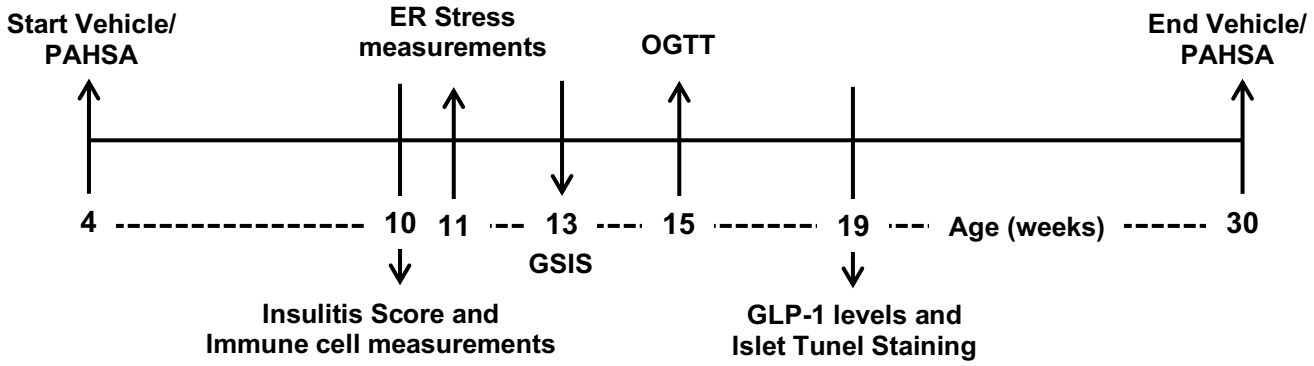
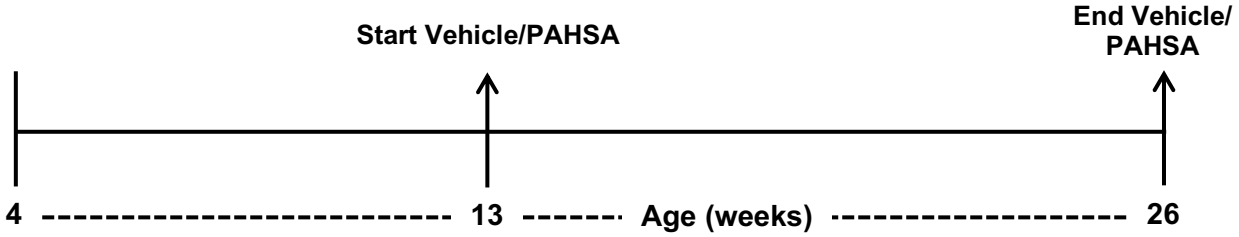
Supplementary Figures and Legends

Supplementary Figure-1:

