Supplemental Figure 1: AT-406 decreases the expression of cIAP1 in donor T cells and host non-hematopoietic target cells after allo-BMT.

BALB/c animals received 8.5Gy on day -1 and were transplanted with $0.5x10^6$ $CD90.2^+$ splenic T cells along with $5x10^6$ T cell depleted bone marrow (TCD-BM) cells from either syngeneic BALB/c or allogeneic MHC mismatched B6 donors. Recipient animals received either AT-406 (10mg/kg) or its diluent subcutaneously on day-1, +1, +3, +5 and +7 after bone marrow transplantation (BMT). cIAP1 expression of donor $CD3^+$ T cells in the spleen and $CD326^+$ epithelial cells of small intestine was evaluated by FACS staining on day 8. A representative figure (left) and pooled data (right) from 5-8 animals are shown. The bar shows the mean ± SEM.

Supplemental Figure 2: AT-406 treatment increases pro-inflammatory cytokine production from donor T cells as well as elevated serum levels of cytokines after all-BMT.

(a-c) BALB/c animals received 8.5Gy on day -1 and were transplanted with $0.5x10^6$ $CD90.2^+$ splenic T cells along with $5x10^6$ TCD-BM cells from either syngeneic BALB/c or allogeneic MHC mismatched B6 donors. Recipient animals received either AT-406 (10mg/kg) or its diluent subcutaneously on day-1, +1, +3, +5 and +7 after BMT. (a-c) Expansion of donor TNF-α (a), IL-2 (b), and IL-17A producing T cells in spleens on day 14 after allo-BMT. n=4-5 per group, pooled from two experiments. The bar shows the mean ± SEM.

Supplemental Figure 3: Phenotypic analysis of various T cell subsets and activation markers in naïve B6-WT, B6-cIAP$^{-/-}$ and B6-XIAP$^{-/-}$ animals.

Splenocytes were isolated from B6-WT, B6-cIAP$^{-/-}$ and B6-XIAP$^{-/-}$ animals that have not been transplanted (n=5-6 per group) and analyzed for their absolute number of $CD4^+$ and $CD8^+$ T cells (a),

naïve ($CD44^{-}CD62L^{+}$), effector memory (EM: $CD44^{+}CD62^{-}$) and central memory (CM: $CD44^{+}CD62L^{+}$) T cell subsets(b), activation marker $CD69^{+}$ expressed on $CD4^{+}$ and $CD8^{+}$ T cells (c) and regulatory T cells (Treg: $CD4^{+}CD25^{+}Foxp3^{+}$)(d). The bar shows the mean ± SEM.

Supplemental Figure 4: The absence of IAPs in donor T cells showed similar apoptosis with non-specific TCR stimulation and allogeneic T cell proliferation in MLR.

(a-b) *In vitro* MLR. Isolated splenic $CD90.2^{+}$ T cells from either B6-WT, B6-$cIAP1^{-/-}$ or B6-$XIAP^{-/-}$ animals were cultured with BMDCs derived from syngeneic B6 or allogeneic BALB/c animals for 56 hours and supernatants were collected. IFN-γ (a) and IL-2 (b) production of T cells was analyzed in the supernatants by ELISA. A representative figure from three independent experiments is shown. The bar shows the mean ± SEM. (c)Isolated splenic $CD90.2^{+}$ T cells from B6-WT animals were stimulated with anti-CD3 (2μg/ml) and anti-CD28 (1μg/ml) in the presence or absence of AT-406 (1μM) for 48 hours and analyzed for proliferation following ^{3}H-thymidine incorporation during the last 6 hours of incubation. The representative data from three independent experiments are shown. **$p<0.01$.

Supplemental Figure 5: IAPs levels in the intestinal epithelial cells is not associated with radiation toxicity.

(a-b) B6-WT animals received 10Gy and IAPs levels in isolated CD326+ cells from small and large intestine were tested by FACS at 24 and 48 hours after irradiation. (a) XIAP and (b) cIAP1 expression. n=3 per each group. *$p<0.05$, ***$p<0.001$, ****$p<0.0001$. The bar shows the mean ± SEM. (c-e) B6-WT, $XIAP^{-/-}$, $cIAP1^{-/-}$ animals received 9Gy, 13Gy, and 15Gy on day -1 and transplanted with $5x10^{6}$BM cells and $3x10^{6}$ splenic T cell from syngeneic B6 animals. Survival, 9Gy (c), 13Gy (d), and 15Gy (e). n=3 per group. (f) B6-WT animals received 10Gy on day -1 and were transplanted with $3x10^{6}$ $CD90.2^{+}$ splenic T

cells along with $5x10^6$ TCD-BM cells from syngeneic B6 donors. Histopathological score in GI tract on day 7 after irradiation was shown. n=3 per group. The bar shows the mean ± SEM.

