Icovamenib and semaglutide combination therapy enhances body weight loss and glycemic control while preserving lean mass in a type 2 diabetes animal model

P. Somanath, T. Zhang, T. Butler, J.P. Frias and **M. Balakrishnan**

Biomea Fusion Inc.

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Presenter Disclosures

Mini Balakrishnan is an employee and stock-holder at Biomea Fusion Inc.

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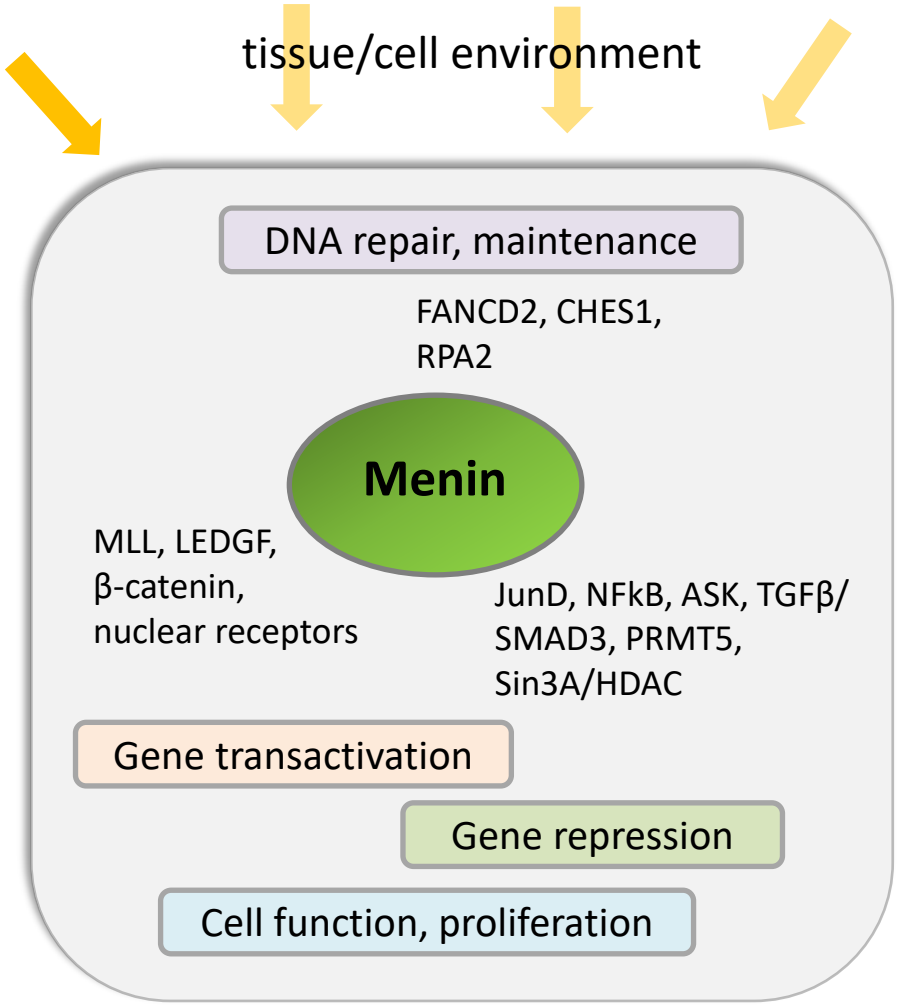
Icovamenib Background

- Icovamenib is an oral, selective, small molecule menin inhibitor that is currently in clinical development for the treatment of type 1 and type 2 diabetes
- In T2D patients, 4 weeks of daily icovamenib resulted in improved glycemic control at Week 26 (22 weeks after cessation of treatment with icovamenib) and was safe and generally well tolerated

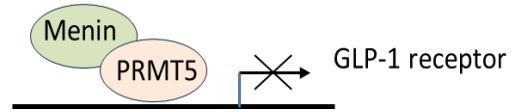
In human islet microtissues *ex vivo*, icovamenib has reproducibly demonstrated:

