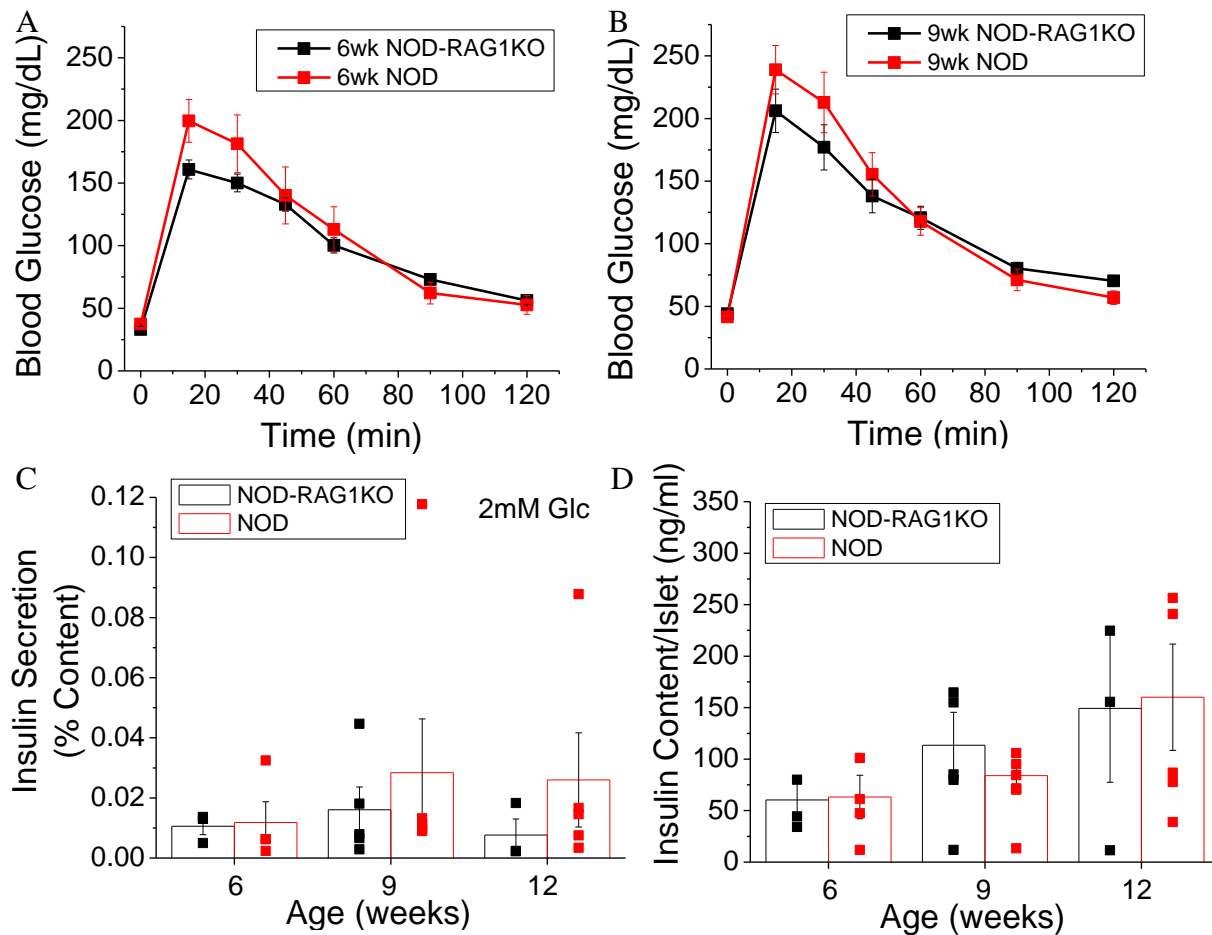
