Supplementary Data

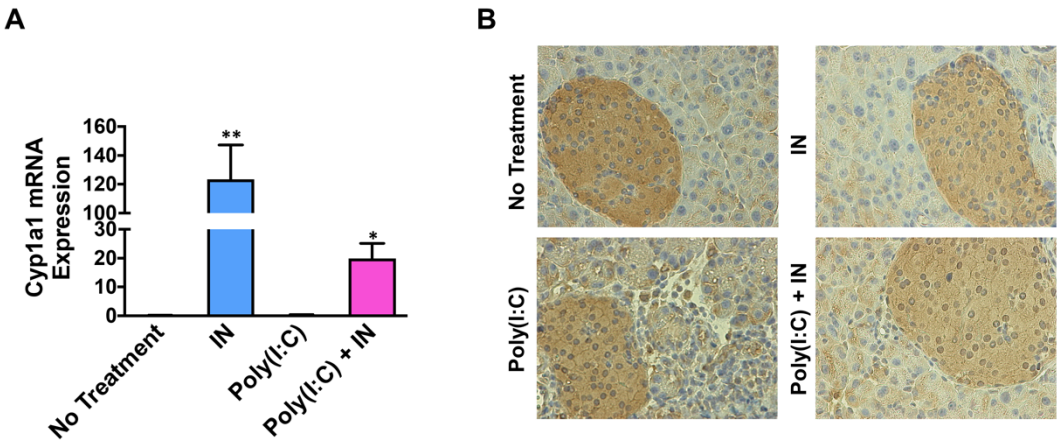

Figure S1

Supplementary Figure 1. mRNA expression of *Cyp1a1* in the pancreas of mice treated with indigo naturalis.

Four groups of MRL/MpJ mice were used: untreated mice (n = 5), mice treated with 4% indigo naturalis (IN) in the diet (n = 5), mice treated with repeated intraperitoneal injections of polyinosinic-polycytidylic acid (poly(I:C), n = 5), and mice co-treated with poly(I:C) and IN (n = 5). Injections of poly(I:C) (100 μg) were performed twice a week for a total of 16 times, and the mice were sacrificed 3 h after the final injection. **(A)** mRNA expression of *Cyp1a1* in the pancreas as determined through quantitative PCR. mRNA expression was normalized to that of *Gapdh*. **(B)** Expression of the aryl hydrocarbon receptor (AhR) in the pancreas. AhR expression was seen in the islet cells and immune cells. Magnification x800. Results are shown as the mean + standard error. $^{**}P < 0.01$, $^{*}P < 0.05$ as compared to values in untreated mice.

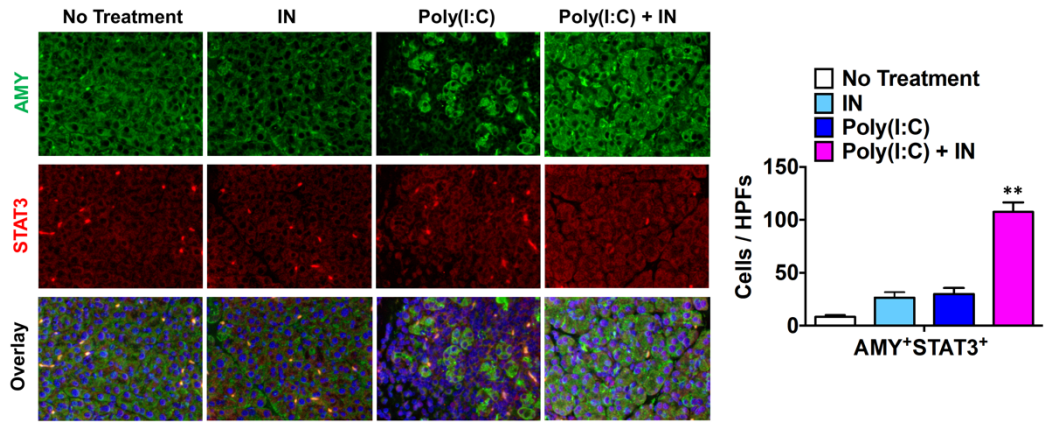

Figure S2

Supplementary Figure 2. Activation of signal transducer and activator of transcription 3 in the pancreas of mice treated with indigo naturalis.

