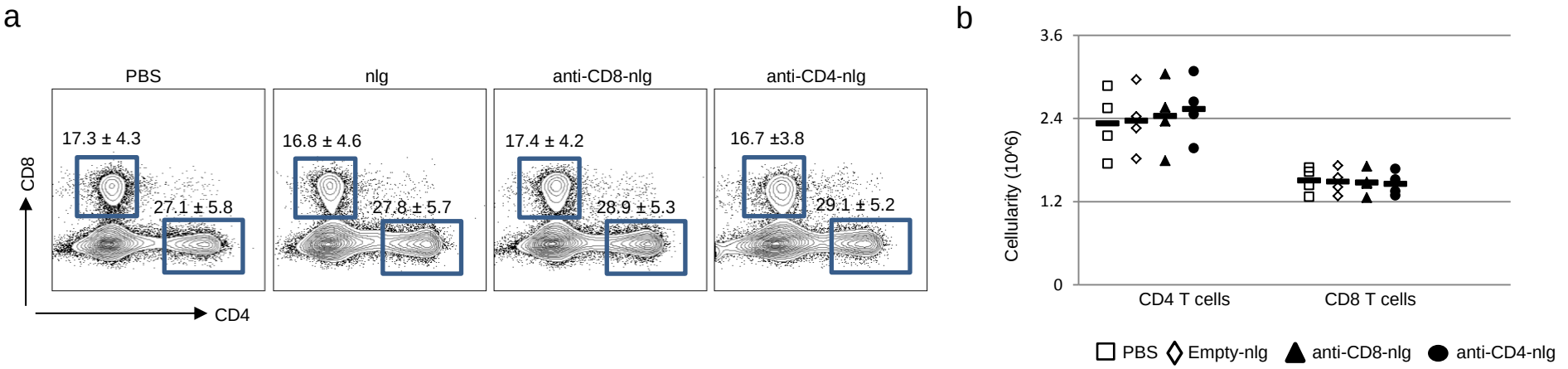
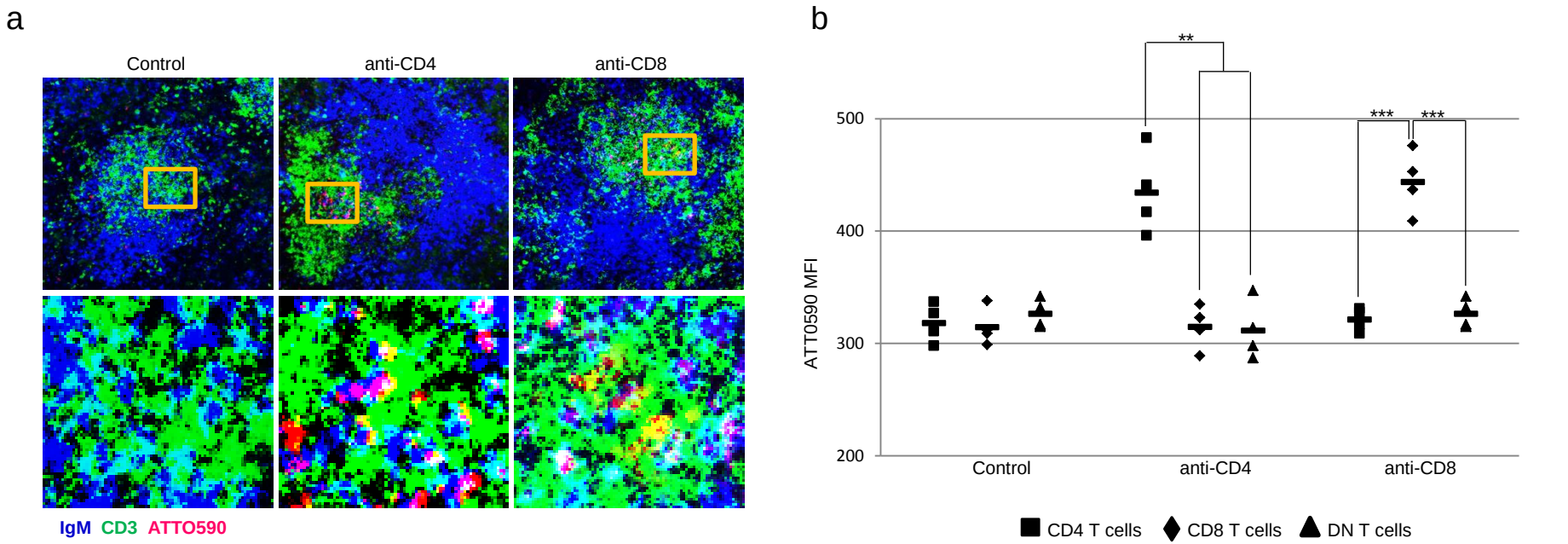
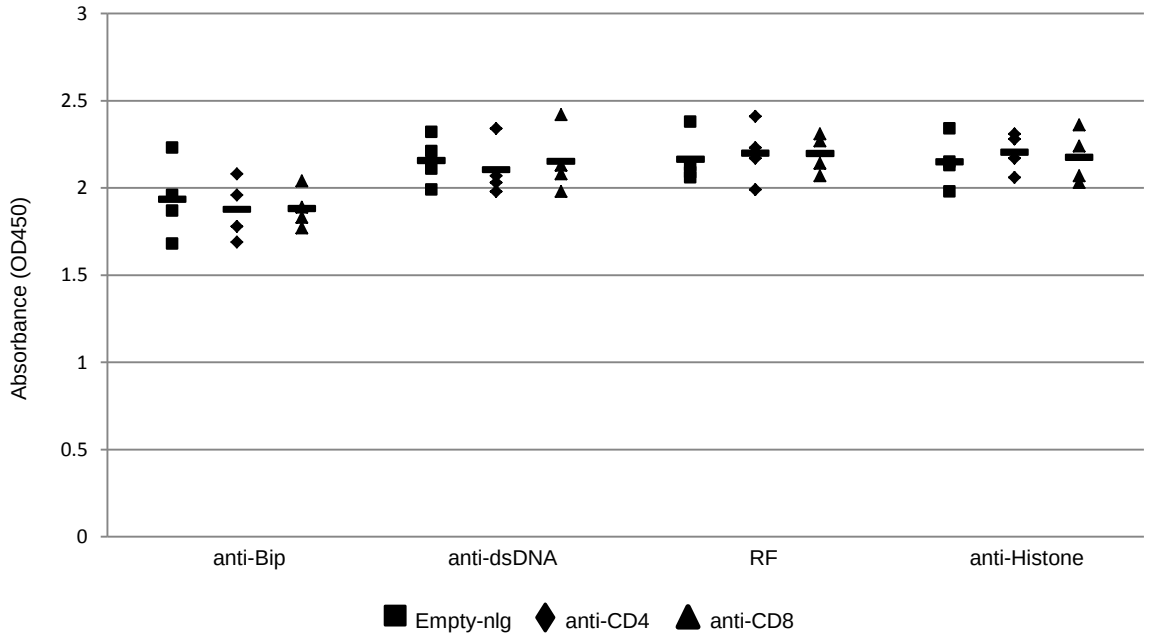


