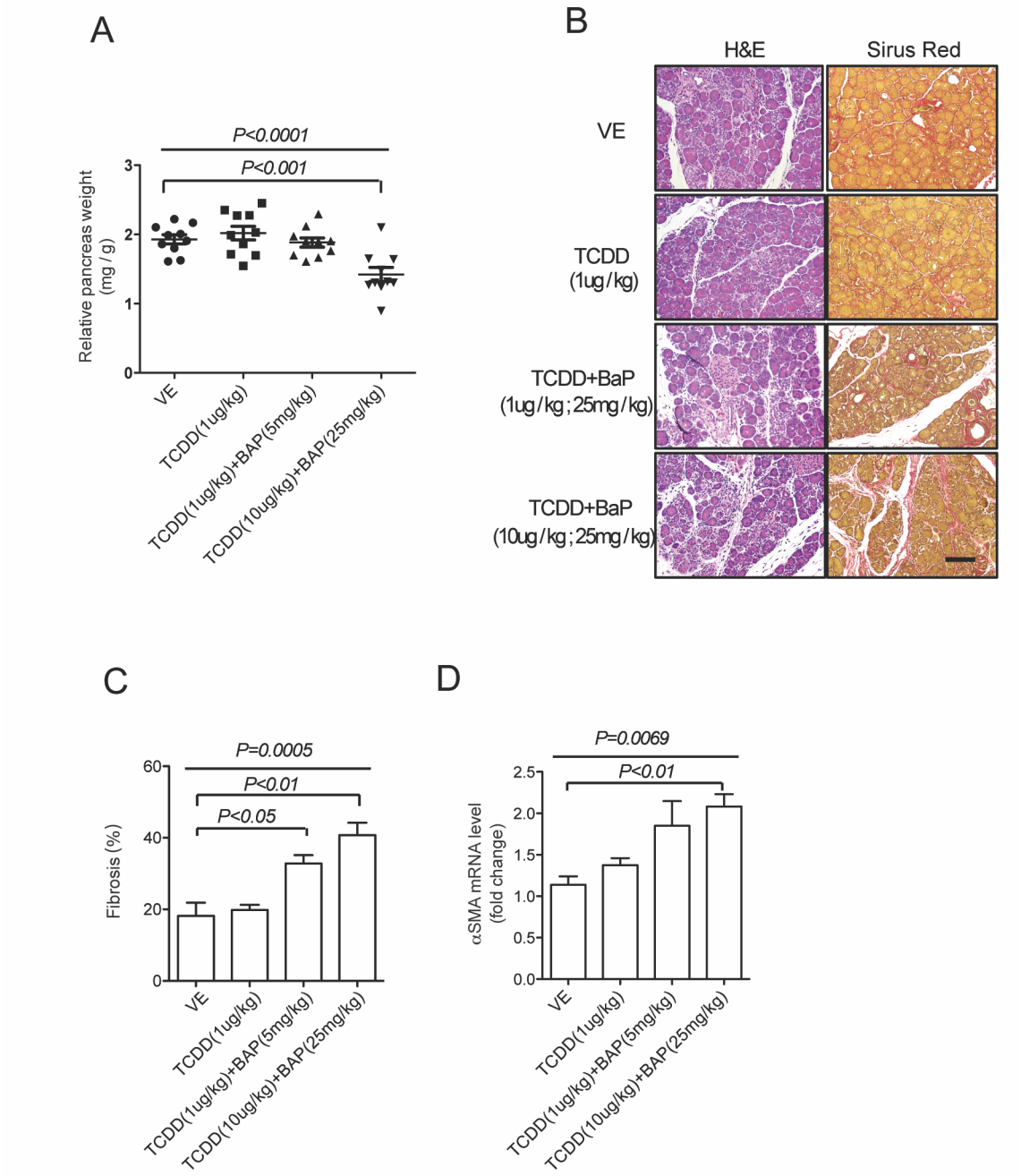
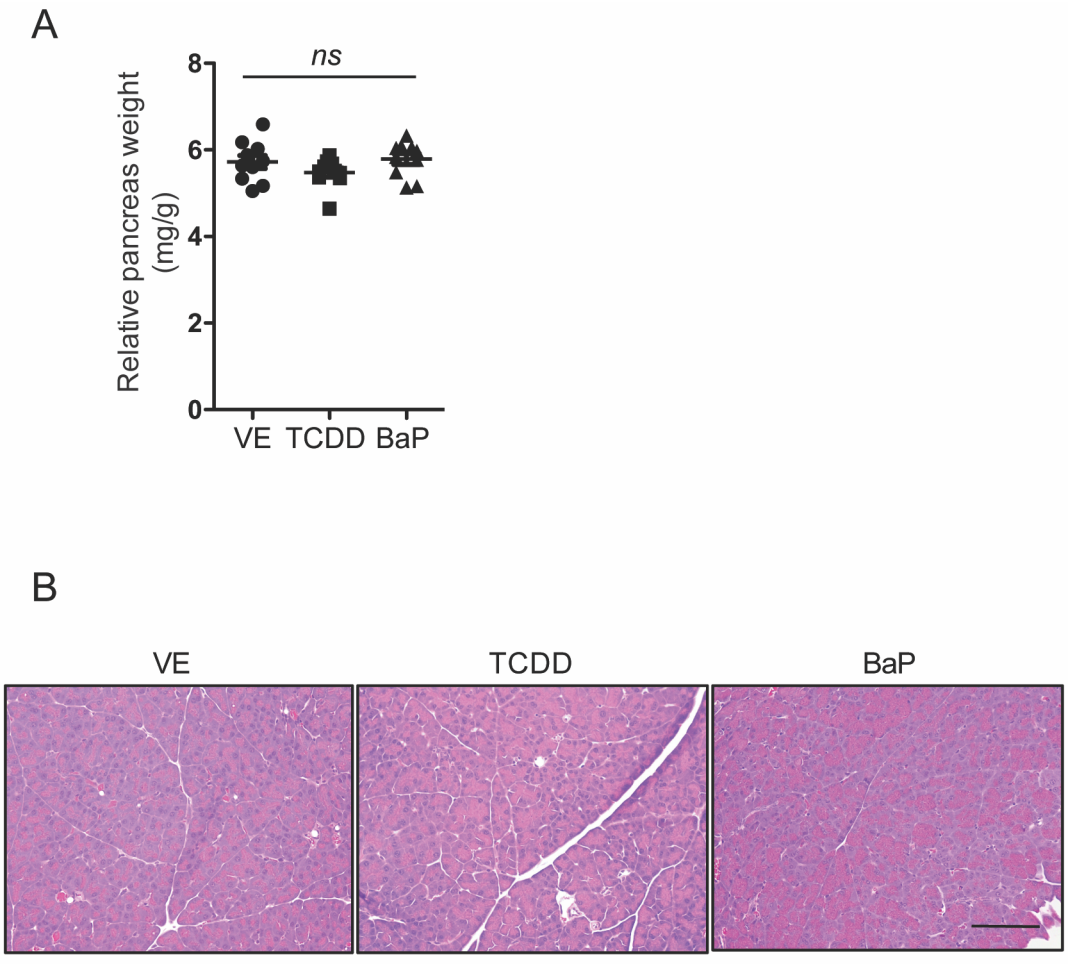
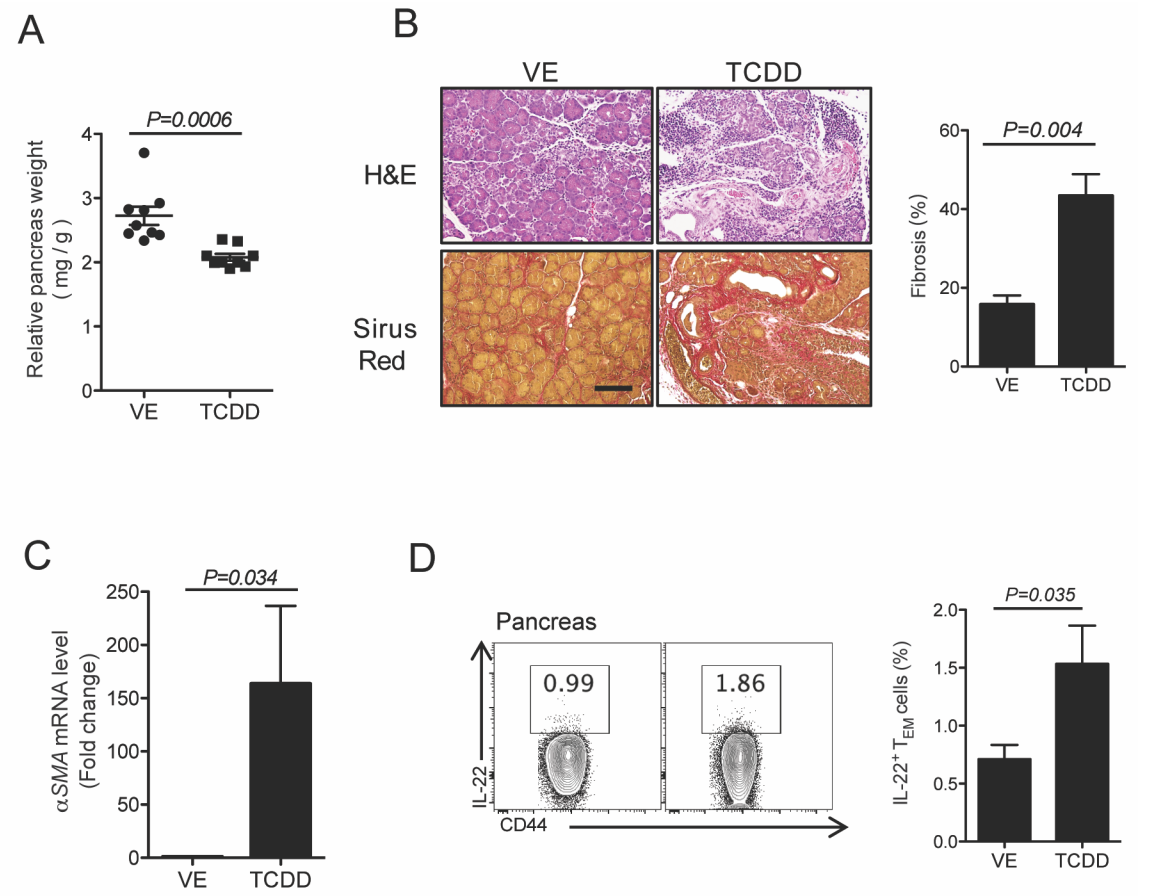


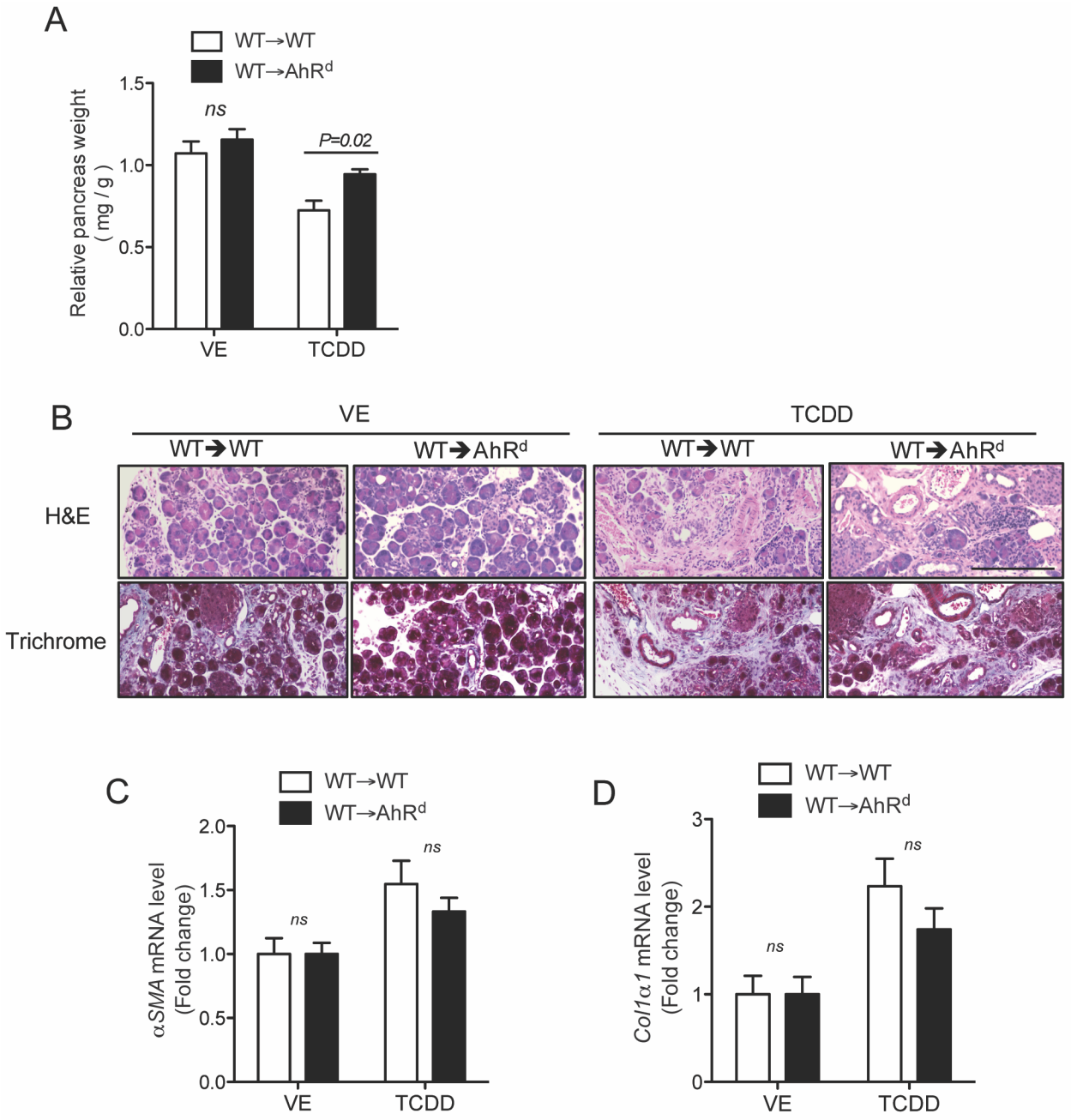
FigureS1. AhR ligands in cigarette smoke have additive effect in promoting fibrosis. Vehicle (VE) or indicated doses of AhR ligands were administrated to Balb/c mice right