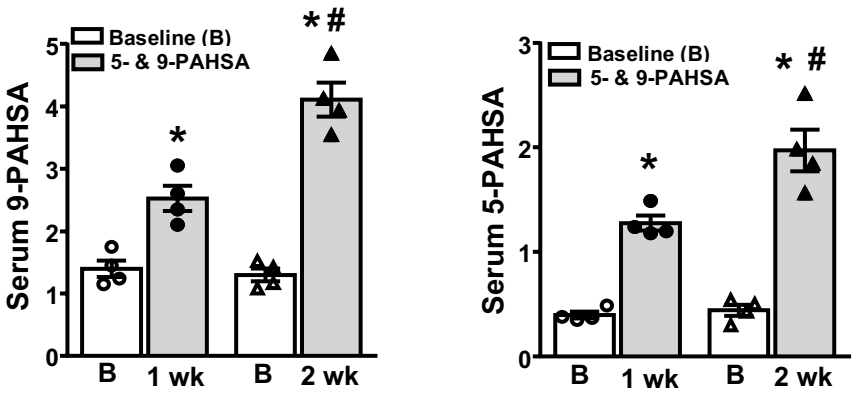
a) Early Intervention Study Design

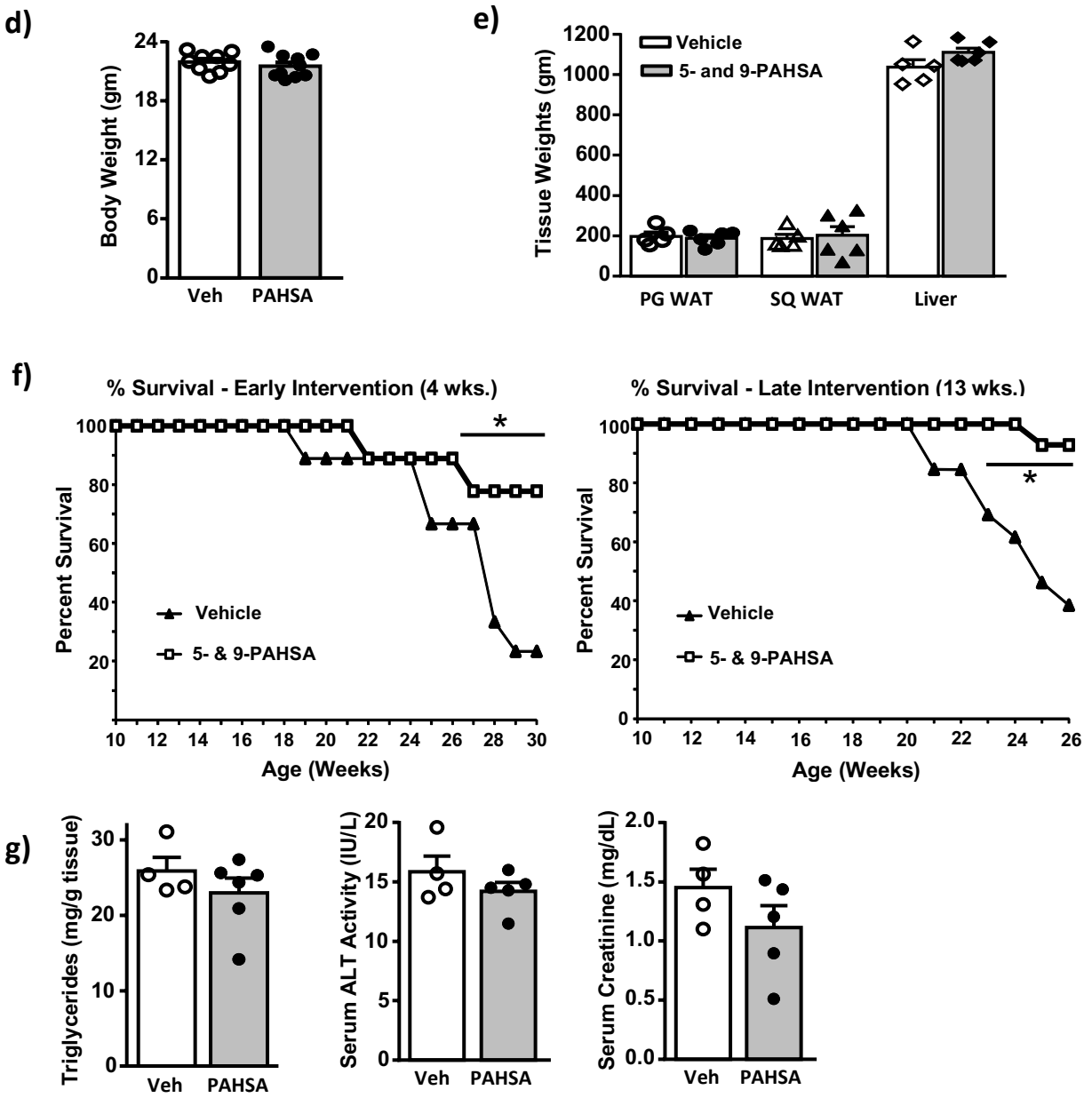


b) Late Intervention Study Design



c)