Four groups of MRL/MpJ mice were used: untreated mice (n = 5), mice treated with 4% indigo naturalis (IN) in the diet (n = 5), mice treated with repeated intraperitoneal injections of polyinosinic-polycytidylic acid (poly(I:C), n = 5), and mice co-treated with poly(I:C) and IN (n = 5). Injections of poly(I:C) (100 μg) were performed twice a week for a total of 16 times, and the mice were sacrificed 3 h after the final injection. The activation of phospho-signal transducer and activator of transcription 3 (p-STAT3, red fluorescence) was visualized in pancreatic acinar cells expressing amylase (AMY, green fluorescence). Pancreatic acinar cells expressing nuclear STAT3 were defined as AMY^+STAT3^+ cells. Magnification, x800. Cell nuclei were counterstained with DAPI. The number of AMY^+STAT3^+ cells was counted semi-quantitatively. Results are shown as the mean + standard error. $^{**}P < 0.01$, as compared to values in mice treated with poly(I:C) alone. HPFs; high-power fields.

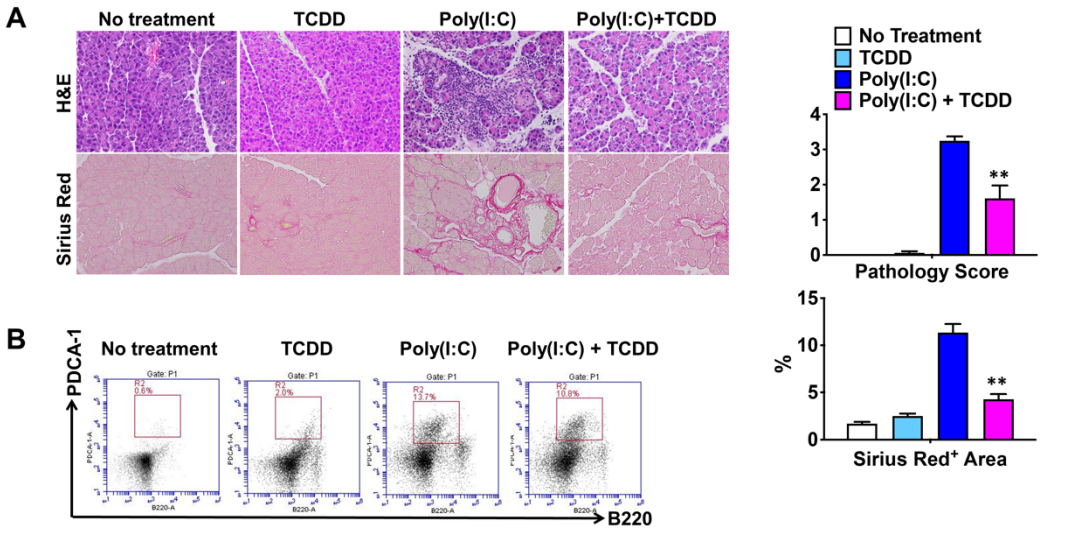

Figure S3

Supplementary Figure 3. Activation of the aryl hydrocarbon receptor by 2,3,7,8-tetrachlorodibenzo-para-dioxin inhibits the development of experimental autoimmune pancreatitis.