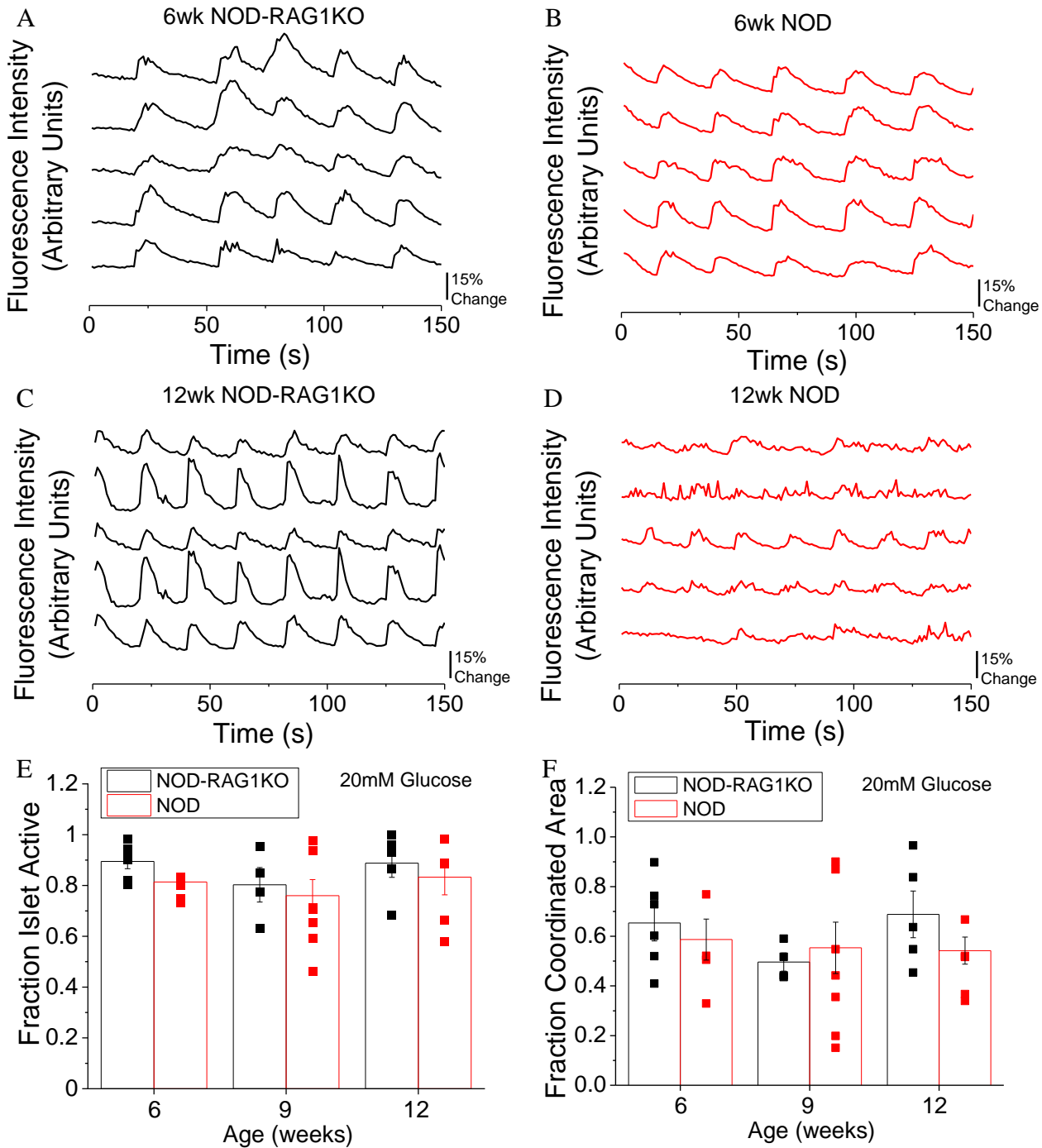