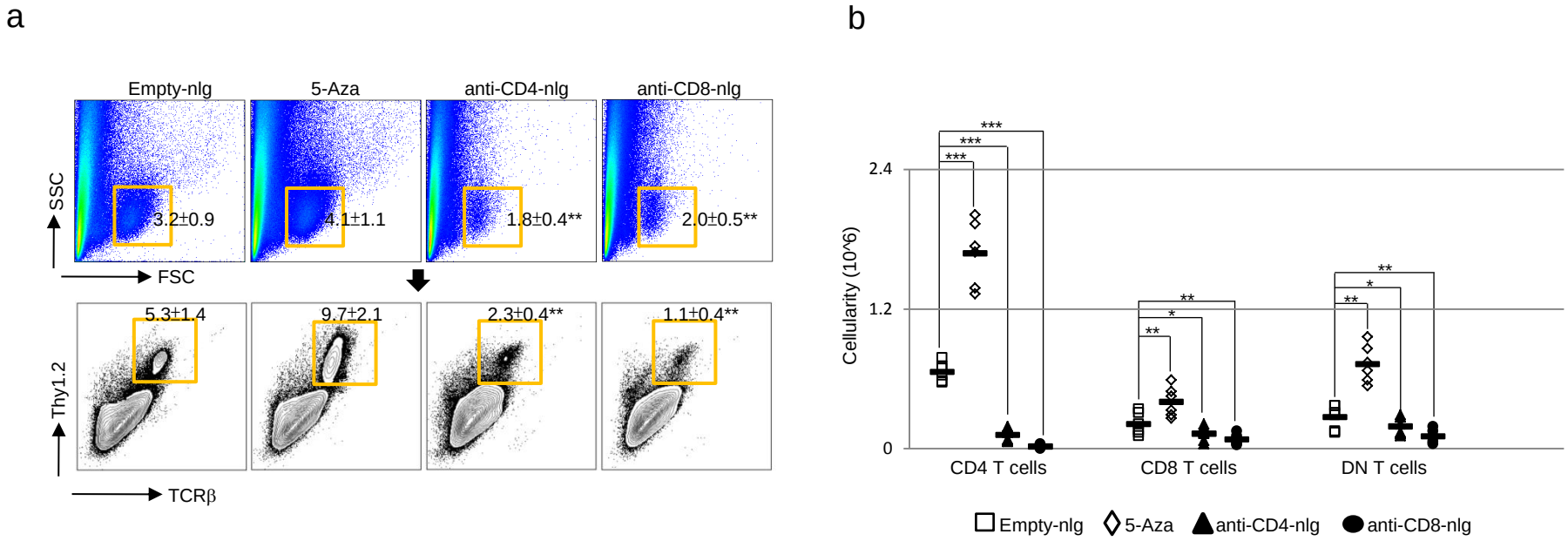
Supplemental Figure 1. Empty nlg targeting to either CD4 or CD8 T cells does not affect T cell cellularity *in vivo.*
Age and sex matched MRL/*lpr* mice were treated i.v. with either anti-CD4 antibody or anti-CD8 antibody coated-empty-nlg (equivalent to 50 μg antibody per mouse) for 48 hrs. PBS or empty-nlg were applied to two control groups separately. (a) Flow cytometry analysis of splenic T cells. Data represent the mean ± SEM (*n* = 4 mice per group). (b) Dot plot graph shows quantitation of the absolute cell numbers of CD4 and CD8 T cells from the spleens of mice subjected to the indicated treatment.