after starting CP induction with caerulein. Mice were euthanized and tissues were harvested after 4 weeks of caerulein injection. (A) Relative pancreas weights from indicated groups are shown (B) Representative of pancreas H&E and Sirus Red staining. Scale bar, 100μm. (C) Quantitated fibrotic areas are shown as bar graph. (D) Quantitative RT-PCR analysis of *αSMA* (α-SMA) gene expression in the pancreas from indicated group (n=10 per group pooled from 2 independent experiments, mean ± SEM, one-way ANOVA, Tukey's *post hoc test*).



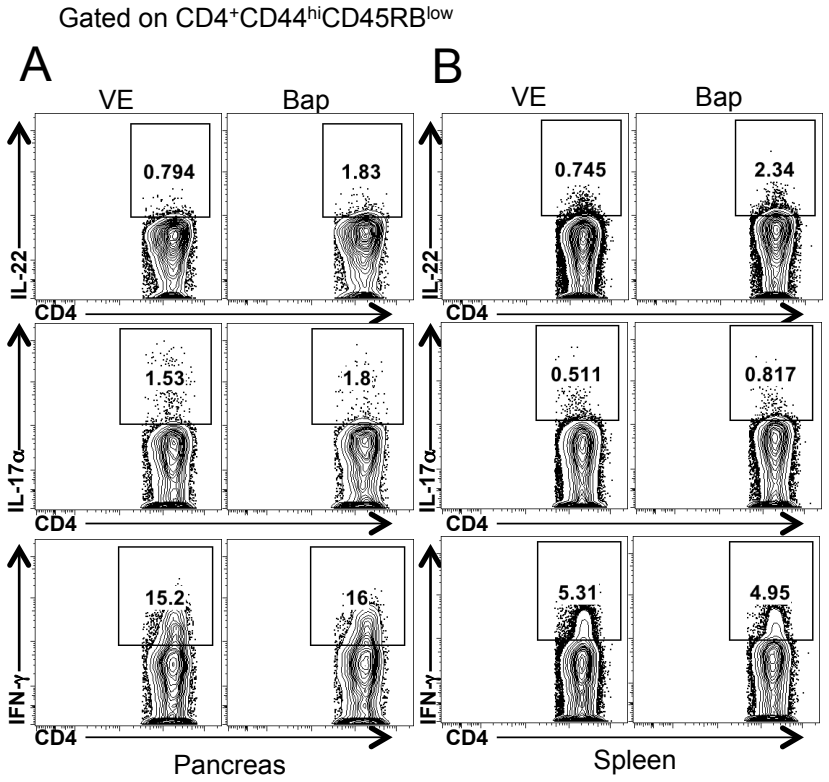
FigureS2. The effect of AhR ligands in control mice. (A) Vehicle (VE) or TCDD (10μg/kg, once per week) or BaP (25mg/kg, daily) was administrated to Balb/c mice treated with saline instead of caerulein for 4 weeks before harvested. Relative pancreas weights from indicated groups are shown (n=10 per group pooled from 2 independent experiments, mean ± SEM, one-way ANOVA test). (B) Representative of pancreas H&E staining shown. Scale bar, 100μm.