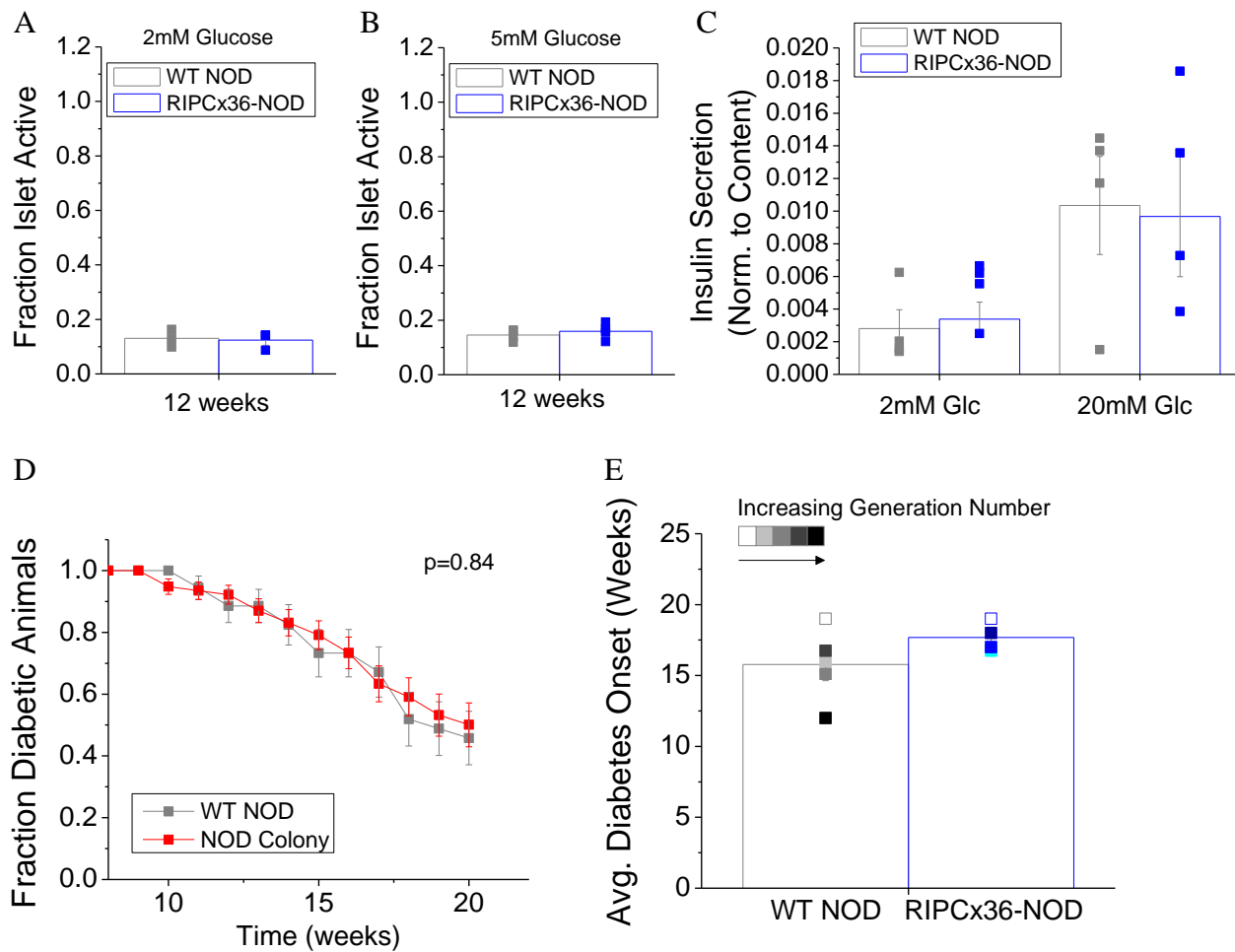
## Supplementary Material



**Supplemental Figure 1: Blood glucose and insulin secretion in NOD and NOD-RAG1KO mice.** Blood glucose levels in (A) 6-week old and (B) 9 week old NOD (red) and NOD-RAG1KO (black) mice following a glucose tolerance test starting at time 0. (C) Insulin secretion normalized to insulin content in isolated islets from 6, 9, and 12-week old NOD and NOD-RAG1KO mice at 2mM glucose. (D) Insulin content per islet in isolated islets from NOD and NOD-RAG1KO mice as in D. Data in all panels represents the mean  $\pm$  SEM. In C-E, data from individual mice are represented by black and red squares for NOD-RAG1KO and NOD mice respectively.

