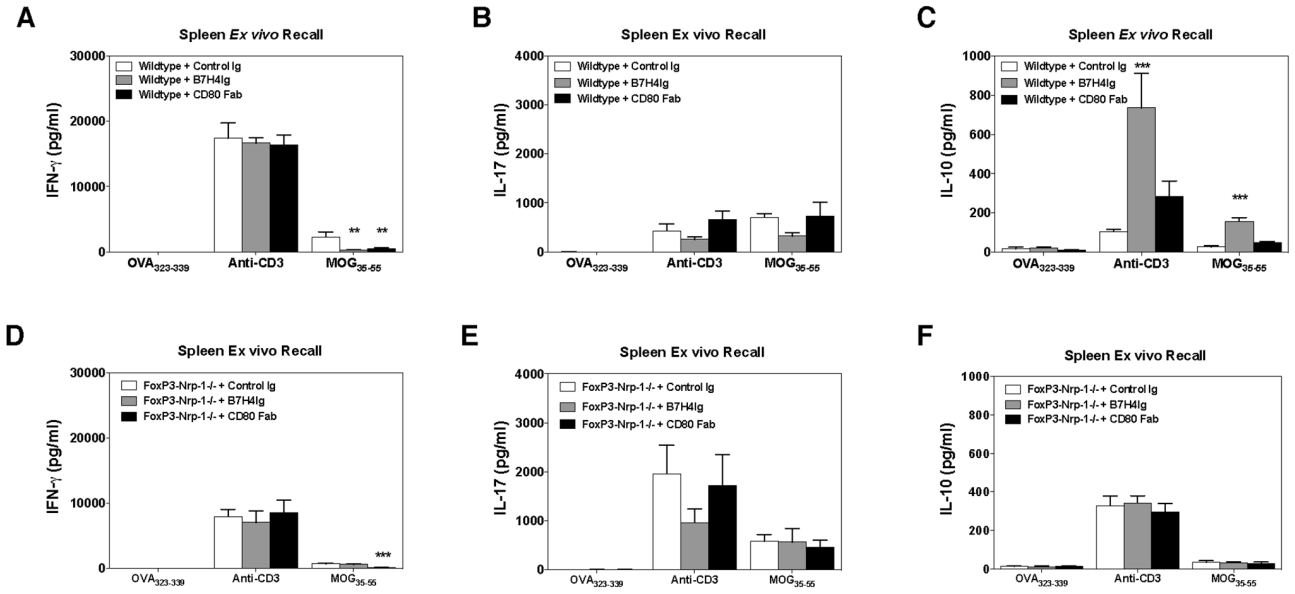
Supplemental Figure 1. B7-H4Ig PBMCs were collected from RR-MS patients (n=6), and the cells (10^6/well in a 96-well plate) were activated for 5 days in the presence of anti-CD3 (0.5μg/ml), MBP_{85-96}, or $TT_{830-843}$ (10μg/ml) plus Control Ig or hB7-H4Ig (10μg/ml) and the levels of proliferation and secreted cytokines **(A-C)** IFN-γ, **(D-F)** IL-17, **(G-I)** IL-10, and **(J-L)** IL-4 were assessed. Asterisks (*, **, ***) indicate a statistically significant difference in proliferation and cytokine production by cells from B7-H4Ig treated cultures in comparison to Control Ig, $p < 0.05$, < 0.01, < 0.001, respectively.



Supplemental Figure 2. B7-H4Ig binds Sema3a$^+$ and PlxnA4$^+$ human CD4$^+$ T cells. PBMCs from healthy donors were activated in the presence of anti-CD3 (0.5μg/ml), and on Day +3 of culture the cells were collected and the binding of hB7-H4Ig to Nrp-1, PlxnA4, and Sema3a bearing cells was assessed via FACS. Live, single cell, dump negative (CD11b, CD11c, CD20, and CD8), and CD3/CD4$^+$ cells were gated into the PlxnA4 vs. Nrp-1 and Sema3a vs. PlxnA4 dot plots. The binding of Control Ig vs. hB7-H4Ig is presented in the respective histograms for each dot-plot quadrant population of cells. One replicate experiment of three is presented.



Supplemental Figure 3. B7-H4Ig treatment induces increased levels of phosphorylated PTEN. (**A**) SJL/J mice were primed with $PLP_{139-151}$/CFA. On day +8 post-priming, draining inguinal lymph nodes cells ($5x10^6$ cells/well in a 24-well plate) were cultured in the presence of $PLP_{139-151}$ (10μg/ml) for 3 days. Following culture the cells were collected and re-cultured for 3 h in the presence of plate-bound Control Ig or hB7-H4Ig (1 or 10μg/ml). (**B**) Naïve $CD4^+$ T cells from SJL-FoxP3/GFP mice were cultured with plate-bound anti-CD3 (1.0μg/ml) and soluble anti-CD28 (1μg/ml) in induced Treg promoting culture conditions [TGF-β (10ng/ml) plus IL-2 (100U/ml)] for 3 days. The resultant FoxP3/GFP^+ cells were re-cultured for 3 h with plate-bound anti-CD3 (1μg/ml) in the presence of either plate-bound Control Ig or hB7-H4Ig (1 and 10μg/ml). The cells were collected, lysed, and the level of β-tubulin, total Akt, phosphorylated Akt, total PTEN, and phosphorylated PTEN was assessed via Luminex assay. All values were normalized to β-tubulin, and the normalized values presented as the fold change compared to the Control Ig treated cells. **(C-F)** Splenocytes ($0.5x10^6$ cells/well in a 96-well plate) from mice in which PTEN is conditionally knocked out within $FoxP3^+$ cells ($PTEN^{fl/fl}xFoxP3^{Cre/YFP}$) vs. wildtype mice (n=2) were cultured in the presence of anti-CD3 (1μg/ml) plus Control Ig or hB7-H4Ig (0-10μg/ml) for three days and the level of cellular proliferation assessed via (**C**) tritiated thymidine incorporation, and the secretion of (**D**) IFN-γ, (**E**) IL-17, and (**F**) IL-10. One representative experiment of two is presented. Asterisks (*, **, ***) indicates a statistically significant alteration in comparison to cells collected from Control Ig treated wells, $p < 0.05$, 0.01, 0.001 respectively.



Supplemental Figure 4. *Ex vivo* recall responses from B7-H4Ig treated EAE mice. Splenocytes ($0.5x10^6$ cells/well in a 96-well plate) from wildtype and Nrp-$1^{fl/fl}$xFoxP3$^{Cre/YFP}$ C57BL/6 mice presented in **Fig. 5** were reactivated *ex vivo* in the presence of $OVA_{323-339}$ (10µg/ml), anti-CD3 (1µg/ml), or MOG_{35-55} (10µg/ml) for 3 days. The levels (**A** and **D**) IFN-γ, (**B** and **E**) IL-17, and (**C** and **F**) IL-10 were assessed following activation. Asterisks (*, **, ***) indicate a statistically significant difference in cytokine production by cells from hB7-H4Ig or anti-mouse CD80Fab treated mice in comparison to cells collected from Control Ig treated mice, $p < 0.05$, 0.01, 0.001, respectively. One representative experiment of two is presented.