Supplemental Figure 6: Absence of IAPs in host exacerbates GVHD in allo-BMT.

B6-WT and B6-XIAP$^{-/-}$ animals received 10Gy on day -1 and were transplanted with $3x10^6$ CD90.2$^+$ splenic T cells along with $5x10^6$ TCD-BM cells from either syngeneic B6 or allogeneic MHC-mismatched BALB/c donors. (a) GVHD clinical score. n=5-13 per group. Pooled data from three independent experiments are shown. ***P<0.001, **p<0.01, and *p<0.05, when allo-WT control and allo-XIAP$^{-/-}$ animals are compared. (b) Donor T cell (H-2k^{d+}CD4$^+$ or H-2k^{d+}CD8$^+$) expansion in spleen, liver and intraepithelial cells (IECs) on day 14 after allo-BMT (n=4-6 per group, pooled from two experiments). The bar shows the mean ± SEM. (c-f) Serum levels of IFN-γ (c) and TNF-α (d) on day 14, and IL-6 (e) and IL-17 (f) on day 7 and 14 after allo-BMT (n=4-6 per group, pooled from two experiments). *p<0.05. The bar shows the mean ± SEM. (g) GVHD clinical score at day 7 after allo-BMT. B6-WT and B6-cIAP1$^{-/-}$ animals received 10Gy on day -1 and were transplanted with $3x10^6$ CD90.2$^+$ splenic T cells along with $5x10^6$ TCD-BM cells from either syngeneic B6 or allogeneic MHC mismatched BALB/c donors. n=3-16 per group. Pooled data from three independent experiments are shown. * P<0.05, when allo-WT control and allo-cIAP1$^{-/-}$ animals are compared.

Supplemental Figure 7: Splenic DC phenotype and innate immune responses of B6-cIAP$^{-/-}$ or B6-XIAP$^{-/-}$ animals is comparable to B6-WT animals.

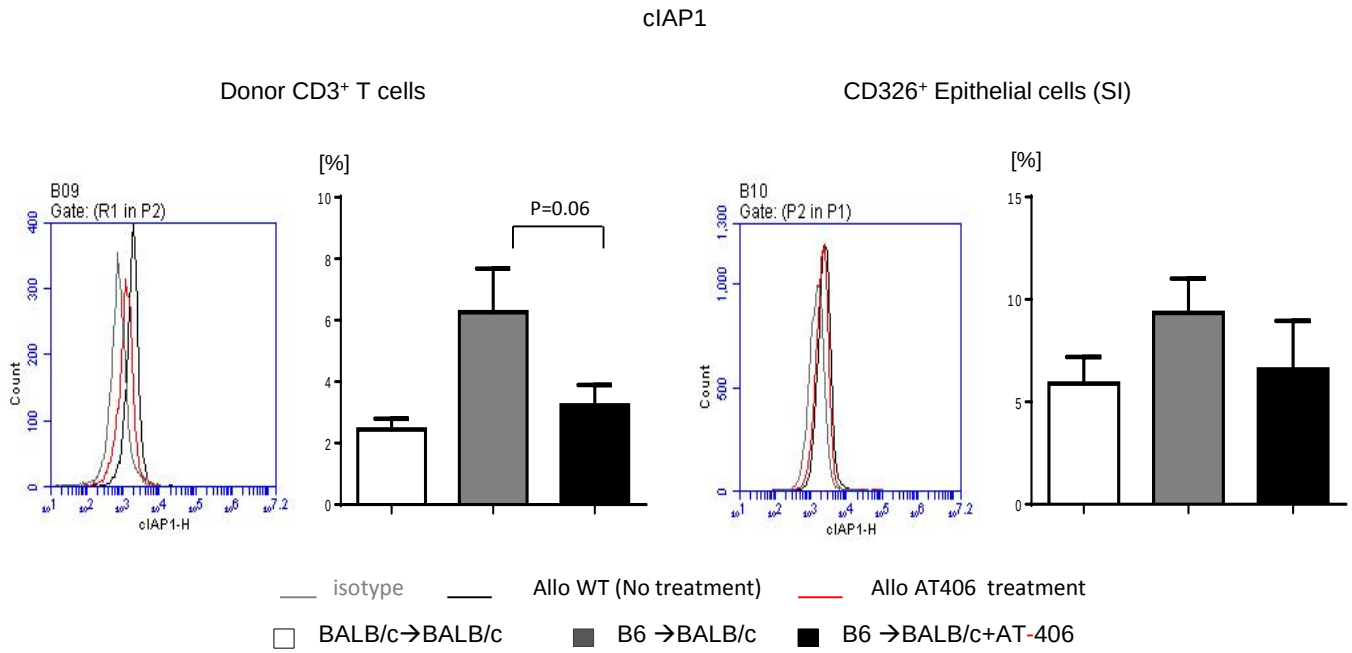
(a-f) The absolute numbers of CD11c$^+$ cells expressing costimulatory molecules in spleens from B6-WT, B6-cIAP1$^{-/-}$ and XIAP$^{-/-}$ animals were analyzed (n=3 per group). (a) The absolute number of CD11c+ DCs. (b-f) The absolute number of costimulatory molecules on CD11c+ DCs: (b) CD80, (c) CD86, (d) B7H1

