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The Menin Inhibitor Ziftomenib Induces Insulin Production and Improves Insulin Sensitivity in a Rat Model of Type 2 Diabetes Mellitus (T2DM)

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Disclosures

- **Asako McCloskey (Presenter), Yahu A. Liu (Co-Author), and Francis Burrows (Co-Author)**
  - Employed by Kura Oncology, Inc.; own stock of Kura Oncology, Inc.; patents and/or patent applications with Kura Oncology, Inc.
- **Xingjuan Wang (Co-Author)**
  - Employed by WuXi AppTec (Hong Kong) Limited; own stock of WuXi AppTec (Hong Kong) Limited

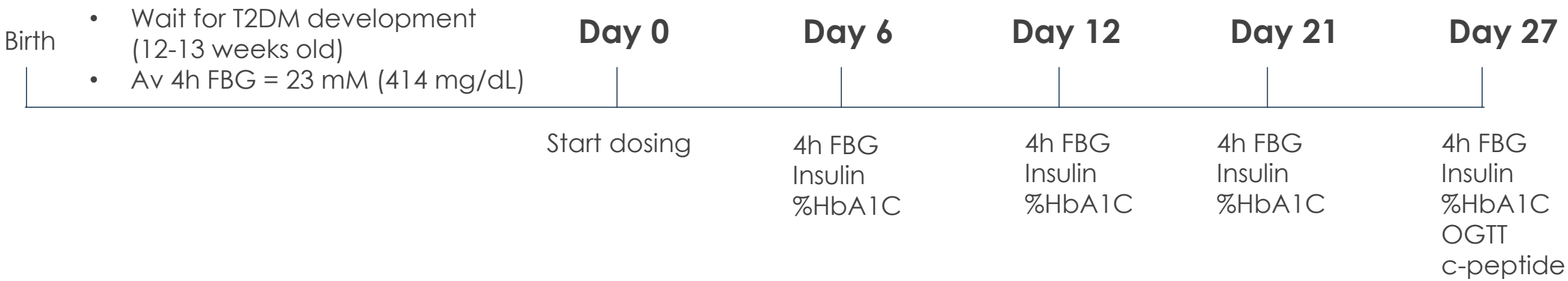
Background

- Menin is a scaffold protein known to regulate epigenetic gene expression in several cell types. Genetic menin loss (MEN1 syndrome) is associated with insulinemia due to upregulated pancreatic β-cell proliferation.
- Inhibiting menin could be a viable option to enhance pancreatic function in diabetic patients.
- Ziftomenib is an orally available, potent, and selective menin inhibitor currently undergoing a registration-enabling, Phase 2 clinical trial in *NPM1*-mutated acute myeloid leukemia.
- **The highly diabetic Zucker Diabetic Fatty (ZDF) rat model of T2DM was used to evaluate ziftomenib.**

NPM1, nucleophosmin-1

Study Design

ZDF male rats (obese, fa/fa)