Four groups of MRL/MpJ mice were used: untreated mice (n = 8), mice treated with repeated intraperitoneal injections of 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) (n = 10), mice treated with repeated intraperitoneal injections of polyinosinic-polycytidylic acid (poly(I:C), n = 10), and mice co-treated with poly(I:C) and TCDD (n = 9). Injections of poly(I:C) (100 μg) were performed twice a week for a total of 16 times, and the mice were sacrificed 3 h after the final injection. **(A)** Representative images of pancreatic sections stained with hematoxylin and eosin (H&E) or Sirius Red are shown in the left panel (magnification ×400). Pathological scores for autoimmune pancreatitis and areas occupied by pancreatic fibrosis derived from the analyses of H&E and Sirius Red staining, respectively, are illustrated in the right panel. Areas positive for Sirius Red staining were semi-quantitatively measured. **(B)** Flow cytometry analyses of

the percentages of pancreatic plasmacytoid dendritic cells (pDCs) defined as PDCA-1^{+}B220^{low} cells. Results are shown as the mean + standard error. $^{**}P < 0.01$, as compared to values in mice treated with poly(I:C) alone.

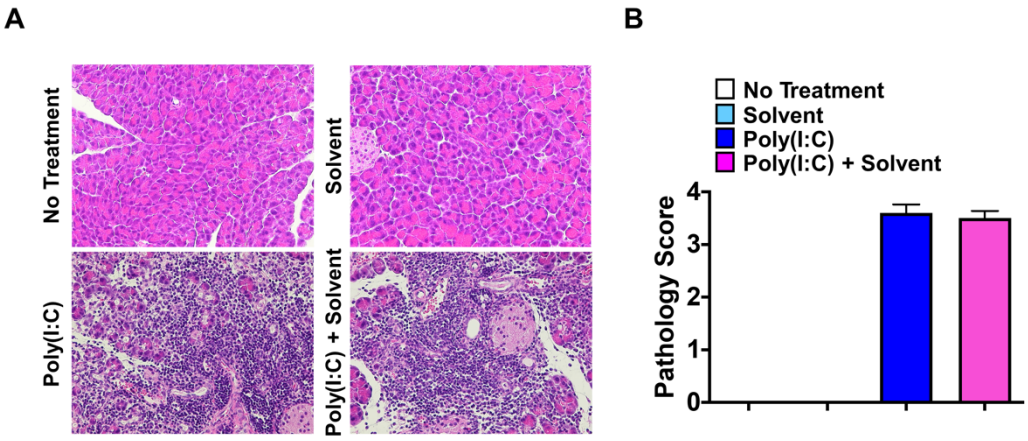

Figure S4

Supplementary Figure 4. Solvent for 2,3,7,8-tetrachlorodibenzo-para-dioxin does not inhibit the development of experimental autoimmune pancreatitis. Four groups of MRL/MpJ mice were used: untreated mice (n = 3), mice treated with repeated intraperitoneal injections of 2,3,7,8-tetrachlorodibenzo-para-dioxin (TCDD) solvent (n = 5, 100 μl, 10% toluene in dimethyl sulfoxide), mice treated with repeated intraperitoneal injections of polyinosinic-polycytidylic acid (poly(I:C)), n = 5), and mice co-treated with poly(I:C) and solvent (n = 7). Injections of poly(I:C) (100 μg) were performed twice a week for a total of 16 times, and the mice were sacrificed 3 h after the final injection. Representative images of pancreatic sections stained with hematoxylin and eosin (H&E) are shown in the left panel (magnification ×400). Pathological scores for autoimmune pancreatitis derived from the analyses of H&E staining are illustrated in the right panel. Results are shown as the mean + standard error.

