Fig. S1. Flow cytometric analysis of IDO expression and kinetics analysis of IDO and IFN-γ expression in the colon after HSCT. Single cells were isolated from the lungs of B6.WT (n = 5) or B6.IDO−/− (n = 5) recipients on day 7. Isolated cells were double stained for EpCAM and IDO (A) or triple stained for F4/80, CD11c, and IDO (B). Representative histograms for IDO expression in epithelial cells (EpCAM+), interstitial macrophages (F4/80+CD11c−), alveolar macrophages (F4/80+CD11c+), and dendritic cells (F4/80−CD11c+) are presented. Open histograms, B6.WT; gray histograms, B6.IDO−/−. IM, interstitial macrophages; AM, alveolar macrophages; DC, dendritic cells. (C and D) Lethally irradiated (950 cGy) B6 recipients were injected with T cells (2 × 10^6) plus TCD-BM (5 × 10^6) from BALB/c. IDO (C) and IFN-γ (D) expression were measured using real-time PCR at the indicated time points after transplantation. Data are combined from two independent experiments (n = 5–6 per group).
Fig. S2. IDO−/− mice exhibit more severe lung and intestinal GVHD at a later time after HSCT in a milder GVHD model. Lethally irradiated (950 cGy) B6.WT (n = 10) or B6.IDO−/− recipients (n = 10) were injected with T cells (2 × 10⁶) plus TCD-BM (5 × 10⁶) from BALB/c donors. (A) Survival. Data are representative of two independent experiments. (B) Lungs and colons were collected on day 35. Tissue sections were stained with H&E (magnification, 100×) and histopathological scores were evaluated. *P < 0.05.
Fig. S3. Examination of IPS in several different GVHD models. (A–C) Lethally irradiated (950 cGy) B6.WT or B6.IDO−/− recipients were injected with T cells (5 × 10⁶) plus TCD-BM (5 × 10⁶) from Bm12 donors. (A) IDO expression was detected in the lung on day 7 by Western blotting. Representative blots of two independent experiments are shown (n = 2 per group). (B) Histopathological scoring of the lungs on day 9 (n = 5 per group). (C) Cytokine mRNA levels in the lungs were measured on day 9. The data are representative of two independent experiments (n = 5 per group). (D–F) Lethally irradiated (950 cGy) B6.WT or B6.IDO−/− recipients were injected with T cells (5 × 10⁶) plus TCD-BM (5 × 10⁶) from 129 donors. (D) IDO expression was analyzed on day 7. Histopathology (E) and cytokine levels (F) were analyzed on day 14. The data are representative of two independent experiments (n = 5 per group). (G–I) B6.WT or B6.IDO−/− recipients received 20 mg/kg busulfan i.p. once daily from day −7 to day −3 and 100 mg/kg cyclophosphamide i.p. once daily from day −5 to day −3. On day 0, mice were injected with T cells (5 × 10⁶) plus TCD-BM (5 × 10⁶) from BALB/c donors. (G) IDO expression was analyzed on day 7. Histopathology (H) and cytokine levels (I) were analyzed on day 10. The data are representative of two independent experiments (n = 5 per group). *P < 0.05; **P < 0.01; ***P < 0.001.
Fig. S4. Absence of IDO does not affect Treg responses in the lung. Lethally irradiated (950 cGy) B6.WT or B6.IDO−/− recipients were injected with 5 × 10⁶ TCD-BM plus 5 × 10⁶ T cells from BALB/c donor. (A) Single-cell suspensions of the lung were prepared on day 14 after HSCT. Isolated cells were stained for CD4 and Foxp3 and their expression was assessed using flow cytometry. (B) Lungs were collected at the indicated time points. Expression of FoxP3, TGF-β, and IL-10 mRNA were analyzed using real-time PCR. Data are representative of three independent experiments (n = 5–7 per group). (C and D) Lethally irradiated (950 cGy) B6.WT or B6.IDO−/− recipients were injected with 5 × 10⁶ TCD-BM plus 5 × 10⁶ T cells or CD25+CD4+ depleted T cells from BALB/c donor. (C) Shown are representative images (100x, Left) of the lung on day 9. Histopathological scoring of IDO−/− recipients is shown in the Right column. (D) Cytokine mRNA levels in the lungs were measured on day 9. The data are representative of two independent experiments (n = 5 per group).