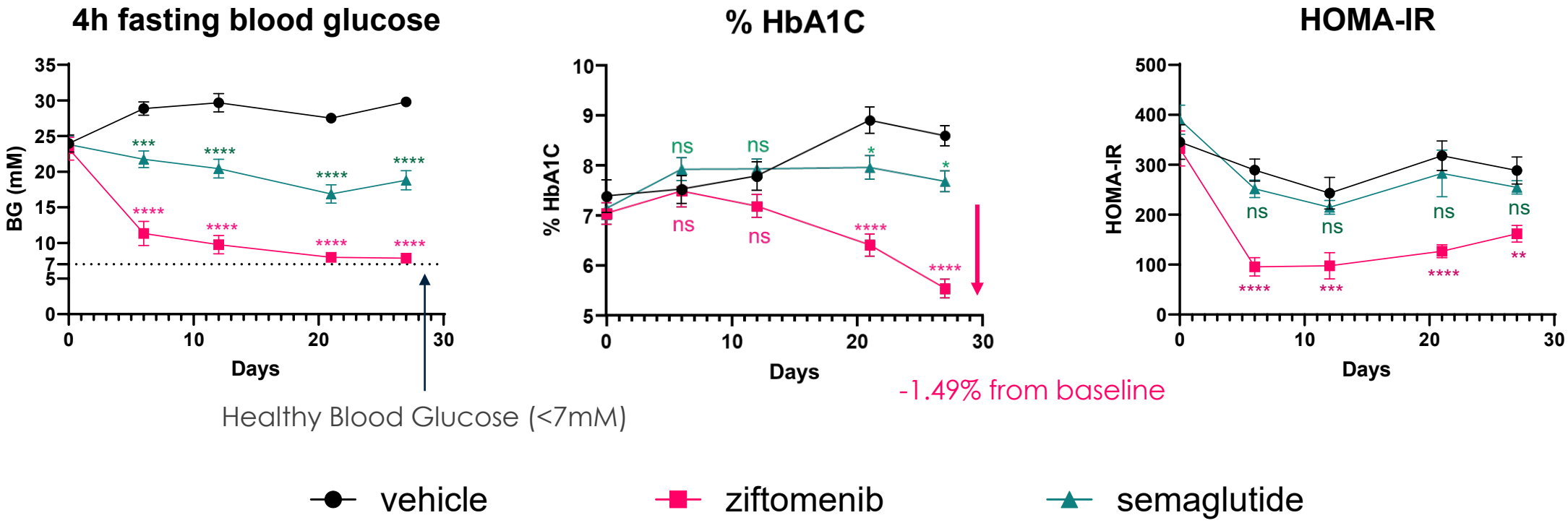


- **Vehicle**: QD, PO
- **Ziftomenib**: 2x (mpk), QD, PO; reduced to 1x (mpk), QD, PO, on Day 10
- **Semaglutide**: step-wise dose escalation; 6.25, 12.5, 25, 50 nmol/kg, Q3D, SC

Av, Average; FBG, fasting blood glucose; mpk; mg/kg; PO, orally; QD, once each day; Q3D, once every 3 days; SC, subcutaneous

Ziftomenib Reduces Blood Glucose and HbA1C Levels and Improves Insulin Sensitivity

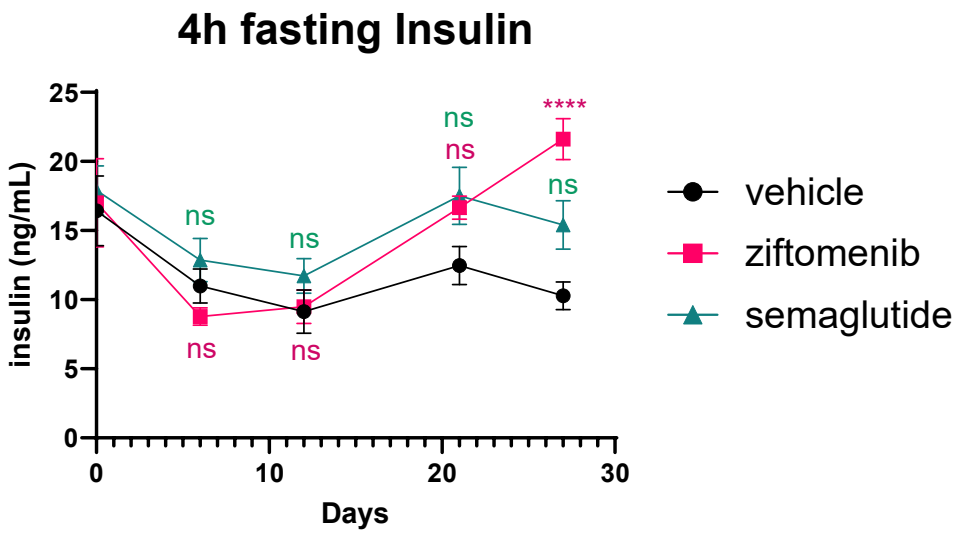
Ziftomenib significantly reduced 4h fasting blood glucose (FBG) levels and %HbA1C within 27 days of treatment; FBG level for the zifto group approached the healthy BG threshold.

