Supplemental Table 1: Characterization of cellular infiltrates in the CNS of several TLR-deficient mice during the early acute (20dpi) and the chronic phase (35dpi). Spinal cords were removed and the number of CD3-positive T cells, MAC-3-positive macrophages, APP-positive axons (as morphological signs axonal damage) as well as the extend of myelin damage (LFB staining) was evaluated. Quantitative analysis was performed from samples shown in table 1. Cells were counted using x 400 microscopical examination (mean ± SD). For each genotype, at least 4 most inflamed spinal cord sections were counted.

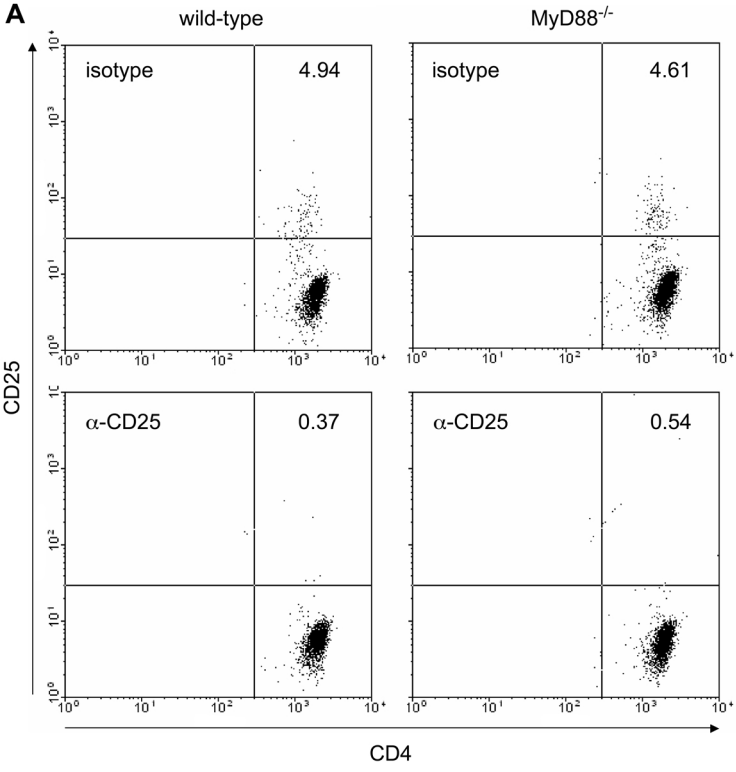
Mouse genotypes	MAC-3-positive cells/mm^2	CD3-positive cells/mm^2	APP-positive axons/mm^2	Demyelinated area of white matter (%)
acute (20dpi)				
Wild-type	71 ± 9	62 ± 18	17 ± 4	1.4 ± 0.2
TLR2$^{-/-}$	84 ± 10	58 ± 4	15 ± 6	1.3. ± 0.3
TLR9$^{-/-}$	77 ± 7	51 ± 9	13± 4	1.5 ± 0.3
MyD88$^{-/-}$	4 ± 1.2	0	0.8 ± 0.2	0
chronic (35dpi)				
Wild-type	84 ± 17	45 ± 13	23 ± 5	2.4 ± 0.5
TLR2$^{-/-}$	97 ± 23	44 ± 17	27 ± 6	2.7 ± 0.6
TLR9$^{-/-}$	62 ± 12	36 ± 11	12 ± 3	1.8 ± 0.4
MyD88$^{-/-}$	2.0 ± 0.4	3 ± 0.5	0	0