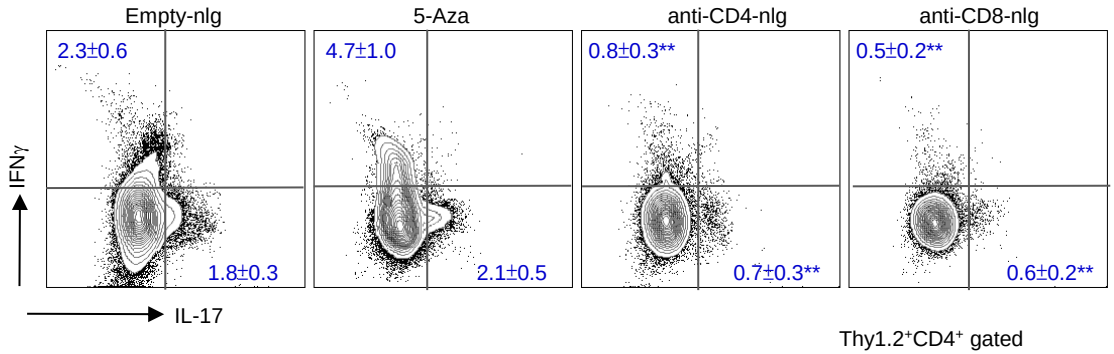
Supplemental Figure 2. Targeted delivery of ATTO590 by antibody-coated nlg.
12 weeks old MRL/*lpr* mice were treated i.v. with either anti-CD4 antibody or anti-CD8 antibody coated-nlg-ATTO590 (a fluorescent dye derived from Rhodamine), and isotype control antibody coated-nlg-ATTO590 was used as control. Mice were euthanized 30 min after nlg administration for analysis, n = 4 mice per group. (a) Confocal microscopic images show the distribution of ATTO590$^+$ cells in representative splenic follicles. Original magnification, ×20; Boxed areas in the upper panel are digitally magnified and shown in the bottom panels (IgM : blue, CD3 : green and ATT0590 : red). (b) Dot plot graph shows quantitation of ATTO590 MFI in different T cell subsets from spleens of mice subjected to the indicated treatment. $^{**}P < 0.01$, $^{***}P < 0.005$ vs. control, a 2-tailed Student's t test.



Supplemental Figure 3. Empty nlg targeting to either CD4 or CD8 T cells does not alter production of auto-antibodies in MRL/*lpr* mice.
Age matched MRL/*lpr* mice were treated i.v. with either anti-CD4 antibody or anti-CD8 antibody coated empty-nlg (15 μl nlg-5-Aza/mouse) weekly for 4 weeks starting at 10 weeks of age. Empty-nlg was used in control group. Dot plot graph shows the ELISA analysis of IgG autoantibodies in the serum from mice subjected to the indicated treatment. *n* = 4 mice per group.

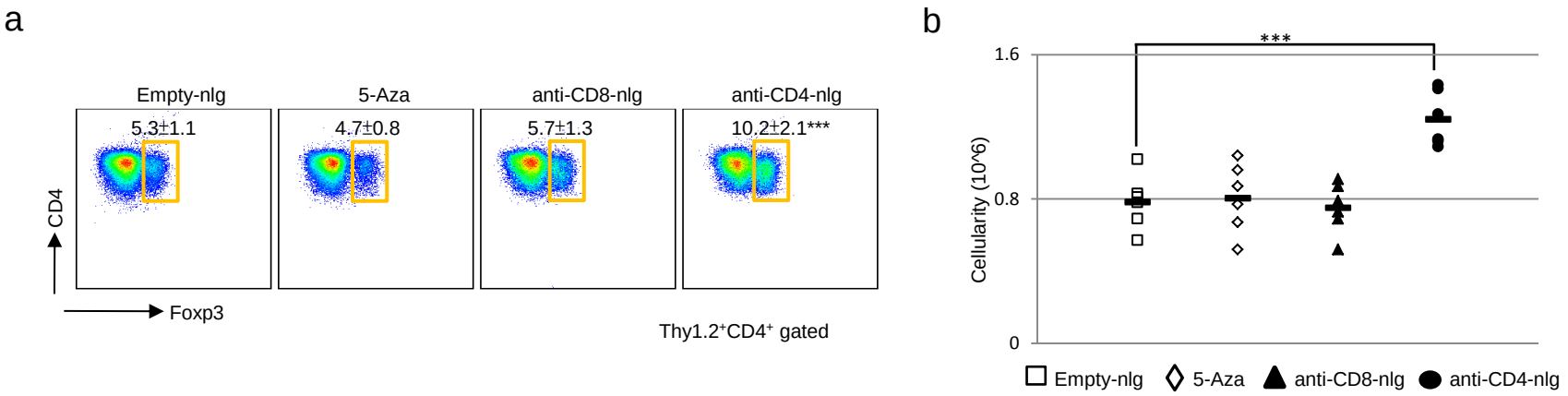


Supplemental Figure 4. Nlg-5-Aza targeting to either CD4 or CD8 T cells dramatically reduces intrarenal CD4, CD8 and DN T cells. MRL/*lpr* mice were treated i.v. with either anti-CD4 antibody coated-nlg-5-Aza (15μl nlg-5-Aza/mouse) or anti-CD8 antibody coated−nlg-5-Aza (15μl nlg-5-Aza/mouse) every ten days for 60 days starting at 12 weeks of age. Free-5-Aza (5μg/mouse) or empty-nlg were applied to two control groups separately. (a) Flow cytometry analysis of intrarenal T cells. Data represent the mean ± SEM. (b) Dot plot graph shows quantitation of the absolute cell numbers of CD4, CD8 and DN T cells from the kidneys of mice subjected to the indicated treatment. **P* < 0.05, ***P* < 0.01, ****P* < 0.005 vs. control, a 2-tailed Student's *t* test. *n* = 5-6 mice per group for 2 independent experiments.