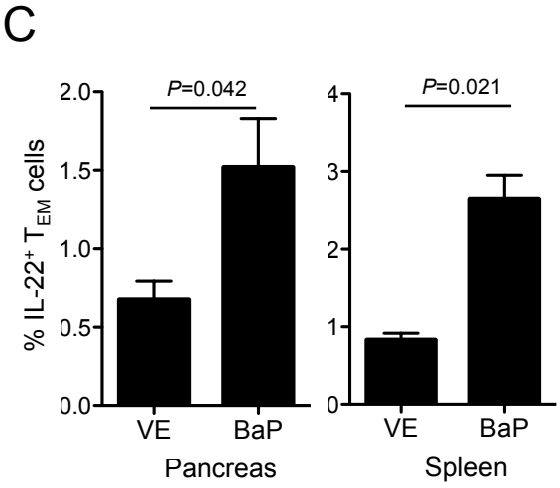


FigureS3. TCDD worsens fibrosis in Caerulein plus lipopolysaccharide (LPS) model of chronic pancreatitis. Balb/c mice were injected with caerulein (50μg/kg, 6 times/day, 3 times/week) and LPS (3mg/kg, once per week) to induce chronic pancreatitis. Vehicle (VE) or TCDD (10μg/kg, once per week) was administrated to mice right after starting CP induction, and mice were euthanized and tissues were harvested after 4 weeks of caerulein+ LPS injection. (A) Relative pancreas weights from indicated groups are shown (n=9 per group pooled from 2 independent experiments, mean ± SEM, unpaired two-tailed Student's *t*-test). (B) Representative of pancreas H&E and Sirus Red staining are shown. Scale bar, 100μm. Quantitated fibrotic areas are shown as bar graph. Mean ± SEM. (C) Quantitative RT-PCR analysis of *αSMA* (α-SMA gene expression in the pancreas from VE- or TCDD-treated mice (mean ± SEM, unpaired one-tailed Student's *t*-test). (D) Frequency of IL-22^{+} T_{EM} (Effector/Memory, CD4^{+}CD44^{hi}CD45RB^{low}) cells in VE- or TCDD-treated mice, at 4 weeks of CP induction (mean ± SEM, unpaired two-tailed Student's *t*-test).

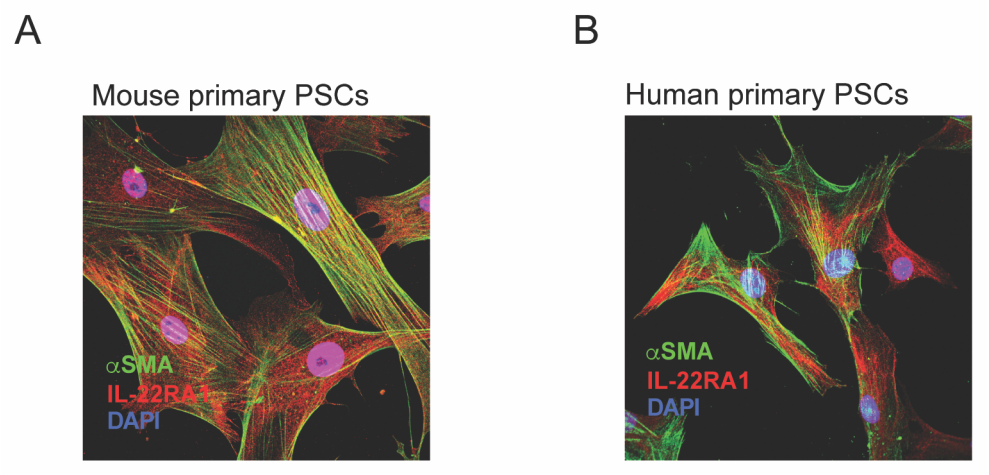


FigureS4. Leukocytes are major contributors to AhR-mediated fibrosis in chronic pancreatitis. Wild-type (WT) or AhR^d mice were lethally irradiated and reconstituted with bone marrow (BM) cells from WT mice and engrafted over 8 weeks. Vehicle (VE) or AhR ligand (TCDD, 10μg/kg, once per week) was administrated to indicated mice right after start of CP induction, mice were then euthanized and tissues harvested after 4 weeks of caerulein injections. (A) Relative pancreas weights from indicated groups are shown (n=5 per group pooled from 2 independent experiments, mean ± SEM, unpaired two-tailed Student's *t*-test). (B) Representative of pancreas H&E and Trichrome staining. Scale bar, 200μm. (C,D) Quantitative RT-PCR analysis of fibrosis-associated genes *αSMA* (α-SMA) and *Col1α1* (Collagen1A1) in the pancreas from indicated mice treated with VE or TCDD (means ± SEM, unpaired one-tailed Student's *t*-test).