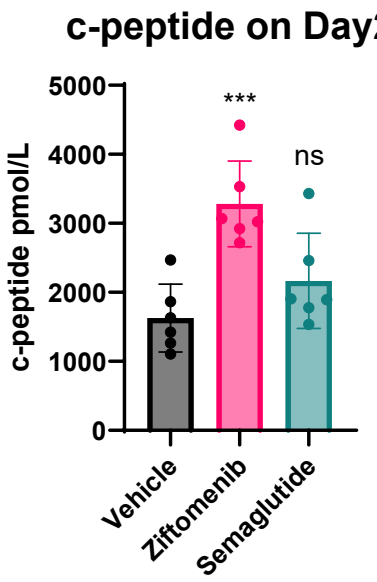


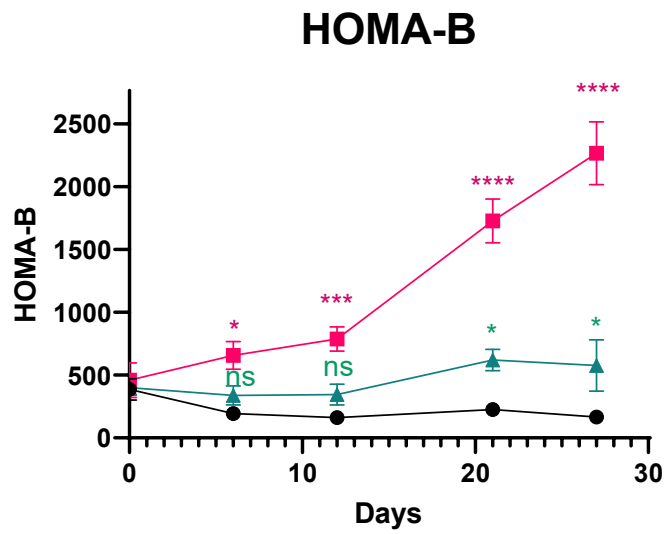
ns; not significant; *, p<0.05; **; p<0.01, ***, p<0.005; ****, p<0.001

Ziftomenib Stimulates Insulin Production

Ziftomenib significantly increased serum insulin and c-peptide levels, indicating significant improvement to steady-state β-cell function