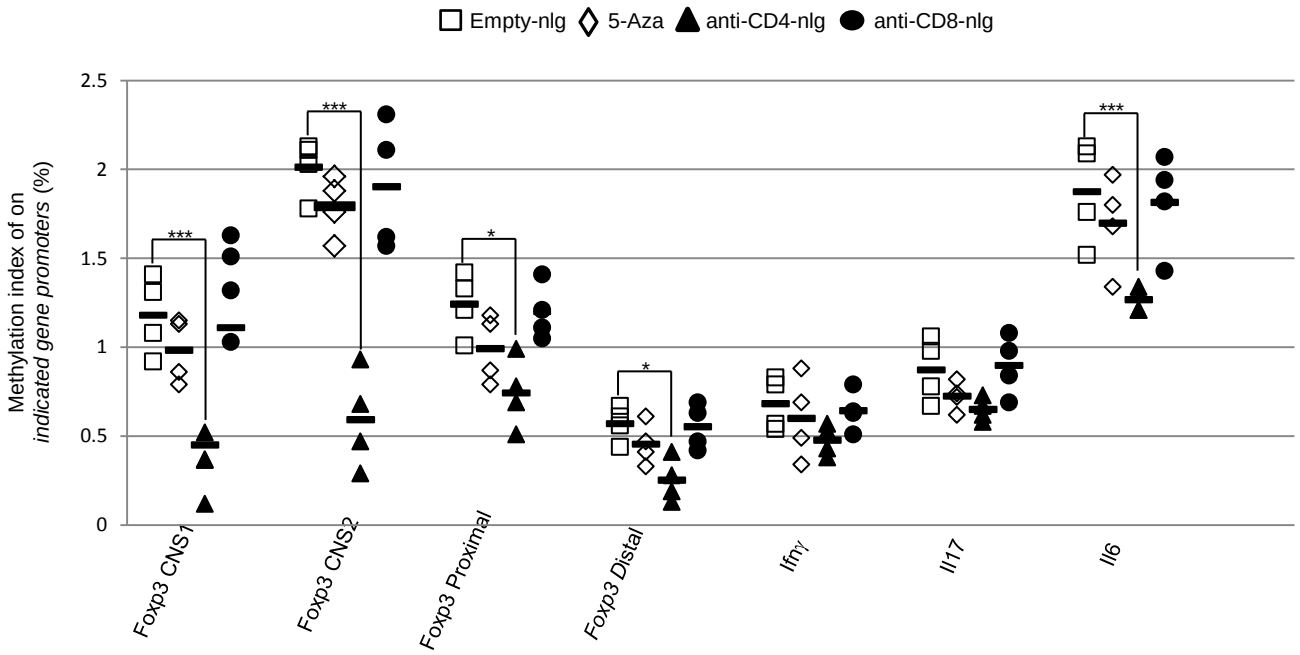


Supplemental Figure 5. Nlg-5-Aza targeting to either CD4 or CD8 T cells dramatically reduces both inflammatory Th1 and Th17 cells in the cervical lymph nodes.

MRL/*lpr* mice were treated i.v. with either anti-CD4 antibody coated-nlg-5-Aza (15μl nlg-5-Aza/mouse) or anti-CD8 antibody coated−nlg-5-Aza (15μl nlg-5-Aza/mouse) every ten days for 60 days starting at 12 weeks of age. Free-5-Aza (5μg/mouse) or empty-nlg were applied to two control groups separately. Flow cytometry analysis of IL-17 and IFNγ expression in $CD4^+$ T cells of spleens from mice subjected to the indicated treatment (gated in $CD3^+CD4^+TCR\beta^+CD49b^-$). Data represents the mean ± SEM (**P < 0.01 vs. Control, a 2-tailed Student's t test. n = 5-6 mice per group for 2 independent experiments).



Supplemental Figure 6. Specific targeting of nlg-5-Aza in CD4⁺ T cells promotes expansion of Tregs in cervical lymph nodes.
MRL/*lpr* mice were treated i.v. with either anti-CD4 antibody coated-nlg-5-Aza (15µl nlg-5-Aza/mouse) or anti-CD8 antibody coated−nlg-5-Aza (15µl nlg-5-Aza/mouse) every ten days for 60 days starting at 12 weeks of age. Free-5-Aza (5µg/mouse) or empty-nlg were applied to two control group separately. (a) Flow cytometry quantization of the percentage of Foxp3⁺CD4 T cells (Thy1.2⁺CD4⁺) in cervical lymph nodes from mice subjected to the indicated treatment. Data represent the mean ± SEM. (b) Dot plot graph shows quantitation of Foxp3⁺CD4 T cells (Thy1.2⁺CD4⁺) in cervical lymph nodes from mice subjected to the indicated treatment. ***$P < 0.005$ vs. control, a 2-tailed Student's *t* test. n = 5-6 mice per group for 2 independent experiments.



Supplemental Figure 7. Nlg-5-Aza targeting to CD4 T cells but not free 5-Aza dramatically reduces Foxp3-associated DNA methylation in CD4 T cells.

MRL/*lpr* mice were treated i.v. with either anti-CD4 antibody or anti-CD8 antibody coated-nlg-5-Aza (15µl nlg-5-Aza/mouse) for 10 hrs, free-5-Aza (5µg/mouse) or Empty-nlg were applied to two control groups separately. *n* = 4 mice per group. Dot plot graph shows quantitation *of DNA methylation* on indicated gene promoters or enhancers in CD4 T cells sorted from mouse spleens 10 hrs after indicated treatment. **P* < 0.05, ****P* < 0.005 vs. control, a 2-tailed Student's *t* test.