(PD-L1) and (e) I-A^b (class II) (f) CD40. *$p<0.05$. (g-i) Both non-treated and AT-406 (1μM) pretreated BMDCs were harvested and stimulated with proteoglycan (5 μg/ml, g), Pam3CSK4 (300ng/ml, h) and HMGB-1 (5μg/ml, i) for 16 hours and were analyzed for the expression of CD80, CD86, I-A^b, and B7H1 (PD-L1) by FACS. The data are representative of three independent experiments. The error bars show the mean ± SEM.

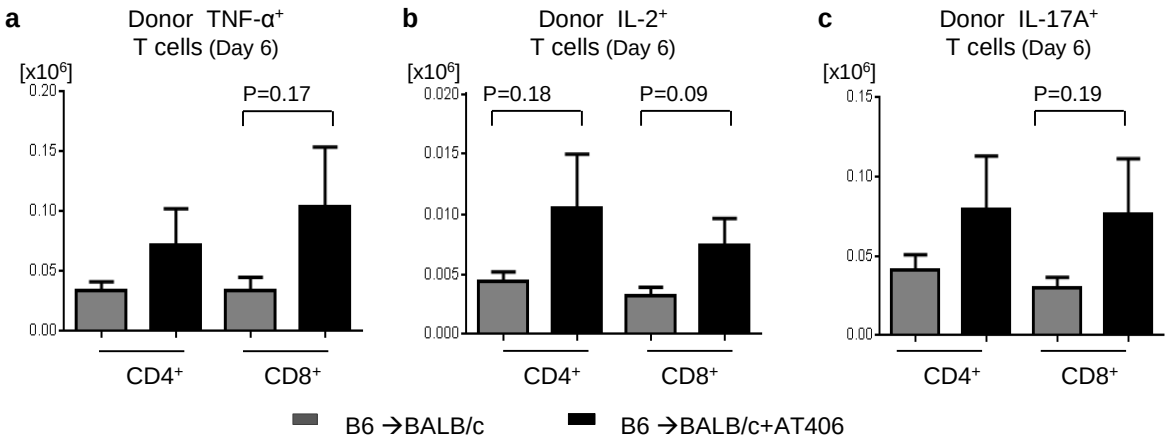
Supplemental Figure 8: LC3, IL-22, and Lgr5 expression in $CD326^+$ cells of GI tract.

(a)LC3-I and II expression was evaluated by western blot in the small intestine epithelial cells of transplanted animals on day 14 after BMT (left panel). The relative intensity of LC3-I and LC3-II bands were adjusted to actin. Graph showing the relative accumulation of total LC3-I and II (right panel). The bar shows the mean ± SEM. (b-c) IL-22 and lgr5 expression in $CD326^+$ cells in small and large intestine in naïve B6-WT, $cIAP1^{-/-}$, and $XIAP^{-/-}$ animals. n=3 per groups. The error bars show the mean ± SEM.

