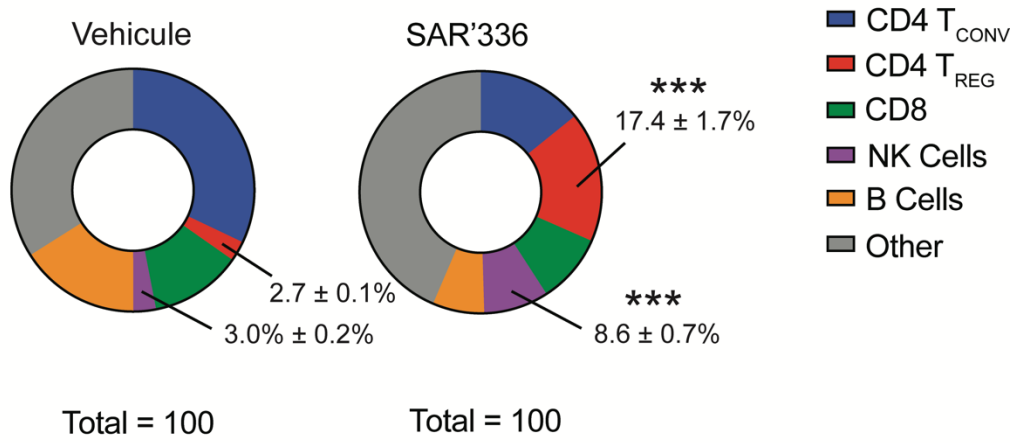
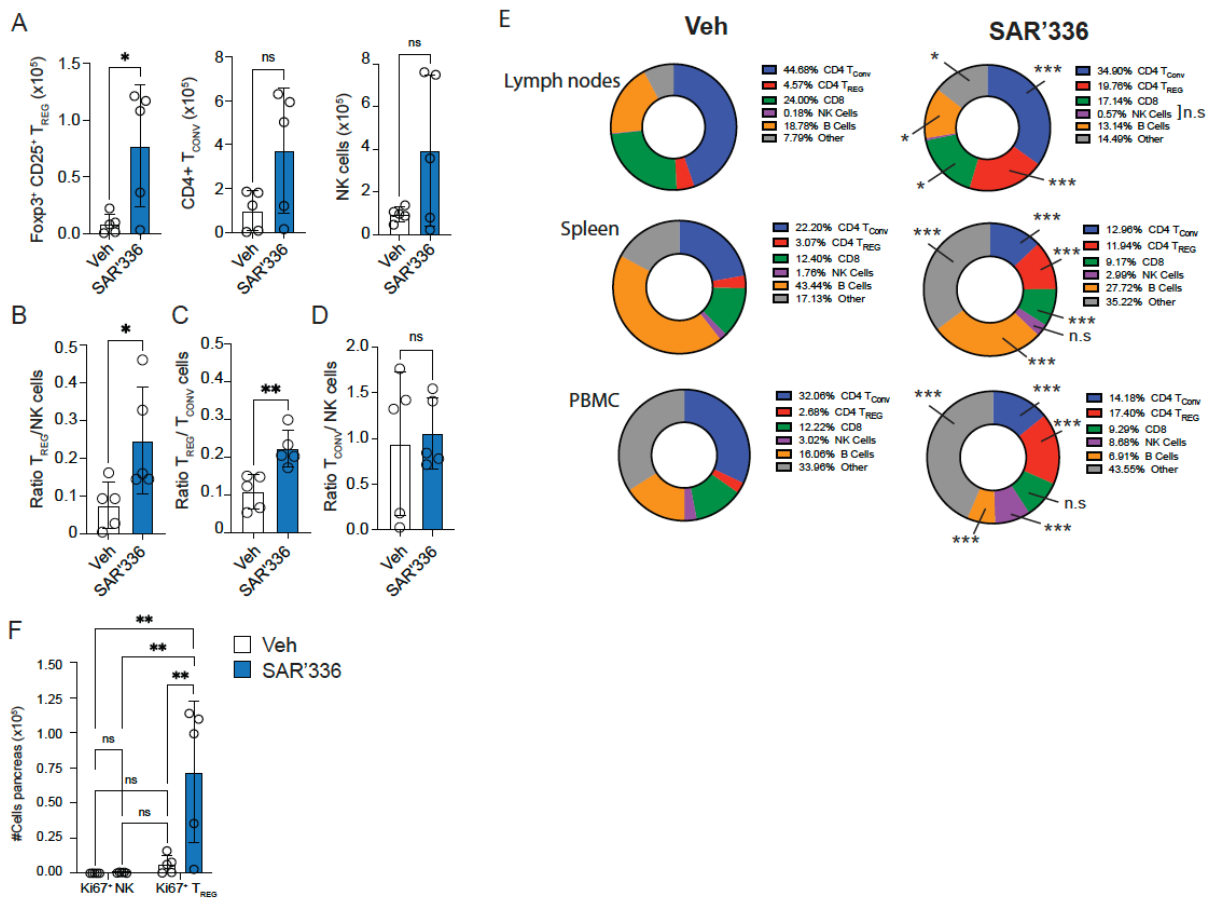