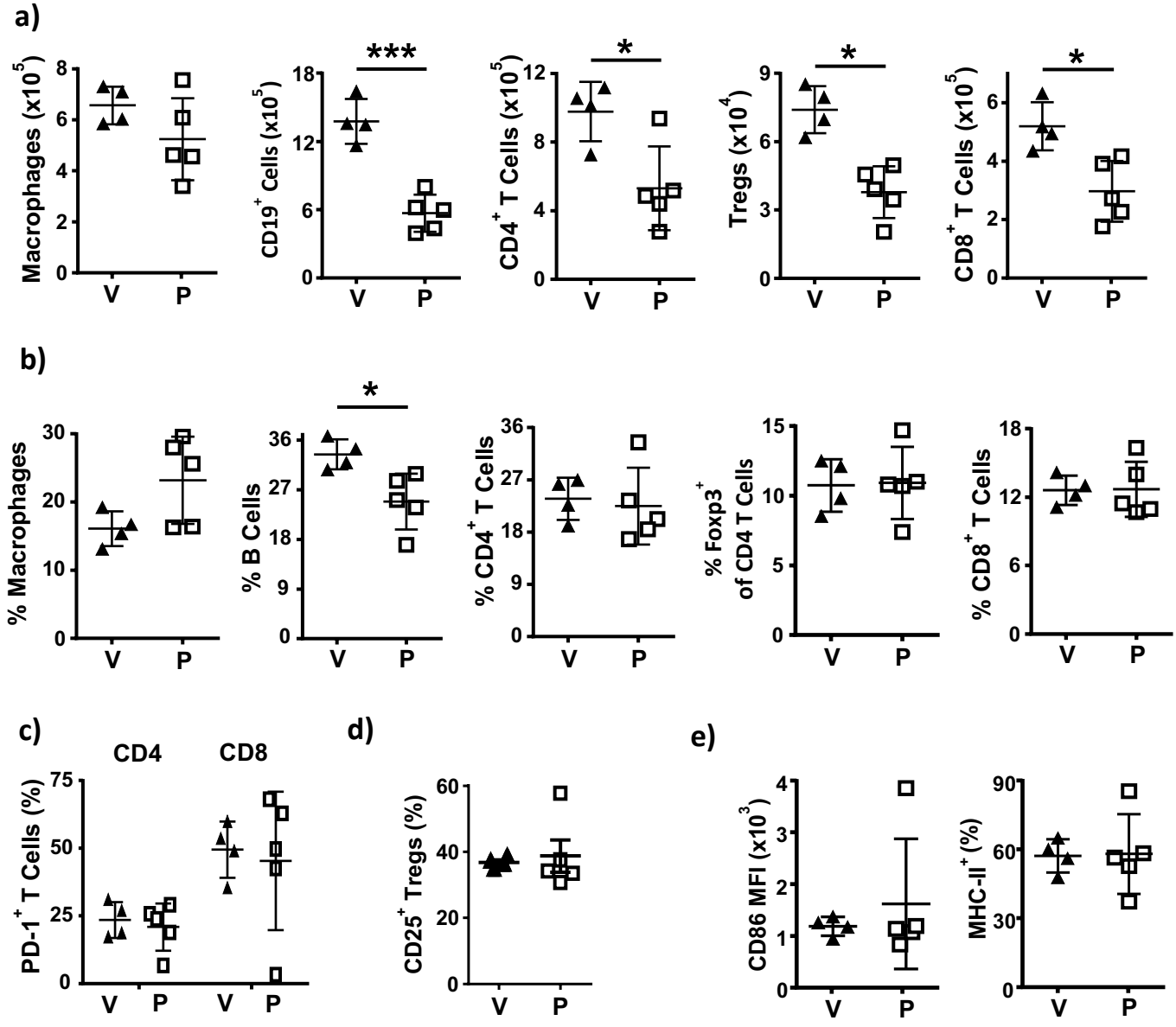




Supplementary Figure 1: Study design for **(a)** early intervention study **(b)** late intervention study. **(c)** Serum 5- and 9-PAHSA levels at baseline and after 5- and 9-PAHSA oral gavage for 1 week and 2weeks in chow-fed, non-diabetic C57blk6 male mice. n=4/group; *p<0.05 vs respective baseline; #p<0.05 vs PAHSA levels at 1 wk. Differences between groups were assessed by one way ANOVA with Newman-Keuls multiple-comparison test. **(d)** Body weight and **(e)** tissue weights in female non obese diabetic (NOD) mice treated with 5- and 9-PAHSAs (15 mg/kg body weight per day of each) via oral gavage for 6 weeks. n=5-10/group. PG WAT – Perigonadal white adipose tissue; SQ WAT – Subcutaneous white adipose tissue. **(f)** Survival rate in female NOD mice treated with 5- and 9-PAHSA for 26 wks starting at 4 wks of age (early intervention). n=22-23/group, and for 13 wks starting at 13 wks of age (later intervention). n=13/group. Differences between groups were assessed by log-rank test. *p<0.05 between groups. **(g)** Liver triglycerides and serum alanine aminotransferase (ALT) and Creatinine levels

in the same vehicle- and PAHSA-treated NOD mice studied in panels (d) and (e). n=4-6/group. Data are means±SEM. For d), e) and g), data were assessed by Student's t-test (two-tailed).