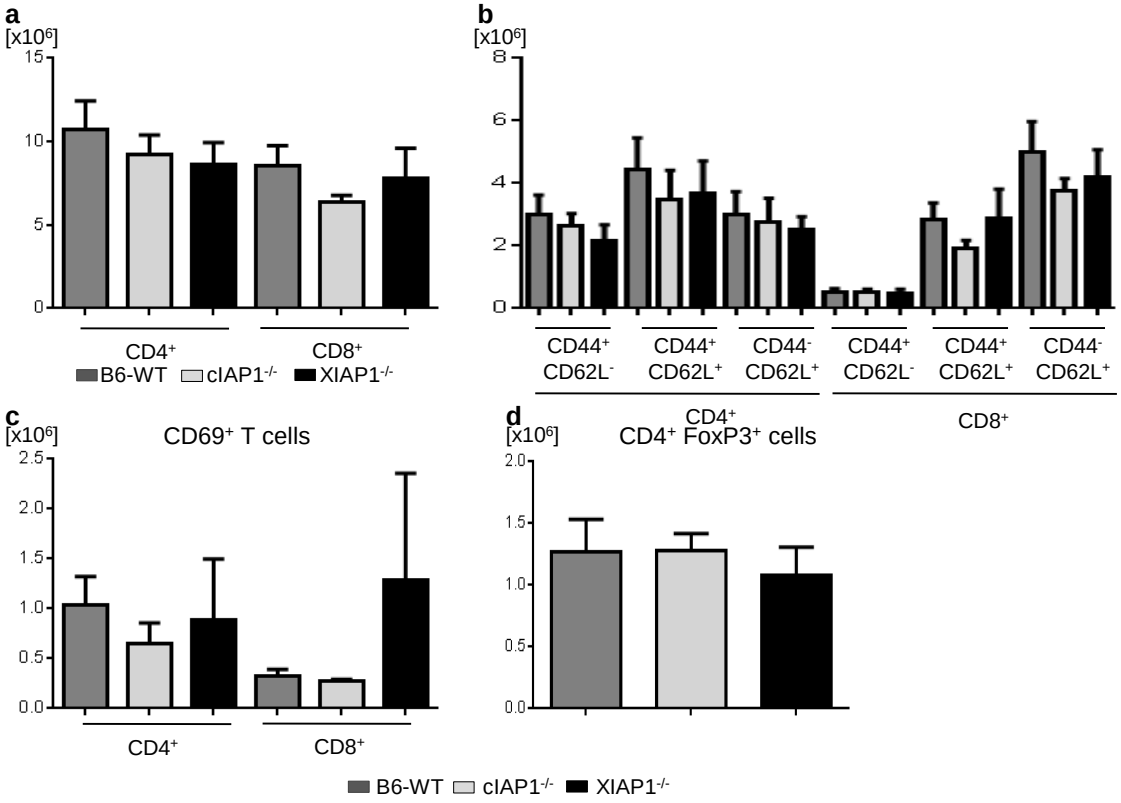
Supplemental Figure 1



Supplemental Figure 2



Supplemental Figure 3



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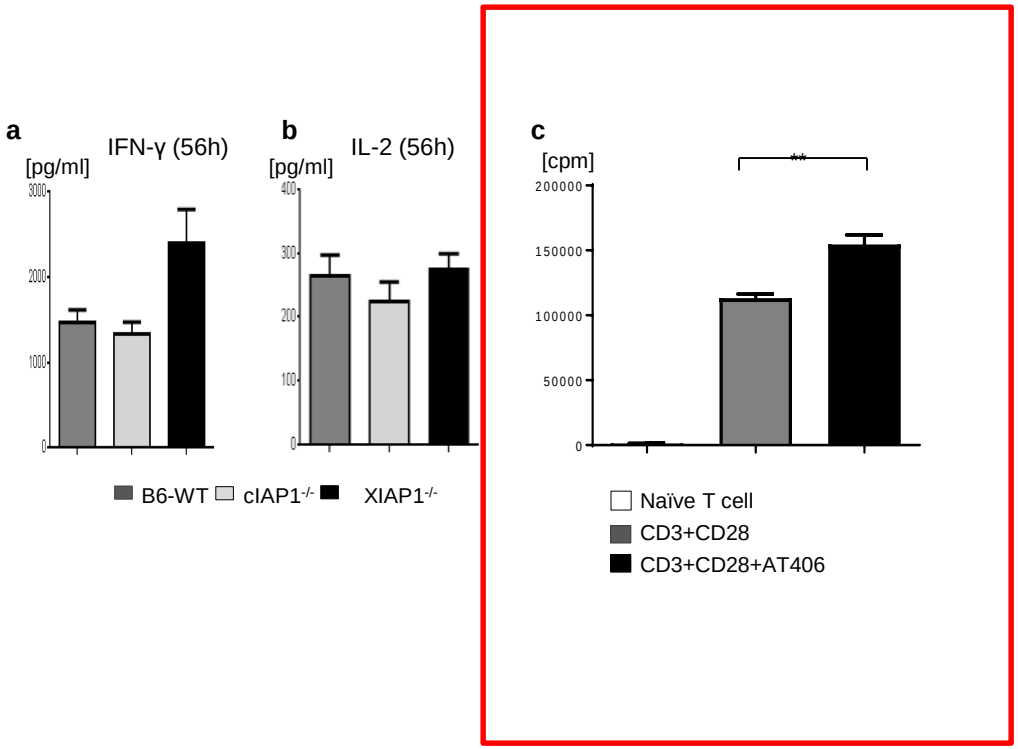