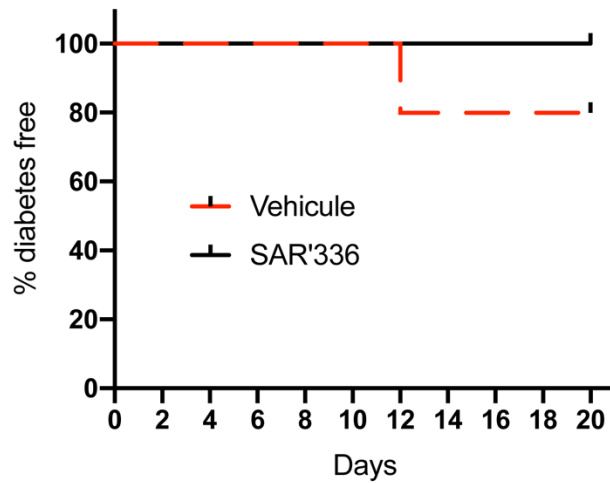
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Supplemental Figure 1. SAR'336 expands circulating T_{REG} upon administration in vivo. (A) Representative piechart of the frequency of CD3+, conventional T cells (T_{CONV}), T_{REG}, CD8α+, NK and B cells in PBMCs in NOD mice between vehicle and SAR'336 treated at day 4 post-injection with 0.3mg/kg of SAR'336. Mean of expression shown (n=5/group). Two-way ANOVA. ***p<0.001

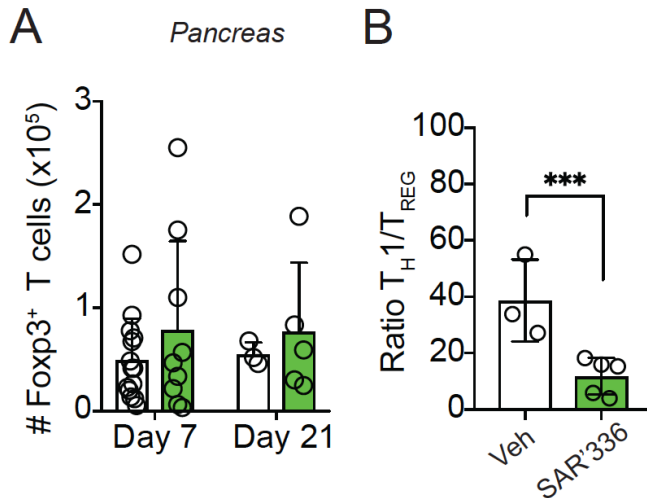


Supplemental Figure 2. SAR'336 preferentially expands circulating T_{REG} over NK and CD4⁺ T cells *in vivo*. NOD female mice were administered 0.3mg/kg of SAR'336 or the vehicle (veh) s.c. and cells from the blood (PBMCs), the spleen, inguinal and axillary LN (pLN) were collected at day 4 post-injection. (n=4-5/group) (A) Number of (CD4⁺ FcγR3⁺CD25⁺) T_{REG} cells, FcγR3⁺CD4⁺ T_{CONV} cells and (NK1.1⁺ CD3⁻) NK cells at day 4 in the spleen. (B) Ratio of T_{REG} over NK cells in the spleen, (C) Ratio of T_{REG} over T_{CONV} cells and (D) Ratio of T_{CONV} over NK cells at day 4. (E) Representative piechart of the frequency of CD3⁺, conventional T cells (T_{CONV}), T_{REG}, CD8⁺, NK and B cells from total CD45⁺ cells isolated from lymph nodes, spleen and the blood (PBMC) in NOD mice between vehicle and SAR'336 treated at day 4 post-injection with 0.3mg/kg of SAR'336. Mean of expression shown (n=5/group). Two-way ANOVA. ***p<0.001. (F) Numbers (Count) of Ki67⁺ (NK1.1⁺ CD3⁻) NK cells and Ki67⁺ (CD4⁺ FcγR3⁺CD25⁺) T_{REG} cells in the pancreas at day 4. One-way ANOVA, **p<0.01.



Supplemental Figure 3. Diabetes onset in NOD mice after 21 days.