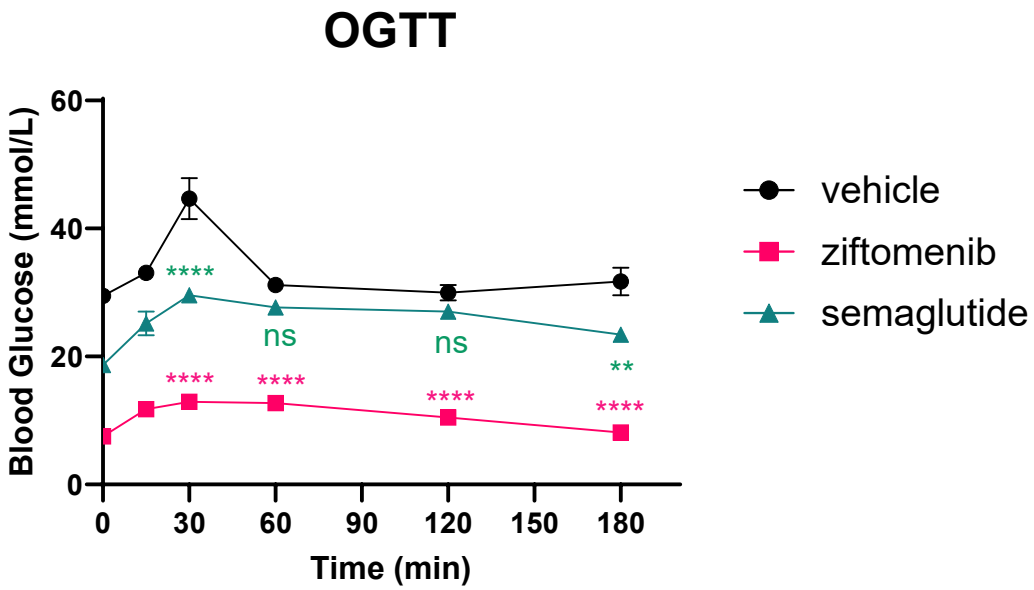


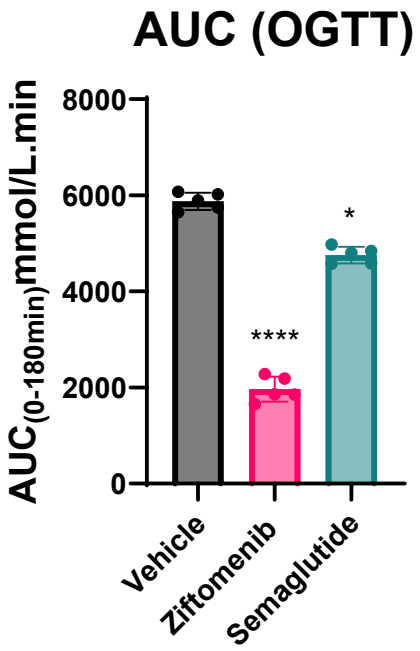


ns; not significant; *, p<0.05; **; p<0.01, ***, p<0.005; ****, p<0.001

Ziftomenib Improves Postprandial Glucose Control

Ziftomenib significantly reduced blood glucose during the glucose challenge after 27 days of treatment





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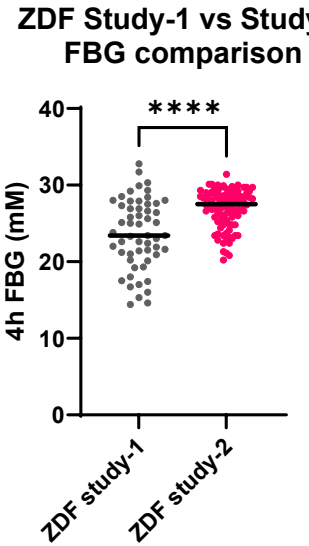
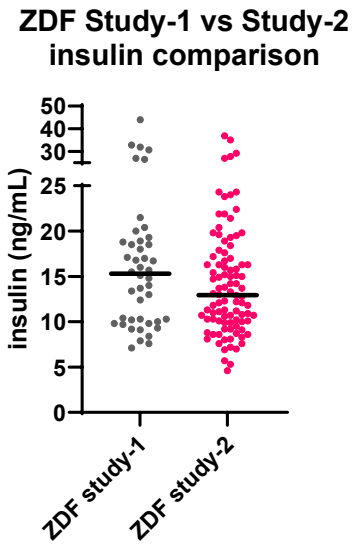
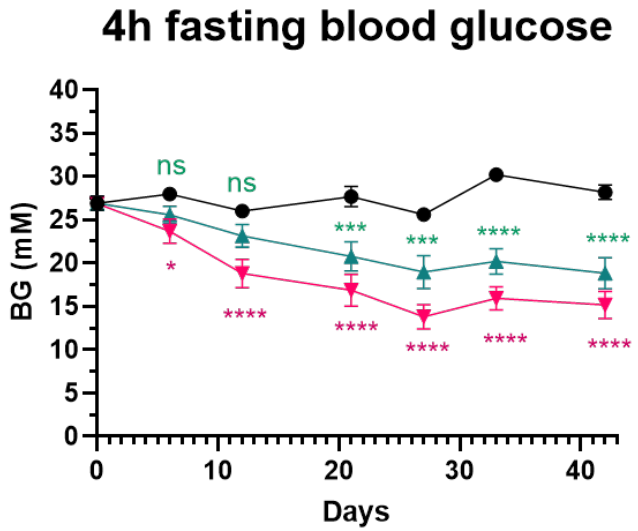
In Model of More Advanced Disease, Ziftomenib Reduces FBG and Improves Insulin Production with Continued Effects during Wash-out Period