Supplementary Figure-2:

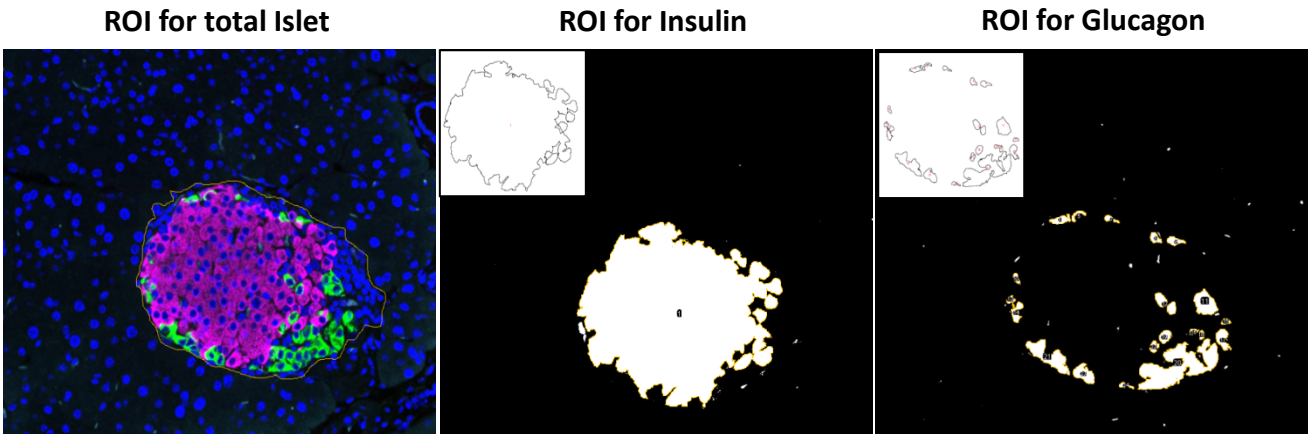


Supplementary Figure 2: Effects of PAHSA treatment in NOD mice on the major immune-cell subsets: **(a)** total number and **(b)** expressed as a fraction of $CD45^+$ cells from the pancreas of mice treated with 5- and 9-PAHSA- or vehicle for 11 weeks (15 weeks of age). n = 4–5. *p<0.05 and ***p<0.0001 vs. vehicle treated mice. **(c)** Proportions of PD-1^+ T cells within the CD4 and CD8 cell populations in the pancreas of 5- and 9-PAHSA- or vehicle-treated mice. n = 4–5. **(d)** Proportions of $CD25^+$ Tregs in the pancreas of PAHSA- or vehicle-treated NOD mice. n = 4–5. **(e)** Mean fluorescence intensity (left panel) and percent of MHC-II^+ cells (right panel) in the

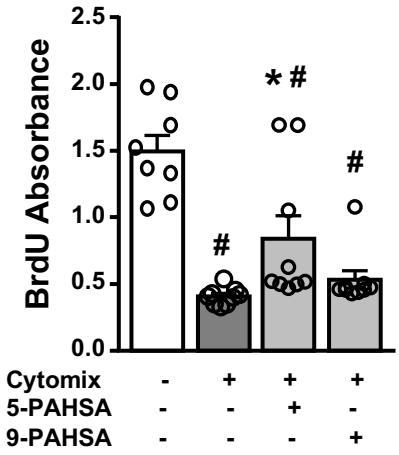
pancreas of 5- and 9-PAHSA- or vehicle-treated NOD mice. Data are means±SEM. Differences between groups were assessed by Student's t-test (two-tailed).