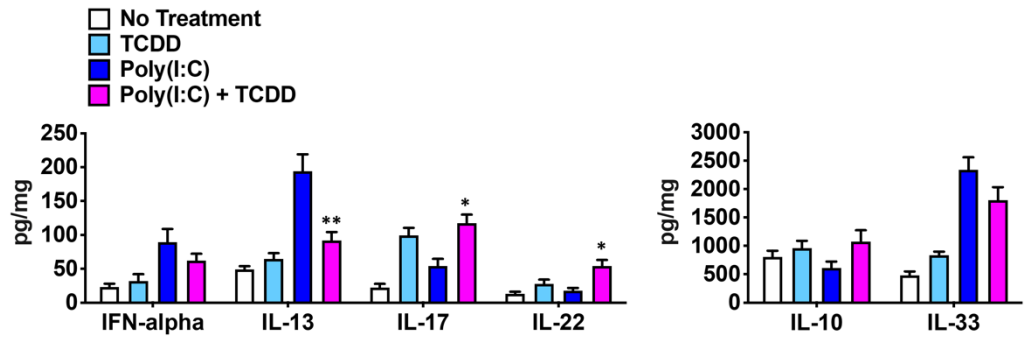

Figure S5

Supplementary Figure 5. Profiles of pancreatic cytokines in mice treated with 2,3,7,8-tetrachlorodibenzo-para-dioxin.

Four groups of MRL/MpJ mice were used, as described in Supplementary Figure 3. Concentrations of IFN-α, IL-10, IL-13, IL-17, IL-22, and IL-33 were determined in pancreatic lysates using enzyme-linked immunosorbent assays. Results are shown as the mean + standard error. *P < 0.05, **P < 0.01, as compared with values in mice treated with poly(I:C) alone.

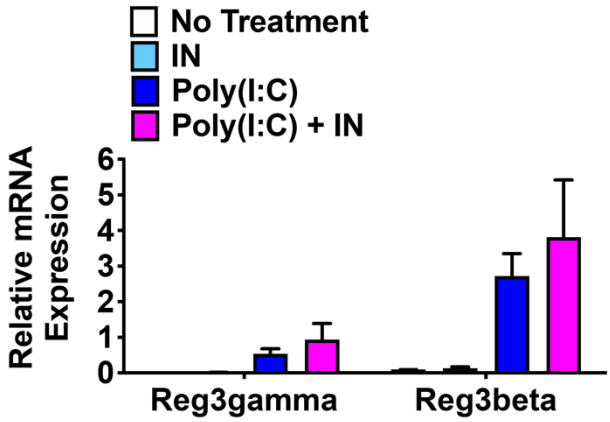

Figure S6

Supplementary Figure 6. Expression of regenerating islet-derived protein 3 in the pancreas.

Four groups of MRL/MpJ mice were used: untreated mice (n = 5), mice treated with 4.0% indigo naturalis (IN) in the diet (n = 5), mice treated with repeated intraperitoneal injections of polyinosinic-polycytidylic acid (poly(I:C), n = 5), and mice co-treated with poly(I:C) and IN (n = 4). Injections of poly(I:C) (100 μg) were performed twice a week for a total of 16 times, and the mice were sacrificed 3 h after the final injection. Expression levels of genes encoding regenerating islet-derived protein 3β (REG3β) and REG3γ were determined by quantitative PCR. The mRNA expression was normalized to that of *Gapdh*. Results are shown as the mean + standard error.