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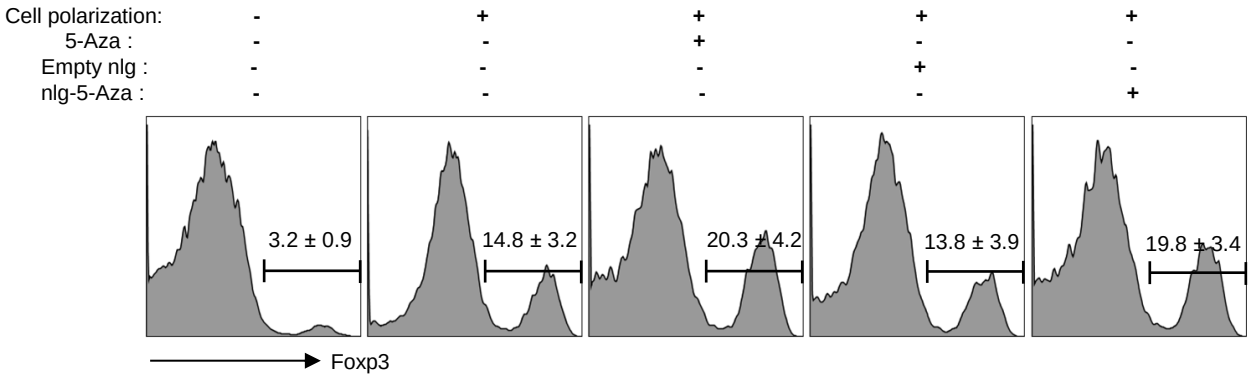

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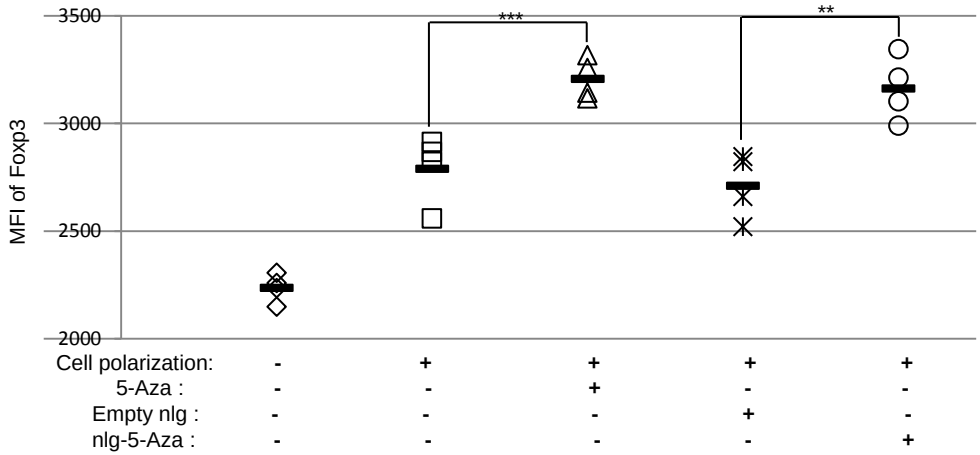
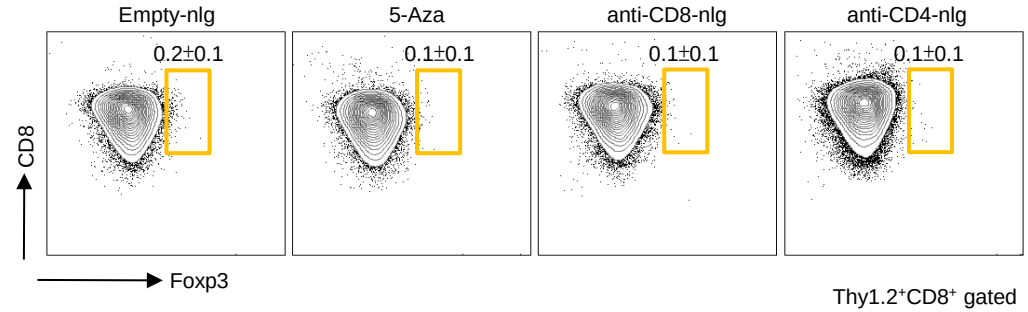
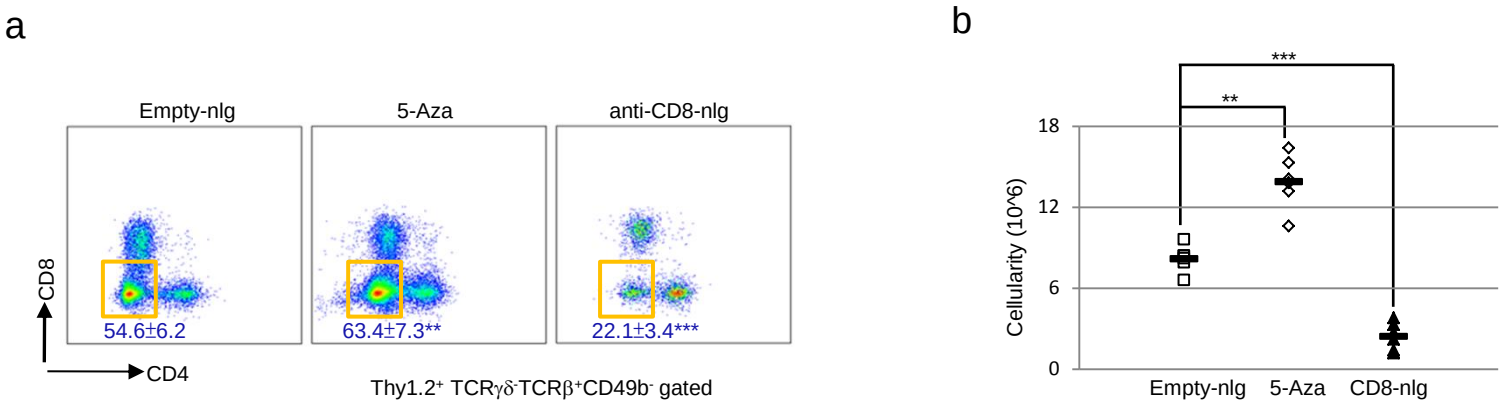