FigureS5. Benzo[a]pyrene (BaP) induces IL-22$^+$ T cells in the pancreas and spleen during chronic pancreatitis. Vehicle (VE) or Benzo[a]pyrene (BaP, 25mg/kg, daily) was orally administrated to WT mice undergoing CP induction, and mice were harvested after 4 weeks of caerulein injection. Frequency of IL-22$^+$, IL-17α$^+$ and IFNγ$^+$ T_{EM} (Effector/ Memory, CD4$^+$CD44^{hi}CD45RB^{low}) cells among pancreatic leukocytes (A) or splenocytes (B) from VE- or BaP-treated mice, 4 weeks after CP induction. Data are representative of 2 independent experiments. (C) Bar graphs show % IL-22$^+$ T_{EM} cells in the pancreas and spleen (n=10 per group pooled from 2 independent experiments, mean ± SEM, unpaired two-tailed Student's *t*-test).

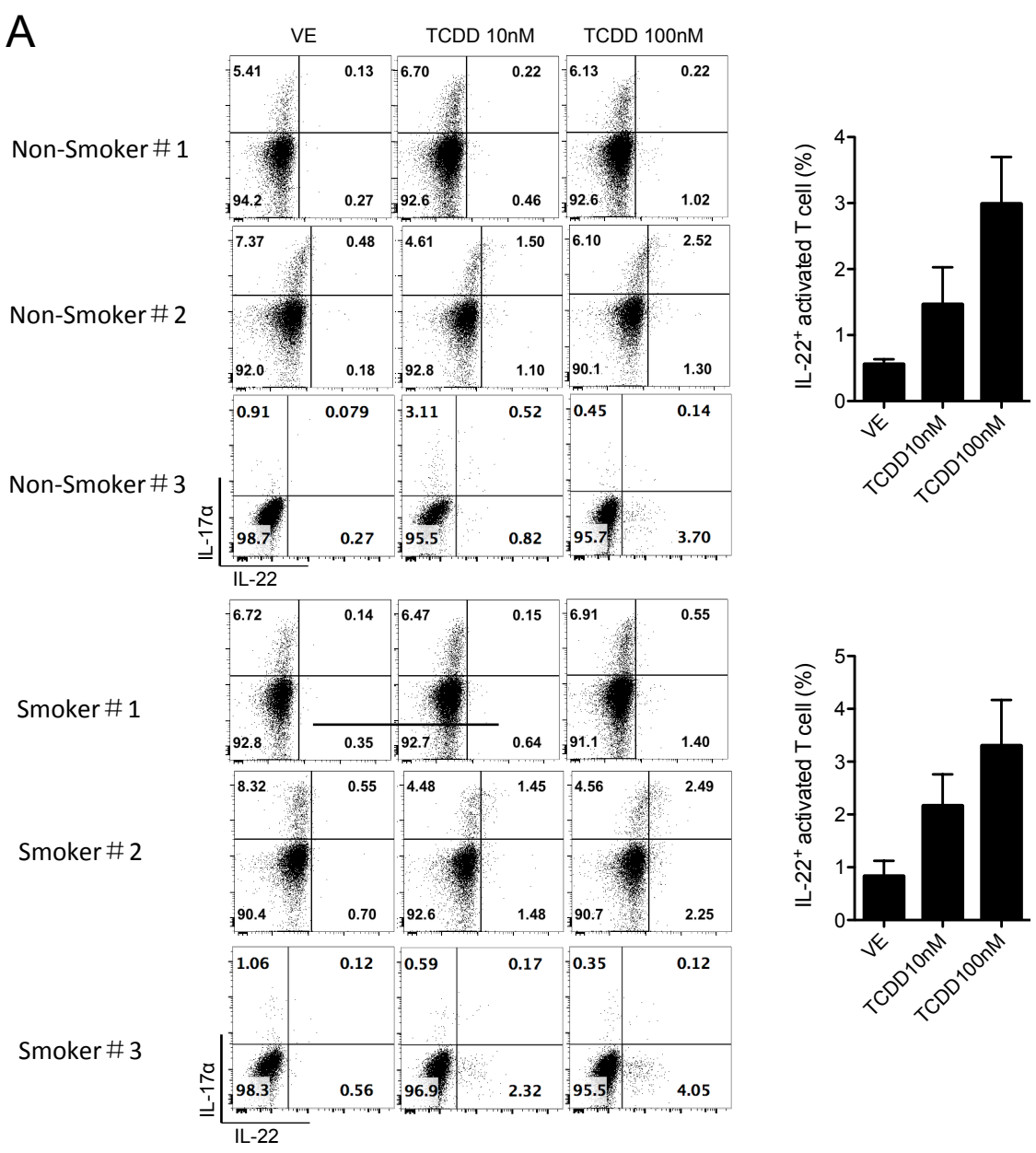


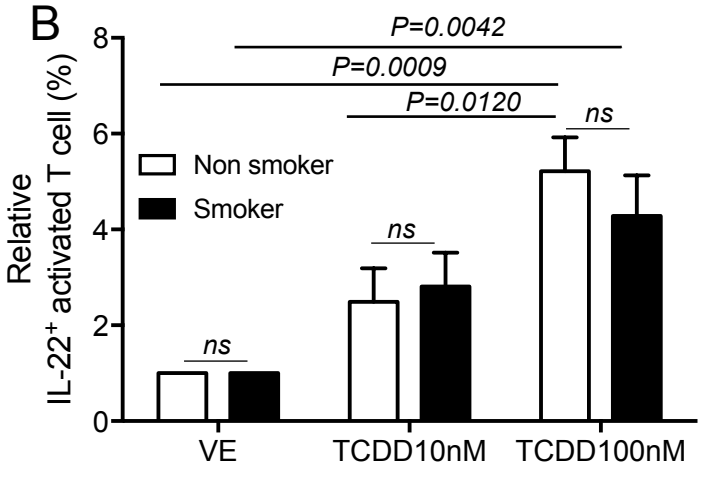
FigureS6. IL-22RA1 expression on primary mouse and human pancreatic stellate cells. Mouse (A) and human (B) primary pancreatic stellate cells were isolated and cultured for about 2 weeks, and immunofluorescence staining of IL-22RA1 (red), α-SMA (green), and nuclei (blue) are shown.

Supplementary Table 1.

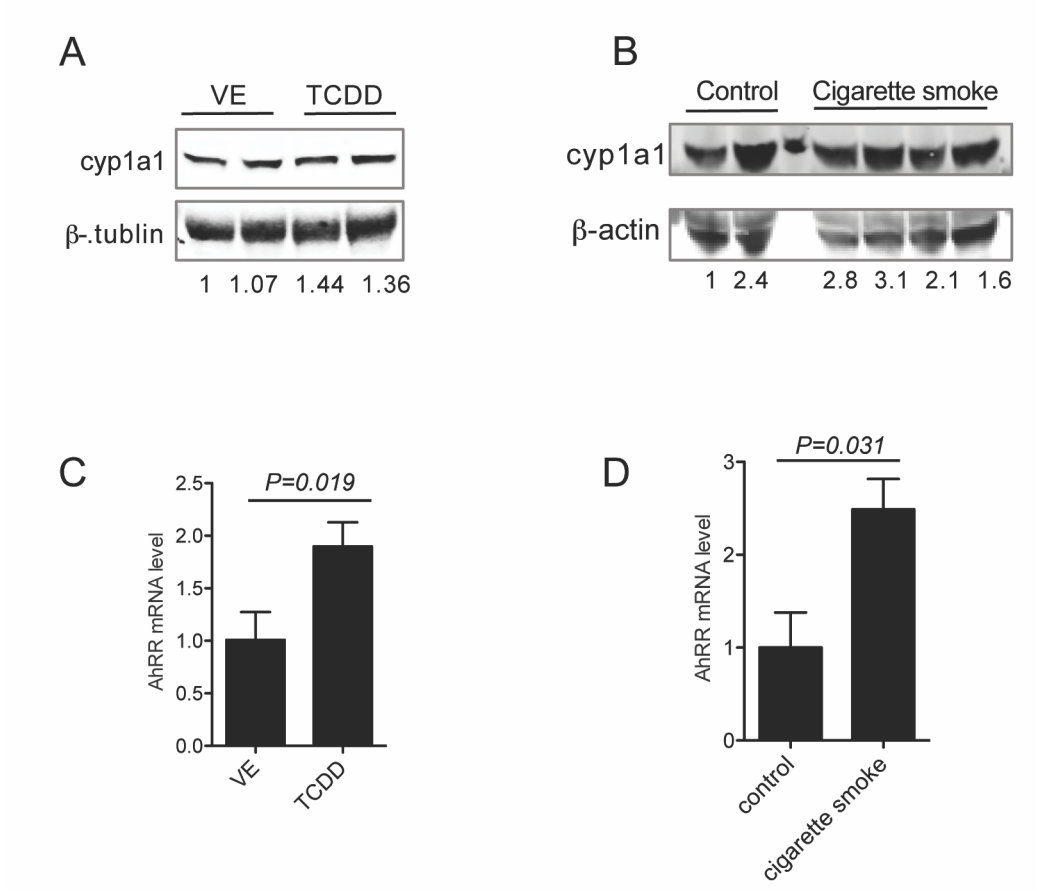