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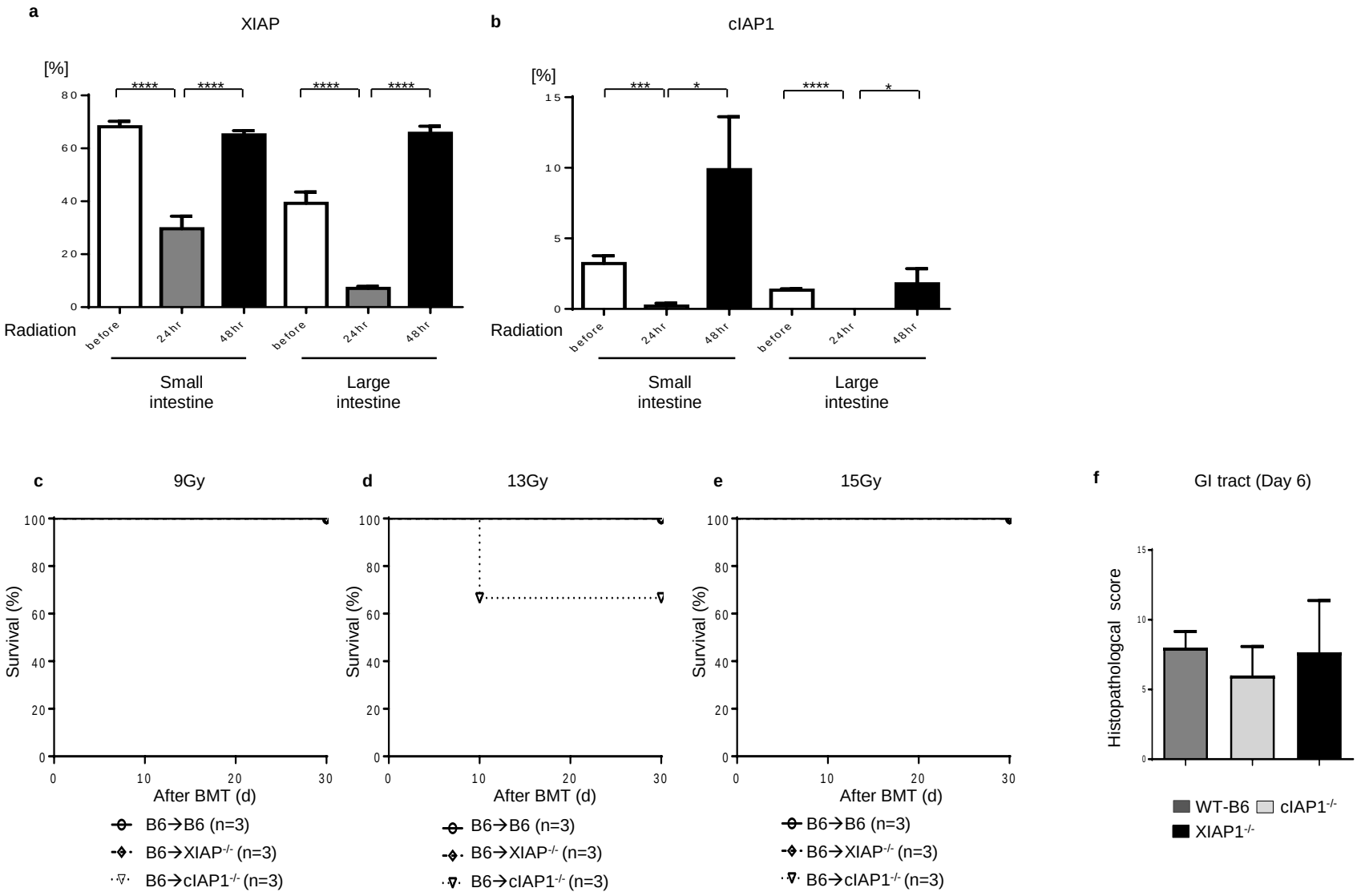