Supplementary Figure-3:

a)



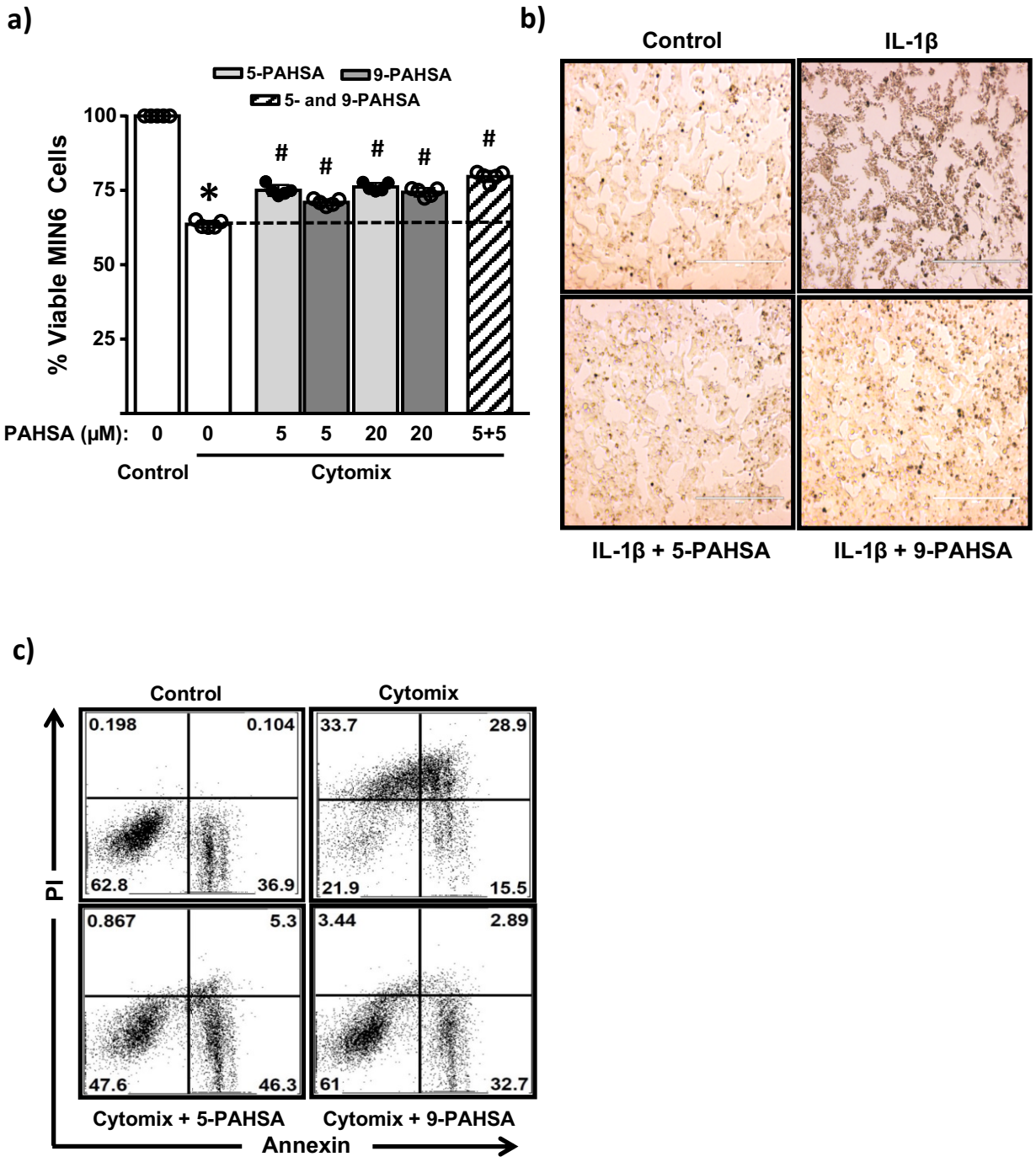
b) **MIN6 Cells – 24 hrs. treatment**



Supplementary Figure 3: (a) Representative image defining the method for outlining islets to perform the calculations for β-cell and α-cell area. ROI – Region of interest. **(b)** MIN6 cells were treated with Cytomix (TNFα + IL-1β + IFN-γ; 5 + 5 + 10 ng/mL) in the continuous presence or absence of 5-PAHSA (20 µM) or 9-PAHSA (20 µM) for 24 hours and β-cell proliferation was measured by BrdU incorporation into cells. n=8, and 12 wells/condition. # $p<0.05$ vs. Control with no PAHSA treatment; *$p<0.05$ vs Cytomix with no PAHSA treatment and control with no