- Selective proliferation of islet beta cells. Limited proliferation, if any, of non-beta cells
- Proliferation only under high glucose (8 and 11 mM). Restricted under euglycemia
- Icovamenib dose- and treatment duration-dependent proliferation

Menin Regulates Gene Expression and Signaling in a Cell Type- and Context-Dependent Manner

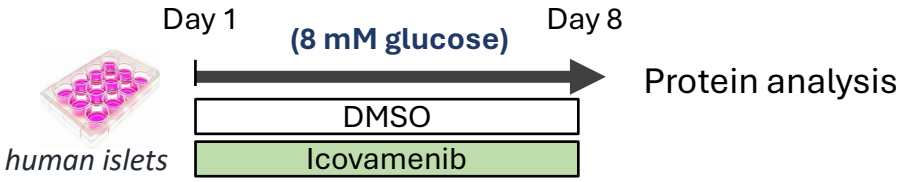


- Regulates compensatory beta cell proliferation in response to physiologic needs (hyperglycemia, gestation, obesity)
  - Menin reduction → beta cell proliferation
- Regulates GLP-1 receptor expression

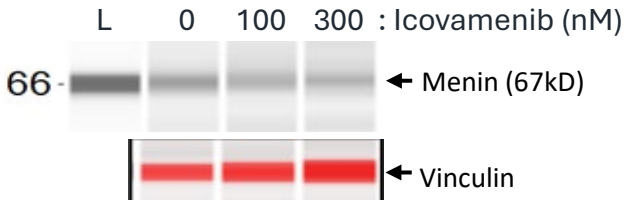


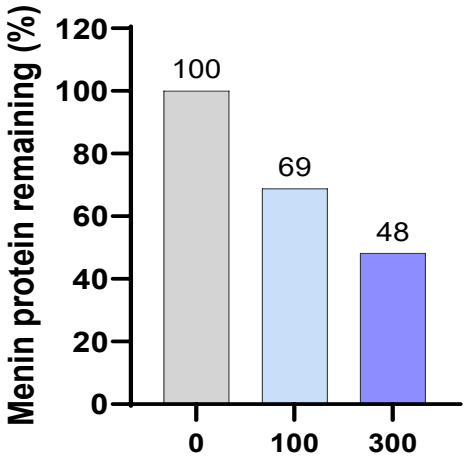
  - Recruitment of PRMT5 represses transcription
- GLP-1 signaling → menin phosphorylation → relieves menin mediated suppression of insulin expression
- Regulates commitment of multipotent mesenchymal cells to osteogenic or myogenic lineages
  - Menin expression antagonizes BMP-2 and TGF-β1 mediated inhibition of myogenesis