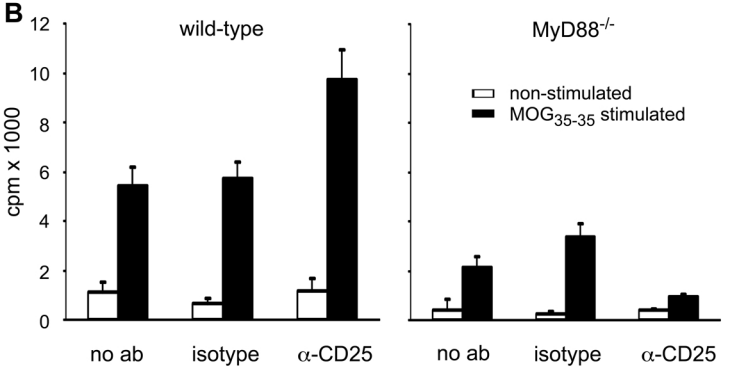
Supplemental Table 2: EAE in MyD88 and TLR9 bone marrow chimeric mice.
Data show clinical parameter of MOG-induced EAE in bone marrow chimeric MyD88$^{-/-}$ and TLR9$^{-/-}$ mice. Disease course is visualized in Fig. 4A,C. [a] of diseased mice.

Genotype BM Donor	Genotype BM Recipient	Incidence (%)	Mean day of disease onset [a]	Mean maximal clinical score (± SEM) [a]
wt	Wt	8/8 (100)	14.7	3.4 ± 0.3
wt	*MyD88-/-*	7/8 (88)	18.2	2.1 ± 0.2
MyD88-/-	wt	0/7 (0)	n.d.	n.d.
MyD88-/-	*MyD88-/-*	0/6 (0)	n.d.	n.d.
wt	wt	6/6 (100)	15.4	3.6 ± 0.4
wt	*TLR9-/-*	5/5 (100)	17.4	2.3 ± 0.3
TLR9-/-	wt	9/10 (90)	20.8	2.8 ± 0.3
TLR9-/-	*TLR9-/-*	7/8 (88)	21.4	2.4 ± 0.2

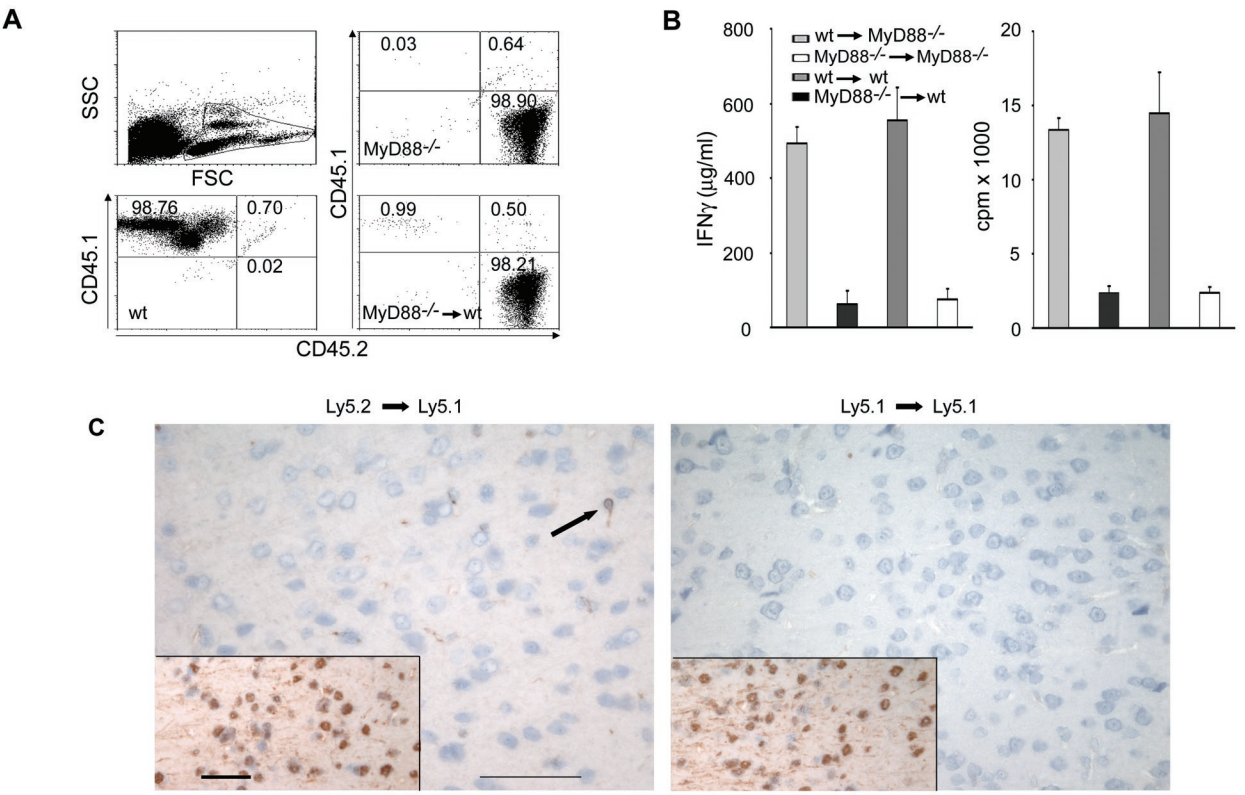
Supplemental Table 3: Quantification of infiltrates, axonal and myelin damage in the CNS of TLR9 chimeras. The number of T cells, macrophages, APP-positive axons as well as the extend of myelin damage (LFB) was quantified. Histological analysis was performed from samples shown in Figure 4C. Cells were counted using x 400 microscopical examination (mean ± SD).