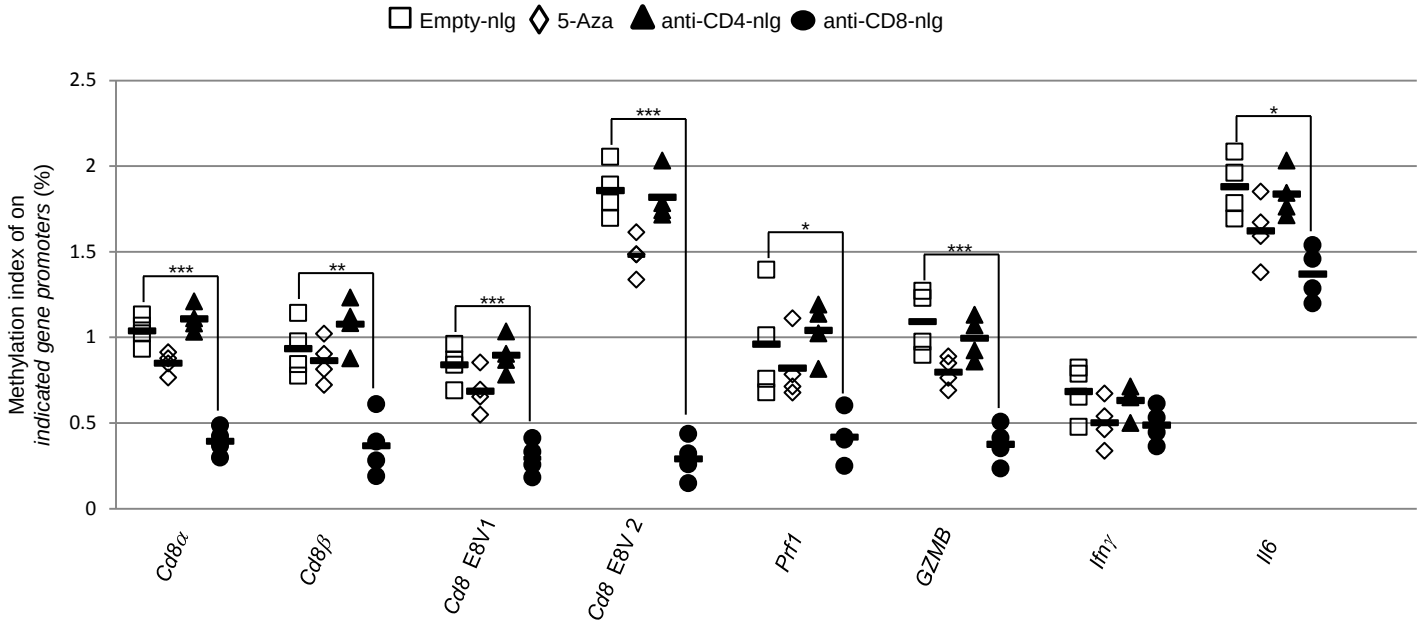
Supplemental Figure 8. 5-Aza or nlg-5-Aza promotes expansion of Tregs under polarization conditions *in vitro*.
Naive CD4 T-cells from healthy donors were polarized under Treg inducing conditions for 7 days, with Aza (1 μM), empty nlg or 5-Aza-nlg (equivalent to 1μM) added 12 hrs before collection. (a) Flow cytometry analysis shows the induction of Foxp3 in CD4 T cells polarized *in vitro*. Data represent the mean ± SEM. (b) Dot plot graph shows Mean fluorescence intensity (MFI) of Foxp3 expression in CD4 T cells polarized *in vitro.* *n*= 4 per group. ***P* < 0.01, ****P* < 0.05 vs. control, a 2-tailed Student's *t* test.



Supplemental Figure 9. Specific targeting of nlg-5-Aza to CD8⁺ T cells did not induce Foxp3 expression in CD8 T cells.
MRL/*lpr* mice were treated i.v. with either anti-CD4 antibody coated-nlg-5-Aza (15μl nlg-5-Aza/mouse) or anti-CD8 antibody coated−nlg-5-Aza (15μl nlg-5-Aza/mouse) every ten days for 60 days starting at 12 weeks of age. Free-5-Aza (5μg/mouse) or empty-nlg were applied to two control group separately. Flow cytometry quantization of the percentage of Foxp3⁺ CD8 T cells (Thy1.2⁺CD8⁺) in spleens from mice subjected to the indicated treatment. Data represent the mean ± SEM (*n* = 5-6 mice per group for 2 independent experiments).