Fig. S5. IPS in IFN-γR−/− mice. Lethally irradiated (950 cGy) B6.WT or B6.IFN-γR−/− recipients were injected with 5 × 10^6 TCD-BM plus 5 × 10^6 T cells from BALB/c donor. (A) Lung tissue was collected from each group of recipient mice on day 9 and stained with H&E and evaluated for histopathological scoring. Representative images of two independent experiments are shown (100×). (B) Cytokine mRNA levels in the lungs were measured using real-time PCR on day 9. The data are representative of two independent experiments (n = 5 per group). **P < 0.01; ***P < 0.001.
Fig. S6. Effect of IFN-γ−/− donor T cells or FK506 treatment on intestinal GVHD. (A and B) Lethally irradiated (950 cGy) B6.WT (n = 10) or B6.IDO−/− (n = 10) recipients were injected with BALB/c.WT (2 × 10^6) or BALB/c.IDO−/− T cells (2 × 10^6) plus BALB/c.WT TCD-BM (1 × 10^7). Recipients were treated i.p. with IFN-γ on days 5 and 7 after transplantation. (A) Colons were collected from each group of recipient mice on day 9 and stained with H&E and evaluated for histopathological scoring. (B) IDO expression was detected in the colon on day 9 by Western blotting. (C) Histopathological scores of lung and intestinal GVHD in mice that received FK506 at days 9 and 21 after HSCT. Lethally irradiated (950 cGy) B6 recipients were injected with TCD-BM (5 × 10^6) plus T cells (5 × 10^6) from BALB/c donor. FK506 (15 mg/kg) was injected every day from day 0 through day 9. Lung and colon tissues were collected on days 9 and 21. Tissue sections were stained with H&E and evaluated for histopathological scoring. *P < 0.05; **P < 0.01.
Fig. S7. IL-6 signaling is required for the therapeutic effect of HDACi on IPS. (A) Lethally irradiated (950 cGy) B6.WT recipients were injected with BALB/c.WT (2 × 10⁶) or BALB/c:IFN-γ−/− T cells (2 × 10⁶) plus BALB/c:WT TCD-BM (1 × 10⁷). The recipients were treated with SB939 or vehicle i.p. once daily from day 0 to day 9. Ac-STAT3 was analyzed in the lung on day 9 using Western blotting. Representative blots of two independent experiments are shown. (B–D) Lethally irradiated (850 cGy) B6.WT recipients were injected with or without BALB/c:IFN-γ−/− T cells (1 × 10⁶) plus BALB/c:WT TCD-BM (5 × 10⁶). The recipients were treated with anti-IL-6R mAb on days 3, 5, and 9 or with SC144 once daily from day 0 to day 9. (B) Lung tissues were collected on day 10 and evaluated for histopathological scoring. (C and D) Cytokine mRNA levels in the lungs were measured using real-time PCR on day 9. The data are representative of two independent experiments (n = 5 per group). *P < 0.05; **P < 0.01; ***P < 0.001.
Fig. S8.  CH-223191 has no side effect on acute GVHD. Lethally irradiated (950 cGy) B6.WT recipients were injected with BALB/c TCD-BM (1 × 10⁷) with or without BALB/c.IFN-γ−/− T cells (2 × 10⁶). (A and B) The recipients were treated with vehicle or 10 mg/kg CH-223191 once daily from day 4 to day 9. (A) Survival. (B) Histopathological scoring for the colon on day 9. The data are representative of two independent experiments (n = 5 per group).

Fig. S9. Reduction in expression of CYP1B1 mRNA in the lung and colon after HSCT. Lethally irradiated (950 cGy) B6.WT or B6.IDO−/− recipients (n = 10) were injected with T cells (5 × 10⁶) plus TCD-BM (5 × 10⁶) from BALB/c donors. Levels of CYP1B1 mRNA in the lung (A) and colon (B) were measured using real-time PCR on day 7. The data are representative of two independent experiments (n = 5 per group). *P < 0.05; ***P < 0.001.

Fig. S10. Decrease in IDO and IFN-γ expression in the lung of recipients of G-CSF–mobilized donor cells. Lethally irradiated (950 cGy) B6.WT recipients were injected with T cells (2 × 10⁶) plus TCD-BM (5 × 10⁶) or G-CSF–mobilized splenocytes (2.5 × 10⁷) from BALB/c. (A) IDO expression was detected in the lung from recipients on day 7 using Western blotting. (B) IDO and IFN-γ mRNA levels in the lung were measured on day 7 using real-time PCR. Data are representative of two independent experiments. *P < 0.05.