Genotype BM Donor	Genotype BM Recipient	MAC-3-positive cells/mm^2	CD3-positive cells/mm^2	APP-positive axons/mm^2	Demyelinated area of white matter (%)
wt	wt	143 ± 27	97 ± 21	31 ± 9	5.5 ± 1.2
wt	*TLR9*$^{-/-}$	87 ± 11	87 ± 12	19 ± 7	3.5 ± 0.8
TLR9$^{-/-}$	wt	102 ± 14	94 ± 10	24± 6	4.0 ± 1.2
TLR9$^{-/-}$	TLR9$^{-/-}$	77 ± 14	64 ± 8	17 ± 6	3.1 ± 0.9

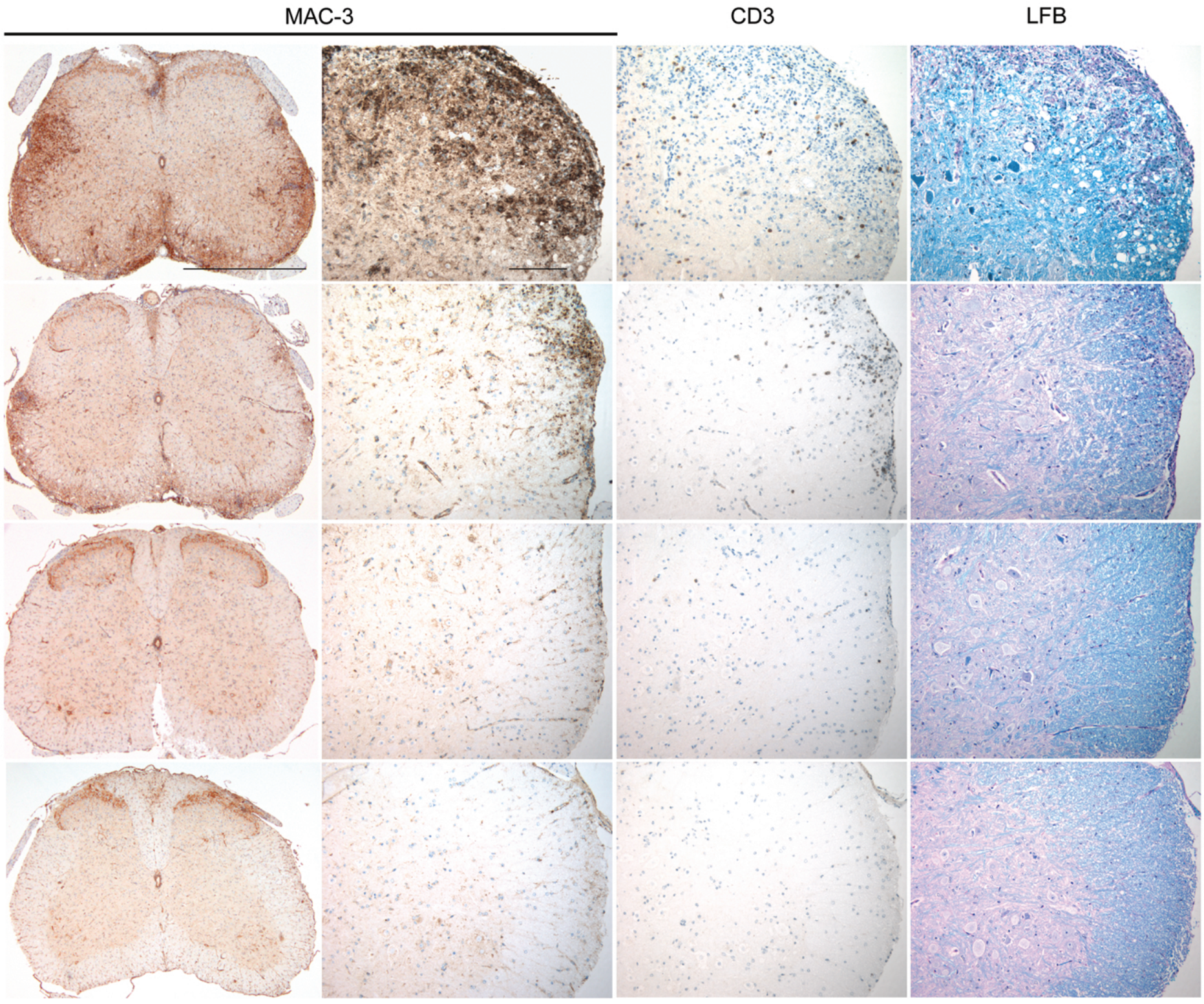




Supplemental Figure 1



Supplemental Figure 2



Supplemental Figure 3

FIGURE LEGENDS

Supplemental Figure 1: Insufficient T cell priming in *MyD88*$^{-/-}$ is independent of CD4^{+}CD25^{+} regulatory T cells.
A: A single intravenous injection (100 µg/mouse) of anti-CD25 monoclonal antibody (clone PC61) or rat control Ig on day -3 of immunization leads to depletion of CD25^{+} cells in vivo. Mice were bled on day three and peripheral blood was stained indicated.
B: T cell proliferation failure in *MyD88*$^{-/-}$ mice upon MOG_{35-55} challenge is not restored after T_{reg} depletion. Lymphocytes were obtained from mice which were either T_{reg}-depleted (α-CD25), rat Ig isotype injected (isotype) or untreated (no ab).

Supplemental Figure 2: BM exchange fully reconstitutes the host ability to drive Th1 autoimmunity.