3×10^5 CD4⁺ T cells isolated from female (V β 4⁺) NOD.BDC2.5⁺Foxp3^{GFPki} mice were adoptively transferred (i.v.) into 8–10-week-old female NOD/ShiLtJ mice to accelerate the onset of pancreatic infiltration into the pancreas. % Diabetes-free represented as a survival curve per group. % Diabetes-free mice established from daily blood glucose measurements. Diabetes threshold established as sustained high glucose >10 mmol/L; lowest value obtained 21mmol/L.

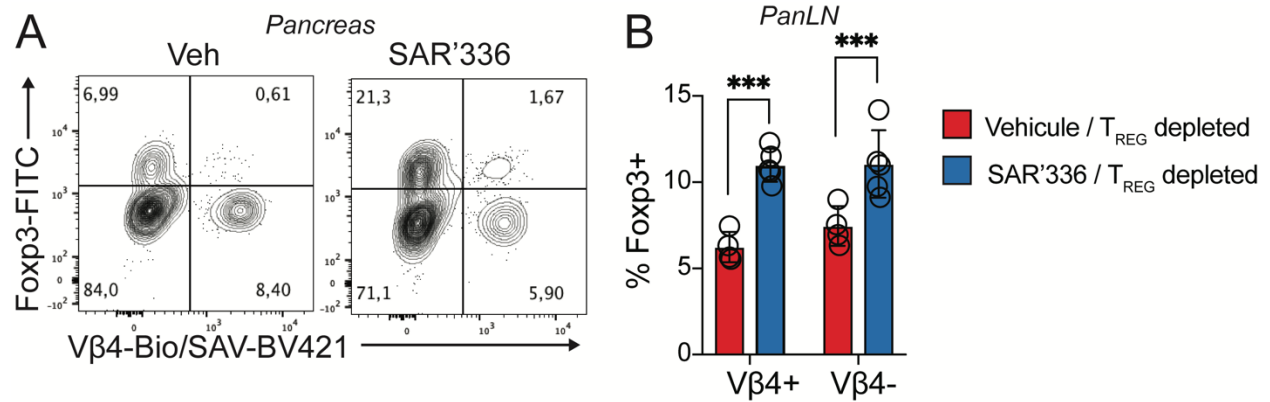


Supplemental Figure 4. T_{REG} cell numbers remain the same in the pancreas throughout treatment

CD4⁺ T cells were isolated from female BDC2.5 NOD mice and 3x10⁵ cells were adoptively transfer i.v. into female NOD mice. 0.03mg/kg of SAR'336 was administered s.c. twice a week up to 21 days. Lymphocytes from the pancreas were collected at day 7 (n=7-8/group) and day 21 (n=3-5/group). Data compiled from two distinct experiments.

(A) T_{REG} cell numbers established by flow cytometry as CD3⁺ CD4⁺ Foxp3⁺ cells.