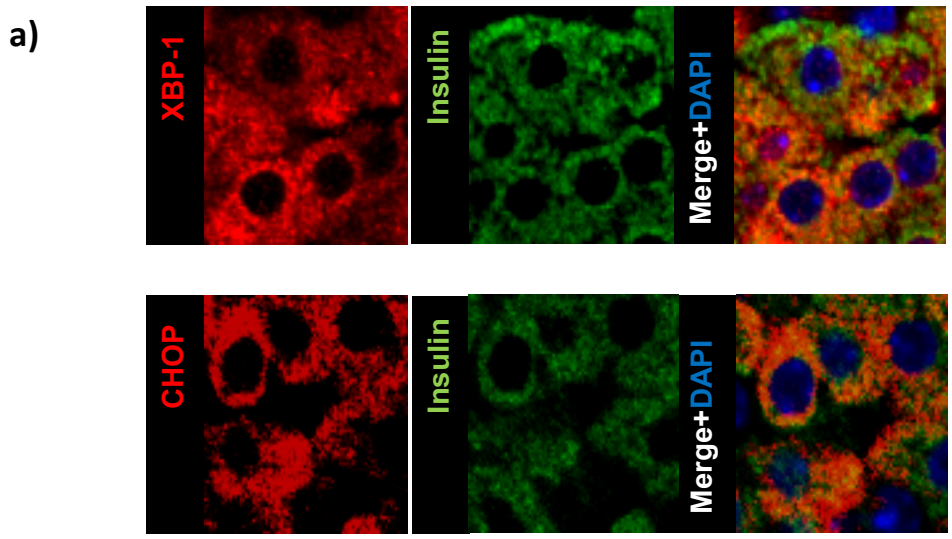
PAHSA treatment. Data are means±SEM. Differences between groups were assessed by one way ANOVA with Newman-Keuls multiple comparison test.

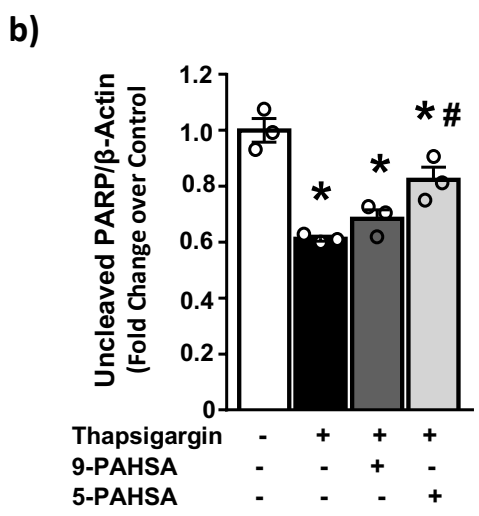
Supplementary Figure-4:

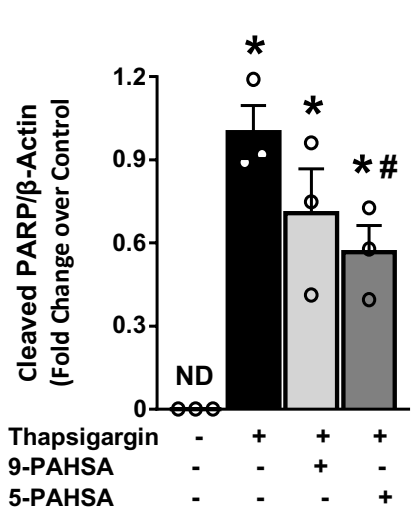


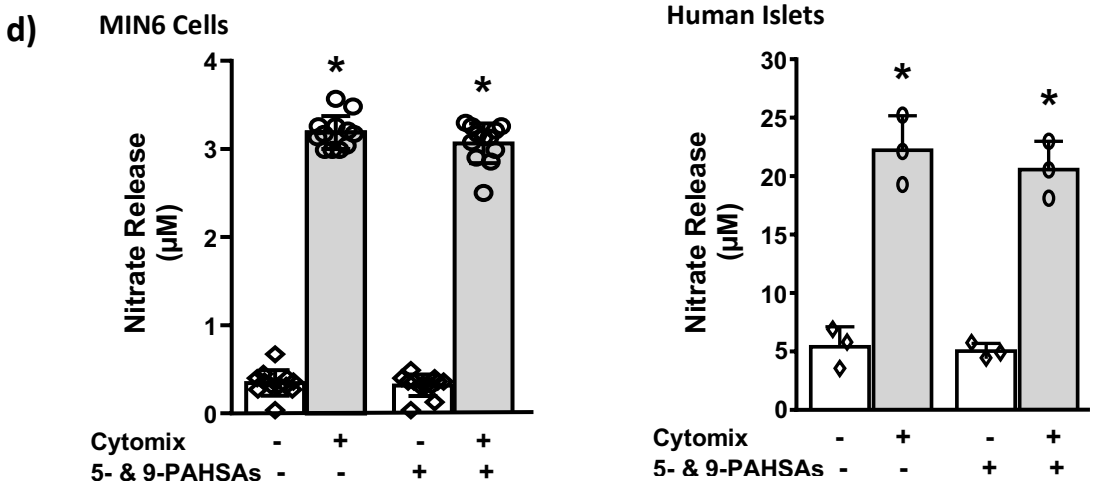
Supplementary Figure 4: (a) MIN6 cells were treated with either DMSO alone or Cytomix (TNFα + IL-1β + IFN-γ; 5 + 5 + 10 ng/mL) for 48 hours in the presence or absence of 5-PAHSA (5 or 20 μM) or 9-PAHSA (5 or 20 μM) or 5- and 9-PAHSA together (5 μM each). The percent viable β-cells were measured by MTT assay. n=5 plates each of which had 6 wells/condition. *$p<0.05$ vs. control alone; #$p<0.05$ vs both control alone and Cytomix alone. Data are means±SEM. Differences between groups were assessed by one way ANOVA with Tukey`s multiple comparison test. **(b)** Morphology of MIN6 cells that were treated with either diluent or Interleukin (IL) 1-β (10 ng/mL) for 48 h in the presence or absence of 5-PAHSA (5 μM) or 9-PAHSA (5 μM). Data are representative of two independent experiments performed in triplicate (Magnification – 20x). **(c)** Represents the gating strategy for the number of viable, late-apoptotic and necrotic MIN6 cells treated with cytomix in the presence or absence of 5- and 9-PAHSA (See Figure 4b)

Supplementary Figure-5:









Supplementary Figure 5: (a) Female NOD mice were treated with vehicle or 5- and 9-PAHSA for 7 weeks starting at 4 weeks of age and XBP-1, CHOP and insulin intensities in pancreatic islets were determined by immunohistochemistry. These insets correspond to Figure 5A and 5B, and demonstrate Xbp1 and CHOP staining in insulin-staining beta cells indicating these proteins are present in beta cells. n=4-5 mice/group. Original magnification, x256. **(b and c)** Human islets from a normal donor were treated with Thapsigargin (2 μmol/L) for 6 hours in the presence or absence of 5-PAHSA or 9-PAHSA (20 μM each). Western blot analysis was performed with the cell lysates to determine PARP cleavage. n=3 wells/condition and each well had 250 islets. Bar graphs show the densitometric analysis of the fold change of **(b)** uncleaved PARP over β-actin compared to the control condition (no Thapsigargin or PAHSAs, White bar) and **(c)** cleaved PARP over β-actin compared to thapsigargin alone with no PAHSAs (black bar). * $p<0.05$ vs control DMSO; # <0.05 vs Thapsigargin plus DMSO. Data are means±SEM. Differences between groups were assessed by one way ANOVA with Newman-Keul`s multiple comparison test. **(d)** MIN6 cells (left panel) or human islets (right panel) were treated with either DMSO alone (-) or Cytomix (TNFα + IL-1β + IFN-γ; 5 + 5 + 10 ng/mL) (+) for 24 hours in the presence or absence of 5- and 9-PAHSA (20 μM of each). The amount of NO release into media was measured by Modified Griess Reagent assay. For MIN6 cells, n=12 wells each of which had 8 wells/condition. For human islets, n=3 wells/condition and each well had 75 islets. *$p<0.05$ vs. no Cytomix treatment. Data are means±SEM. Differences between groups were assessed by one way ANOVA with Newman-Keul`s multiple comparison test.