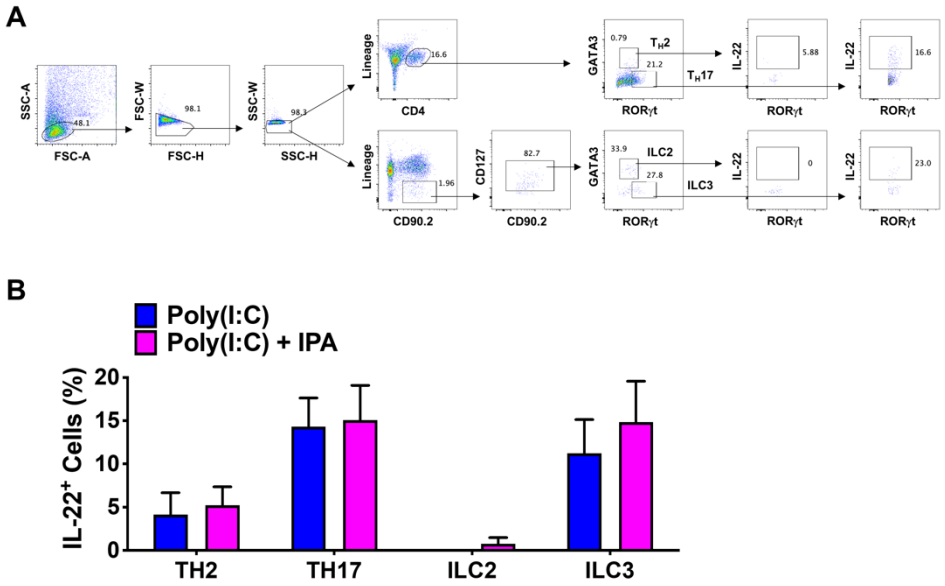

Figure S7

Supplementary Figure 7. Fractions of IL-22$^+$ cells in different immune cell populations.

Mice fed a normal diet or that containing 0.1% indole-3-pyruvic acid (IPA) received 16 intraperitoneal injections of polyinosinic-polycytidylic acid (poly(I:C)), 100 μg) as described in Fig. 3. Three hours after the final injection, the cells were isolated from the pancreas and stimulated *in vitro* with phorbol 12-myristate 13-acetate and ionomycin for 5 h. Mice were treated with poly(I:C) alone (n = 5) or co-treated with poly(I:C) and IPA (n = 5). **(A)** Gating protocol for analyzing subsets of CD4$^+$ T cells and innate lymphoid cells (ILCs) in the pancreas. **(B)** Fractions of IL-22$^+$ cells in the indicated populations. Results are shown as the mean + standard error.

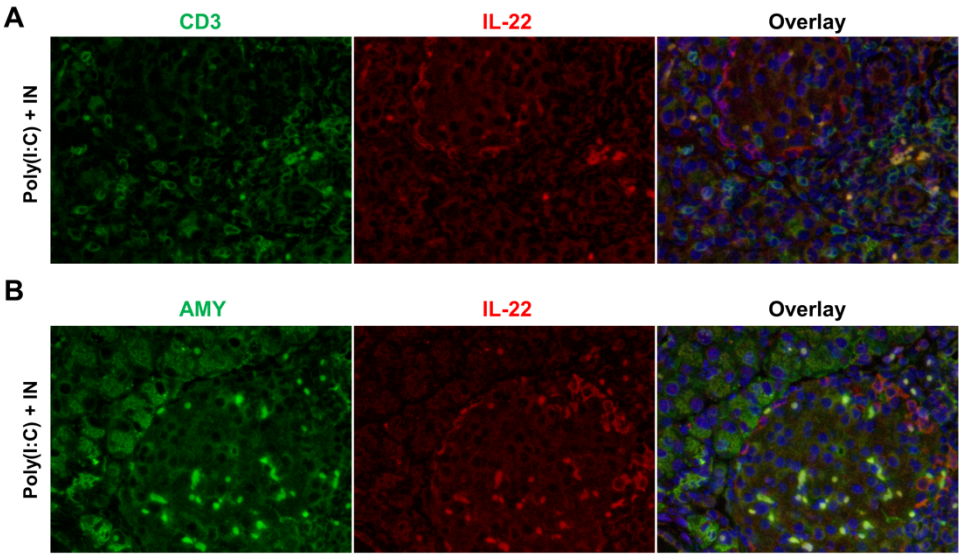

Figure S8

Supplementary Figure 8. IL-22 is not produced by CD3$^+$ T cells or acinar cells in response to indigo naturalis-mediated aryl hydrocarbon receptor activation.

Mice were received repeated intraperitoneal injections of polyinosinic-polycytidylic acid (poly(I:C)) twice a week for eight weeks in combination with indigo naturalis (IN) in the diet. Localization of IL-22$^+$ cells, CD3$^+$ T cells (A), or amylase$^+$ cells (B) in the pancreas of mice co-treated with poly(I:C) and IN. Cell nuclei were counterstained with DAPI. Green fluorescence, CD3 or amylase; red fluorescence, IL-22 (magnification ×800).