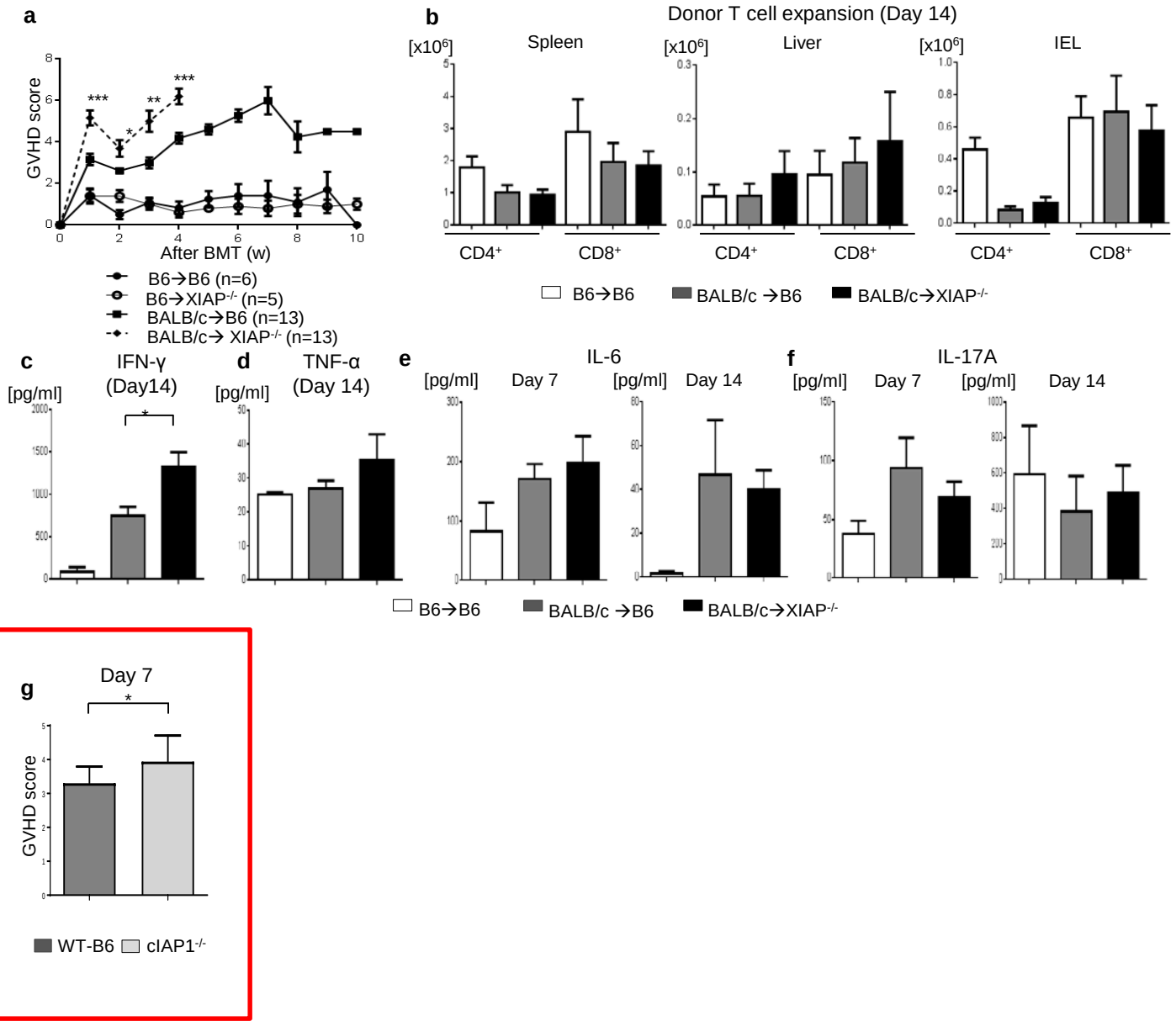
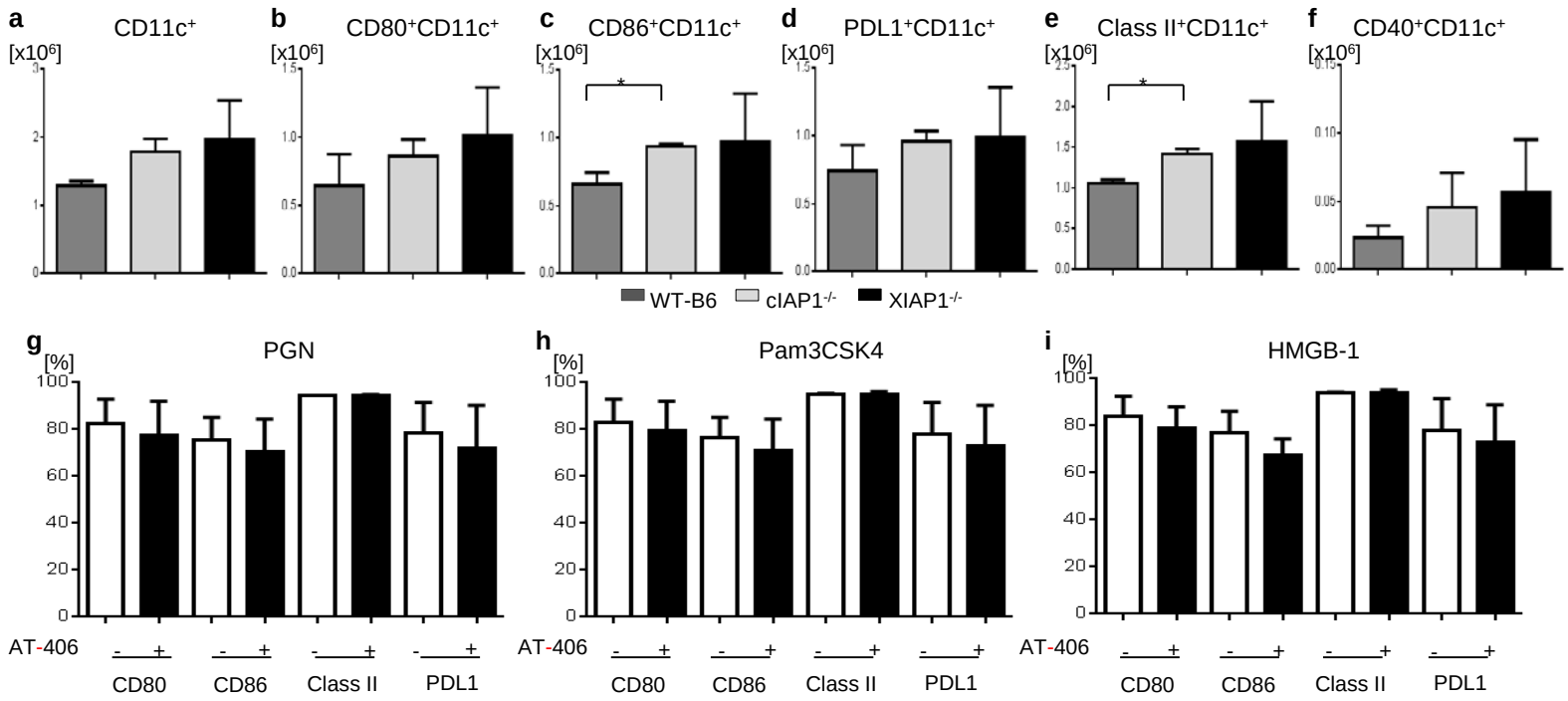


Supplemental Figure 6



Supplemental Figure 7



Supplemental Figure 8