	Chronic Pancreatitis			Healthy Controls (N=11)
	Current Smokers (N = 10)	Ex-Smokers (N = 11)	Never Smokers (N = 18)	
Demographics				
Mean Age (SD)	51 (±16)	59 (±17)	51 (±17)	50 (±16)
Male (%)/Female (%)	5 (50%)/5 (50%)	7 (64%)/ 4 (36%)	9 (50%)/9 (50%)	8 (73%)/ 3 (27%)
Clinical History				
Positive CT/MR/EUS for CP (%)*	10 (100%)	10 (91%)	18 (100%)	N/A
Exocrine Insufficiency (%)**	5 (50%)	5 (45%)	7 (39%)	N/A
Endocrine Insufficiency (%)+	6 (60%)	1 (9%)	4 (22%)	N/A
Smoking History				
Average Pack Years (SD)	22 (±29)	24 (±23)	N/A	N/A
Average Years Since Last Tobacco Use (SD)	N/A	18 (±14)	N/A	N/A

*Pancreatic calcifications, atrophy, or lobularity of tissue, **Positive fecal elastase, secretin function, or 72 hour fecal fat collection, + Diabetes Mellitus





FigureS7. Similar IL-22 induction by CD4⁺ T cells isolated from smoker and non-smoker blood. Total CD4⁺ T cells were enriched from smokers and non-smokers blood (not buffy coat) and activated with anti-CD3 and -CD28 in the presence of TCDD for 5 days. (A) Flow cytometry plots show frequency of IL-17α and IL-22 expression in activated CD4⁺ T cells and frequency of IL-22⁺ activated T cells shown in the bar graphs. (B) Bar graph shows frequency of IL-22+ activated T cells relative to VE control (n=3 from each group run as 3 independent experiments, mean ± SEM, two-way ANOVA with Bonferroni *post hoc test).*



FigureS8. TCDD and cigarette smoke up regulate comparable Cyp1a1 and *AhRR* expression in the pancreas. (A) Balb/c mice were treated with VE or TCDD (10μg/kg, once per week) for 4 week before harvesting the pancreas. Pancreatic Cyp1a1 and β-tubulin level were determined by immunoblotting, and number below the blot indicate relative intensity. (B) Mice were exposed to fresh air (control) or cigarette smoke for 6 hours per day, 5 days per week for duration of 7 weeks before euthanasia as reported previously[15]. Pancreatic Cyp1a1 and β-actin level were determined by immunoblotting, and number below the blot indicate relative intensity. (C) Pancreatic *AhRR* mRNA expression from VE or TCDD-treated mice was determined by qPCR assay (mean ± SEM, n=10 per group, unpaired two-tailed Student's t-test). (D) Pancreatic *AhRR* mRNA expression from control or cigarette smoke exposed mice were determined by qPCR assay (mean ± SEM, n=3 control and n=4 cigarette smoke exposed mice, unpaired two-tailed Student's t-test).