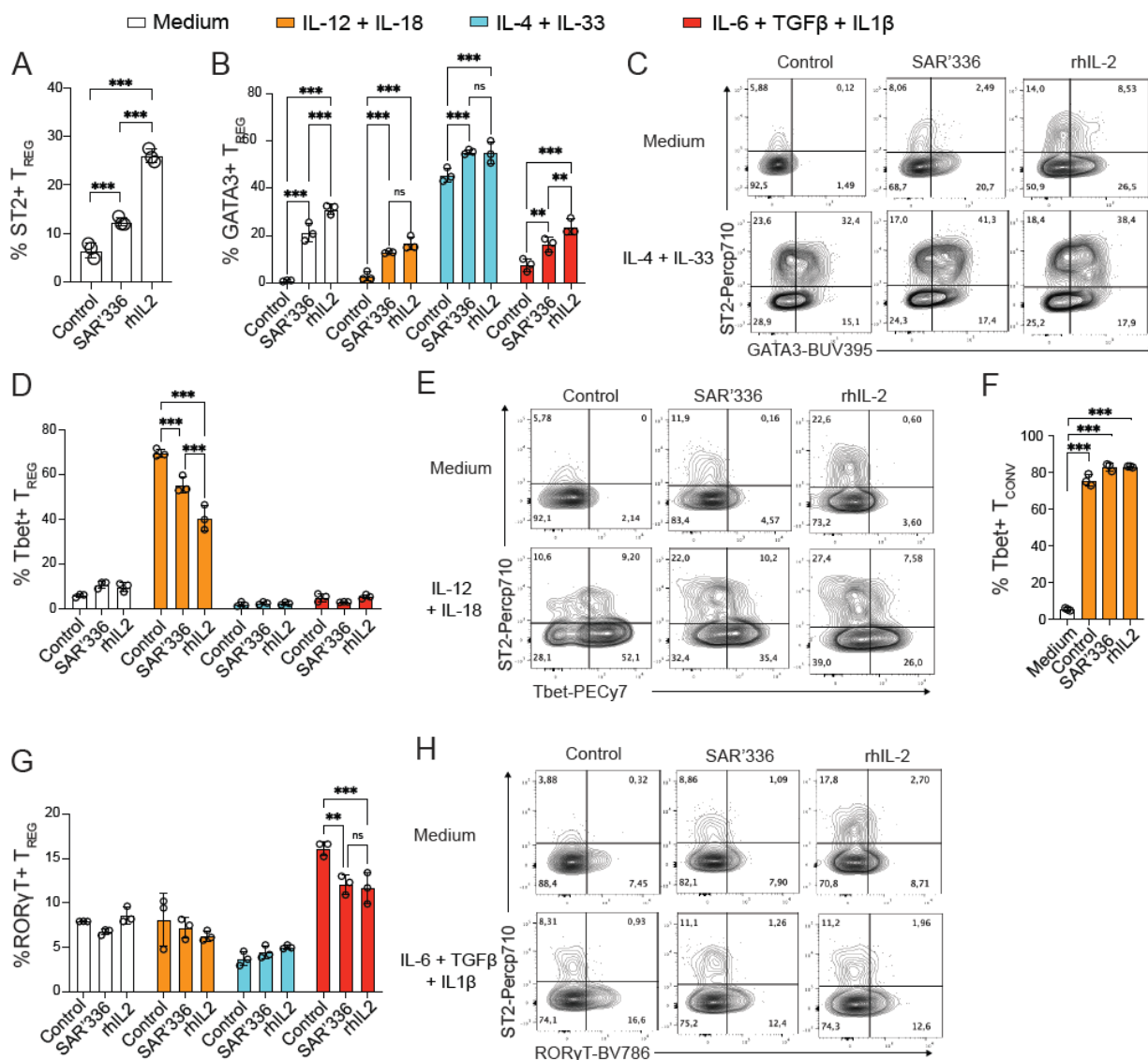
(B) Ratio of the number of IFN γ ⁺ CD4⁺ T cells (T_H1) over the number of Foxp3⁺ CD4⁺ T_{REG} in the pancreas at day 21.



Supplemental Figure 5. SAR'336 promotes pT_{REG} cell accumulation.

(A) Representative flow cytometry plot of Foxp3 and VB4 expression among CD3⁺CD4⁺ T cells in the pancreas at day 7.

(B) Frequency of Foxp3⁺ among VB4⁺ and VB4⁻ CD3⁺CD4⁺ T cells in pancreatic LN. One-way ANOVA. Tukey post-hoc correction. **p<0.01; ***p<0.001.



Supplemental Figure 6. SAR'336 promotes the induction of GATA3 in an IL-4 and IL-33 environment over Tbet and RORγT in activated T_{REG} cells *in vitro*.

Splenic CD4⁺Foxp3-GFP^{neg} CTV-labelled T_{EFF} cells and Foxp3-GFP⁺ T_{REG} cells were co-cultured at a ratio of 1 T_{REG} : 4 T_{EFF} in the presence of APCs and soluble anti-CD3 (1 µg/ml) in medium (white bar), TH1 conditions IL-12 (10ng/ml) + IL-18 (10ng/ml) (orange bar), TH2 conditions IL-4 (10ng/ml) + IL-33 (10ng/ml) (Blue bar) or TH17 conditions IL-6 (10ng/ml) + TGFβ (1ng/ml) + IL-1β (50ng/ml) (red bar) +/- 1 µg/ml of SAR'336 for 72 hours. Two-way ANOVA. **p<0.01; ***p<0.001.

(A) Frequency of ST2⁺ T_{REG} in medium with/without SAR'336 or rhIL-2 at 1µg/ml (B) Frequency of GATA3⁺ T_{REG} in all conditions at 72 hours, (C) Representative flow cytometry of the expression of ST2 and GATA3 in CD4⁺GFP⁺ CTV-negative T_{REG} cells at 72 hours.

(D) Frequency of Tbet⁺ T_{REG} in all conditions at 72 hours (E) Representative flow cytometry of the expression of ST2 and Tbet in CD4⁺GFP⁺ CTV-negative T_{REG} cells at 72 hours.

(F) Frequency of Tbet⁺ among T_{CONV}

(G) Frequency of RORγT⁺ T_{REG} cells at 72 hours. (H) Representative flow cytometry of the expression of ST2 and RORγT in CD4⁺GFP⁺ CTV-negative T_{REG} cells at 72 hours. Two-way ANOVA. **p<0.01; ***p<0.001. Representative of 4 independent experiments.