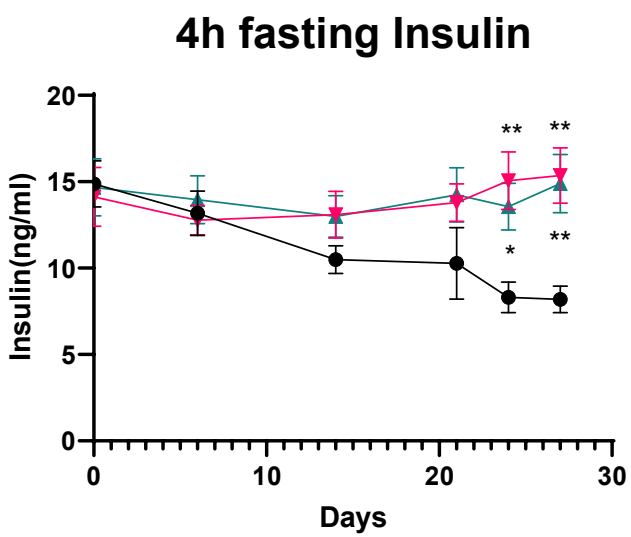
Ziftomenib maintained meaningful activity during the wash-out period, suggesting restoration of β-cell mass

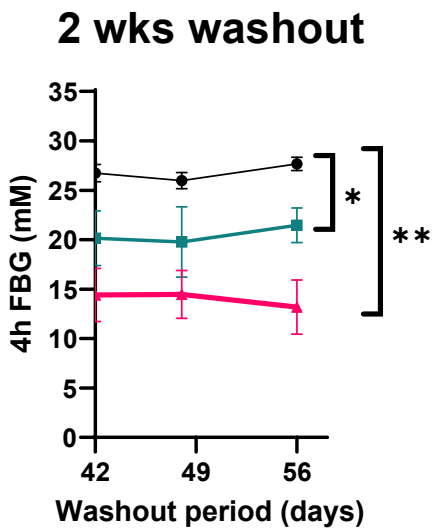
Day 0 → zifto 0.5x mpk or 1x mpk, QD, for 42 days (12 rats) → Day 42 → Wash-out (2 weeks) (4 rats) → Day 56