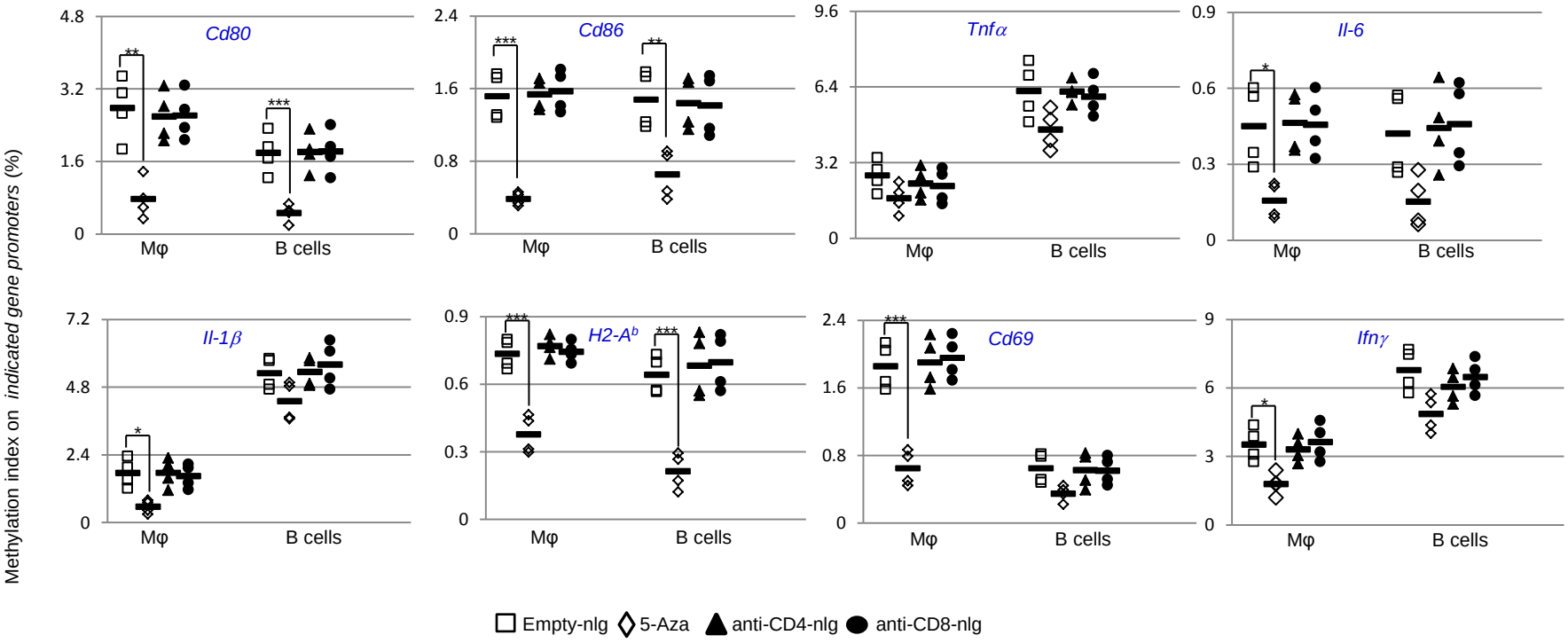


Supplemental Figure 10. Specific targeting of nlg-5-Aza to CD8⁺ T cells significantly reduces DN T cells in cervical lymph nodes. MRL/*lpr* mice were treated i.v. with anti-CD8 antibody coated-nlg-5-Aza (15μl nlg-5-Aza/mouse) every ten days for total 60 days total starting at 12 weeks of age. Free-5-Aza (5μg/mouse) or empty-nlg were applied to two control group separately. (a) Flow cytometry quantization of the percentage of Thy1.2$^+$TCRβ$^+$TCRγδ$^-$CD49b$^-$CD4$^-$CD8$^-$T cells in cervical lymph nodes from mice subjected to the indicated treatment. Data represent the mean ± SEM. (b) Dot plots show quantitation of the absolute cell numbers of Thy1.2$^+$TCRβ$^+$TCRγδ$^-$CD49b$^-$CD4$^-$CD8$^-$T cells in cervical lymph nodes from mice subjected to the indicated treatment. $^{**}P < 0.01$, $^{***}P < 0.005$ vs. control, a 2-tailed Student's *t* test. $n = 5$-6 mice per group for 2 independent experiments.



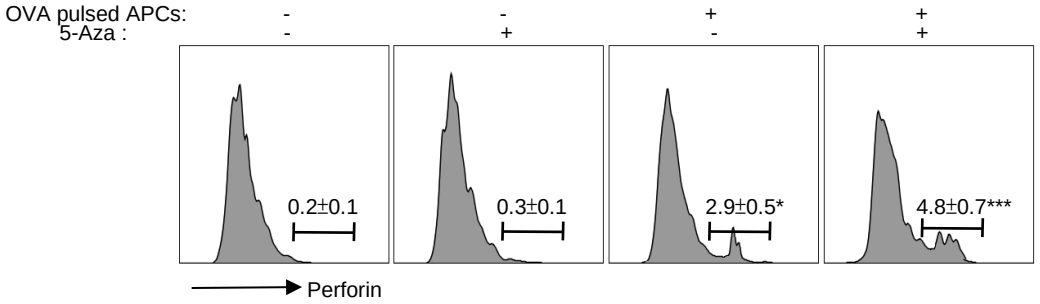
Supplemental Figure 11. Nlg-5-Aza targeting to CD8 T cells but not free 5-Aza dramatically reduces cytolytic activity associated DNA methylation in CD8 T cells.

MRL/*lpr* mice were treated i.v. with either anti-CD4 antibody or anti-CD8 antibody coated-nlg-5-Aza (15μl nlg-5-Aza/mouse) for 10 hrs, free-5-Aza (5μg/mouse) or Empty-nlg were applied to two control groups separately. *n* = 4 mice per group. Dot plots show quantitation *of DNA methylation* on indicated gene promoters or enhancers in CD8 T cells sorted from mouse spleens 10 hrs after indicated treatment. **P* < 0.05, ***P* < 0.01, ****P* < 0.005 vs. control, a 2-tailed Student's *t* test.