A: Flow cytometry of peripheral blood of BM reconstituted mice was monitored by the expression of the congenic marker Ly5.1 (CD45.1) in wt and Ly5.2 (CD45.2) in knock out mice. Blood samples were taken 6-8 weeks after BM reconstitution.
B: BM exchange fully reconstitutes the host ability to drive Th1 autoimmunity. Recall responses of lymph nodes cells after challenge to MOG peptide was assessed *in vitro* by assesing IFNγ production (left panel) and cell-proliferation (right panel).
C: Limited BM cell engraftment into the CNS of recipient mice. Immunohistochemical staining of the surface markers Ly5.2 (CD45.2, large pictures) or Ly5.1 (CD45.1, inserts) in neocortical brain sections of *MyD88*$^{-/-}$ (CD45.2) → wt (CD45.1, left panel) or wt (CD45.1) → wt (CD45.1, right panel) chimeras. Scale bar = 30µm. The arrow indicates a single bone marrow-derived Ly5.2 positive cell with microglial morphology. Brain tissue samples were taken 12 weeks after BM reconstitution.

Supplemental Figure 3: Deletion of TLR signaling in the radio-resistant non-hematopoietic compartment modulates spinal cord imflammation during autoimmune brain disease.
Immunohistochemistry from MyD88 chimeric mice. Animals were taken at the 35 dpi. MAC-3 staining for macrophages, CD3 for lymphocytes and LFB for myelin damage were performed. Scale bar = 500µm (in the first column) or 30µm (second column). Data of mice shown in Figure 4 A,B.