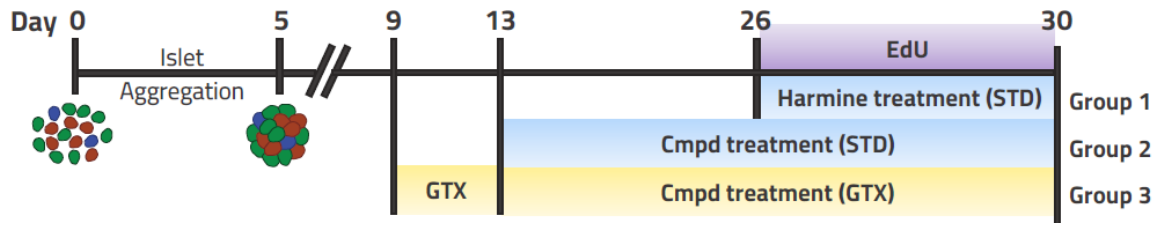


Vehicle Zifto-0.5x Zifto-1x

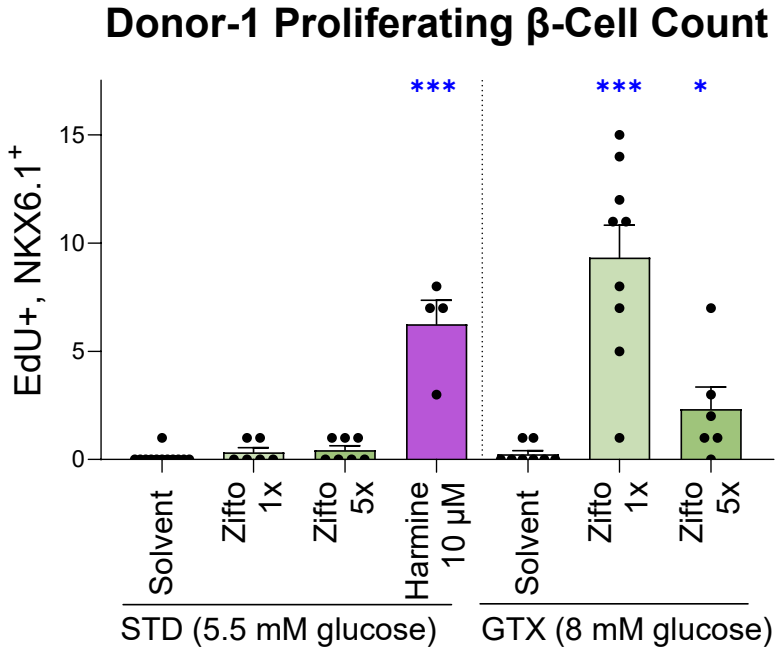
ns; not significant; *, p<0.05; **; p<0.01, ***, p<0.005; ****, p<0.001

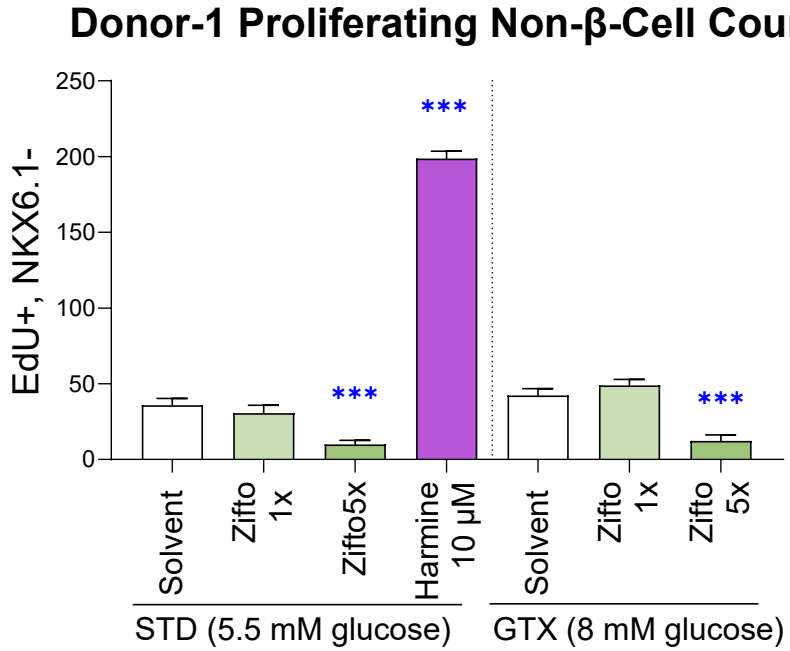
Ziftomenib Stimulates β-cell Proliferation with Minimal Effects on Non-β-cells in Human Pancreatic Islet Microtissues

Ziftomenib stimulated the proliferation of β-cells specifically in both donor samples



- Ziftomenib: 1x (nM) or 5x (nM)
- Harmine: 10 µM (only used in STD, toxic under GTX)
- Proliferating β-cells: NKX6.2+, EdU+
- Proliferating non-β-cells: NKX6.2-, EdU+





GTX, glucotoxic conditions; STD, standard conditions

*, p<0.05; ***, p<0.005

Conclusions

- Ziftomenib induced β-cell proliferation in human islet microtissues. Induction of non-β-cell proliferation was not detectable, indicating menin is a viable therapeutic target for β-cell mass specific expansion.
- Ziftomenib treatment showed consistent progressive improvement in both insulin sensitivity and insulin production in ZDF rats.
- The efficacy was fully maintained after the dosing discontinuation, likely due to the restoration of pancreatic β-cell mass.
- Ziftomenib is currently in a registration-enabling, Phase 2 clinical investigation in *NPM1*-mutated acute myeloid leukemia. Further study of ziftomenib and next-generation menin inhibitors in T2DM is warranted.