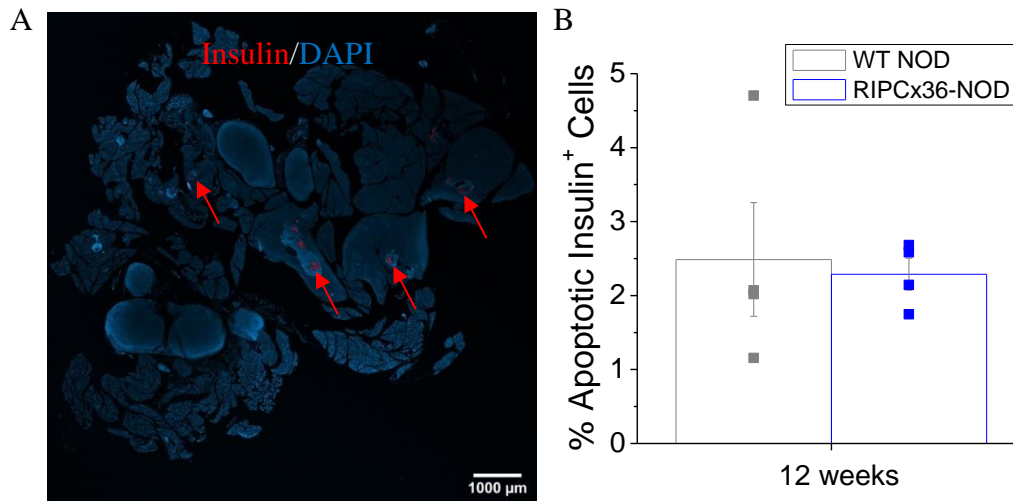


**Supplemental Figure 2: Intracellular  $\text{Ca}^{2+}$  signaling in NOD and NOD-RAG1KO mice.** Representative plots of intracellular  $\text{Ca}^{2+}$  as measured by fluorescence intensity at 11mM glucose in 5 individual cells in the same islet over time in 6 week NOD-RAG1KO (black) (A), 6 week NOD (red) (B), 12 week NOD-RAG1KO (C), and 12 week NOD mice (D). Quantification of (E) the fraction of the islet area showing intracellular  $\text{Ca}^{2+}$  activity and (F) the fraction of the islet area with coordinated  $\text{Ca}^{2+}$  oscillations at 20mM glucose in isolated islets from 6, 9, and 12 week old NOD and NOD-RAG1KO mice. Data in E and F represents the mean  $\pm$  SEM. Data from individual mice are represented by black and red squares for NOD-RAG1KO and NOD mice respectively (n=3-6).



### Supplemental Figure 3: Characterization of WT NOD and RIPCx36-NOD diabetic phenotype.

Quantification of the fraction of the islet area showing intracellular  $\text{Ca}^{2+}$  activity at (A) 2mM glucose and (B) 5mM glucose in isolated islets from 12-week old WT NOD and RIPCx36-NOD mice ( $n=3-4$ ). (C) Insulin secretion in isolated islets from 12-week old WT NOD and RIPCx36-NOD mice at 2 and 20mM glucose ( $n=4$ ). (D) Kaplan-Meier survival curves for diabetes incidence in WT NOD (grey) and NOD colony (red) mice with Breslow test for significance between survival distributions, where  $p<0.05$  is significant. (E) Average age of diabetes onset in WT NOD (grey) and RIPCx36-NOD (blue) mice. The average age of diabetes onset for each generation of mice is represented by black and blue squares for WT NOD and RIPCx36-NOD mice respectively, where increasing color intensity of the squares indicates increasing generation number ( $n=4-5$ ). Data in all panels represents the mean  $\pm$  SEM. Data from individual mice are represented by black, red, grey, or blue squares for NOD-RAG1KO, NOD, WT NOD, and RIPCx36-NOD mice respectively.  $p<0.05$  is significant as determined by ANOVA.



**Supplemental Figure 4: Characterization of WT NOD and RIPCx36-NOD Islet Mass and Beta Cell Death.** (A) Representative image of a pancreas slice from an NOD mouse stained using IHC for insulin (orange) and nuclei (DAPI, blue) where individual images were stitched together to achieve a continuous image of the entire pancreas slice. Pancreatic islets are indicated by red arrows. (B) Percent apoptotic (TUNEL<sup>+</sup>) insulin<sup>+</sup> cells per islet averaged over 6 slices per pancreas in 12-week old WT NOD (grey) and RIPCx36-NOD (blue) pancreata. Data represents the mean  $\pm$  SEM. Data from individual mice are represented by grey or blue squares for WT NOD and RIPCx36-NOD mice respectively.

<b>Agent</b>	<b>Pharmacological Role</b>	<b>Anticipated Ca<sup>2+</sup> Modulation</b>
TEA	Closes K <sub>ATP</sub> channels	Increased cytosolic Ca <sup>2+</sup>
Diazoxide	Opens K <sub>ATP</sub> channels	Decreased cytosolic Ca <sup>2+</sup>
Ochratoxin A	Open SERCA channels	Increased ER Ca <sup>2+</sup> , decreased cytosolic Ca <sup>2+</sup>
Thapsigargin	Closes SERCA channels	Decreased ER Ca <sup>2+</sup> , increased cytosolic Ca <sup>2+</sup>

**Supplementary Table 1:** Outline of therapeutic agents cultured with isolated islets, the expected pharmacological role in the cell, and the anticipated modulation of intracellular Ca<sup>2+</sup> with treatment.