Supplemental Figure 12. Free-5-Aza but not Nlg-5-Aza targeting to either CD4 or CD8 T cells dramatically reduces Inflammation-associated DNA methylation in macrophages and B cells.

Age matched MRL/*lpr* mice were treated i.v. with either anti-CD4 antibody or anti-CD8 antibody coated-nlg-5-Aza (15μl nlg-5-Aza/mouse) for 10 hrs, free-5-Aza (5μg/mouse) or Empty-nlg were applied to two control groups separately. *n* = 4 mice per group. Dot plot graph shows show quantitation *of DNA methylation* on indicated gene promoters or enhancers in macrophages (Mφ,CD11b$^+$) or B cells (CD19$^+$) sorted from MRL/*lpr* mouse spleens 10 hrs after indicated treatment. **P* < 0.05, ***P* < 0.01, ****P* < 0.005 vs. control, a 2-tailed Student's *t* test.



Supplemental Figure 13. 5-Aza did not induce perforin expression in naïve CD8 T cells but could enhance perforin expression in activated CD8 T cells .

Flow cytometry analysis of intracellular perforin expression in CD45.1^{+}OT-I TCR Tg T cells from CD45.1 OT-I TCR Tg Rag1$^{-/-}$ B6 mice (CD45.1^{+}TCRβ^{+} gated) co-cultured with or without $OVA_{257-264}$ loaded antigen-presenting cells (*APC*) for 12 hrs in the absence or presence of 5-Aza (1μM). Data represent the mean $\pm$ SEM (*n* = 3-4 per group. **P* < 0.05, ****P* < 0.005 vs. control, a 2-tailed Student's *t* test).

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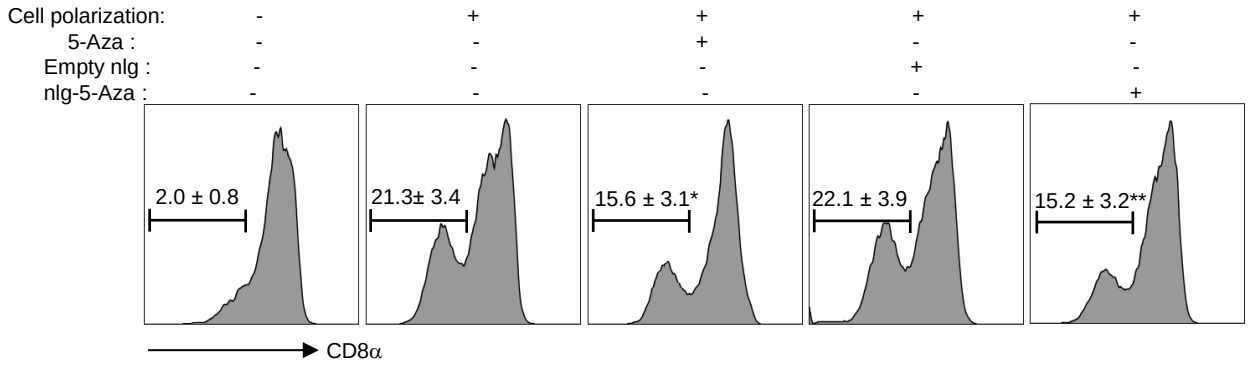

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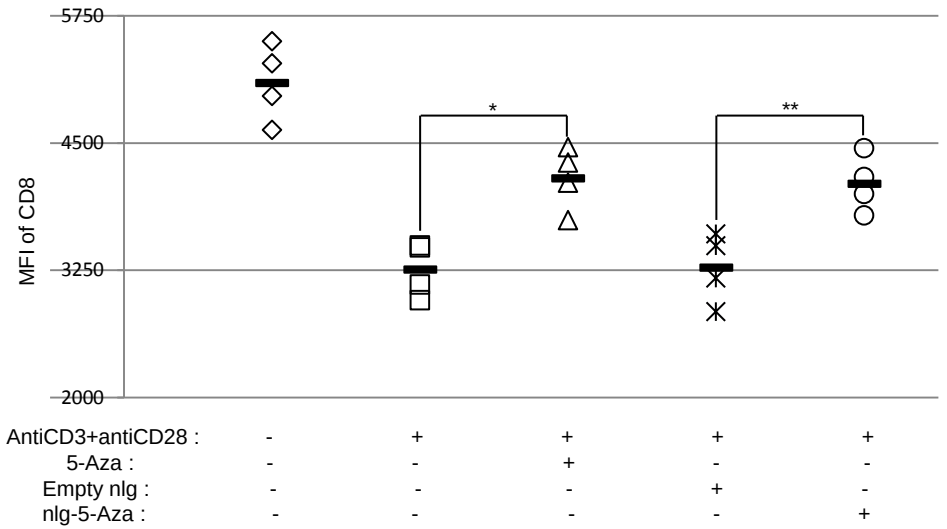

Supplemental Figure 14. 5-Aza or nlg-5-Aza reduced activation induced CD8 downregulation *in vitro*.
MACS enriched peripheral CD8 T cells from healthy donors were cultured with anti-CD3/anti-CD28 stimulus for 12 hrs with 5-Aza (1μM), empty-nlg or nlg-5-Azd (equivalent to 1μM). *n* = 4 per group. (a) Flow cytometry analysis shows the activation induced CD8 downregulation on cell surface. Data represent the mean ± SEM. (b) Dot plots graph shows MFI of CD8 expression after stimulation. **P* < 0.05, ***P* < 0.01 vs. indicated control, a 2-tailed Student's *t* test.