Icovamenib Downregulates Menin Protein Levels in Human Islets



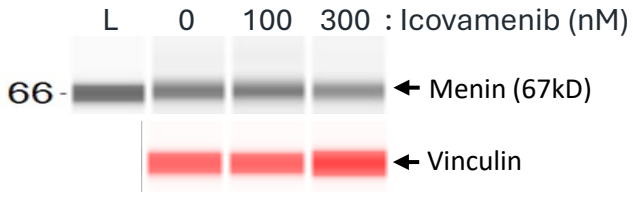
Donor 1

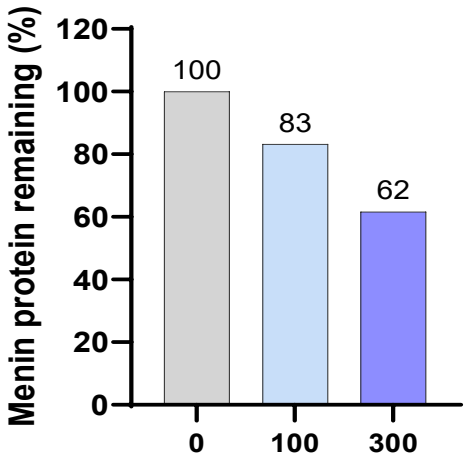




Donor 1: 49-yo male, 167 lbs, BMI 24.5, HbA1C 5.0%

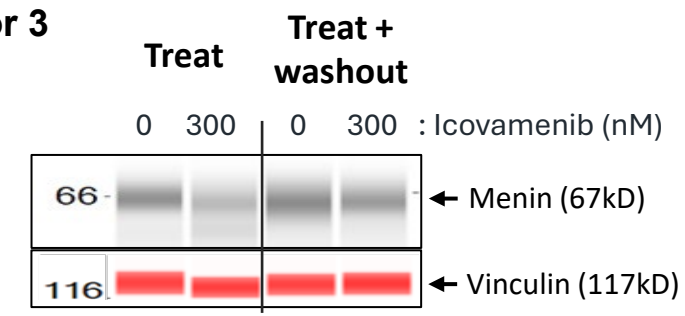
Donor 2

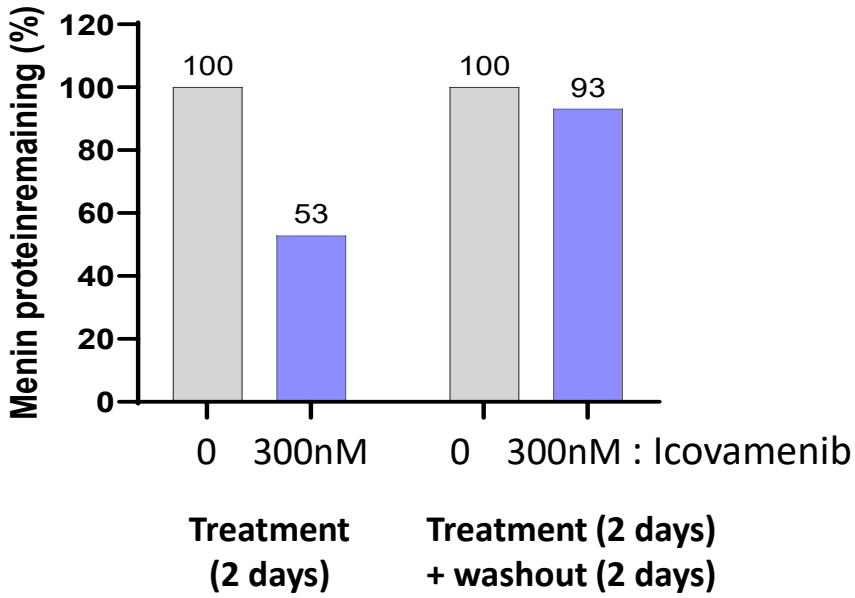




Donor 2: 66-yo male, 248 lbs, BMI 33.7, HbA1C 5.9%

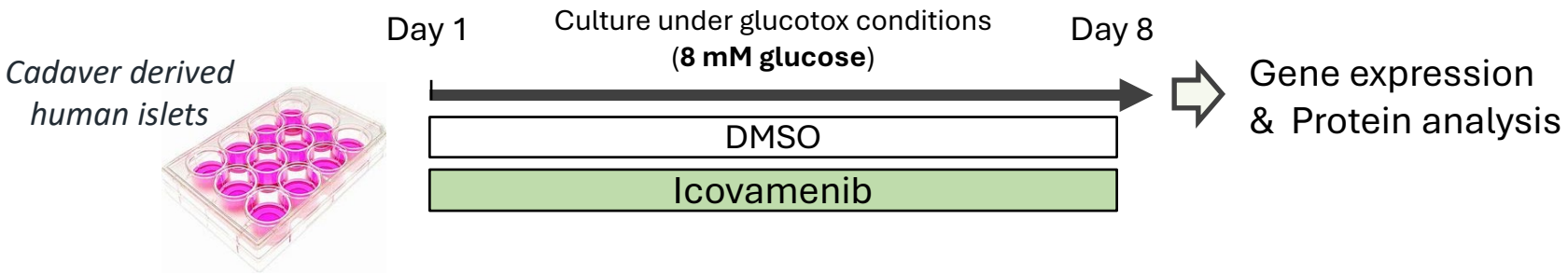
Donor 3



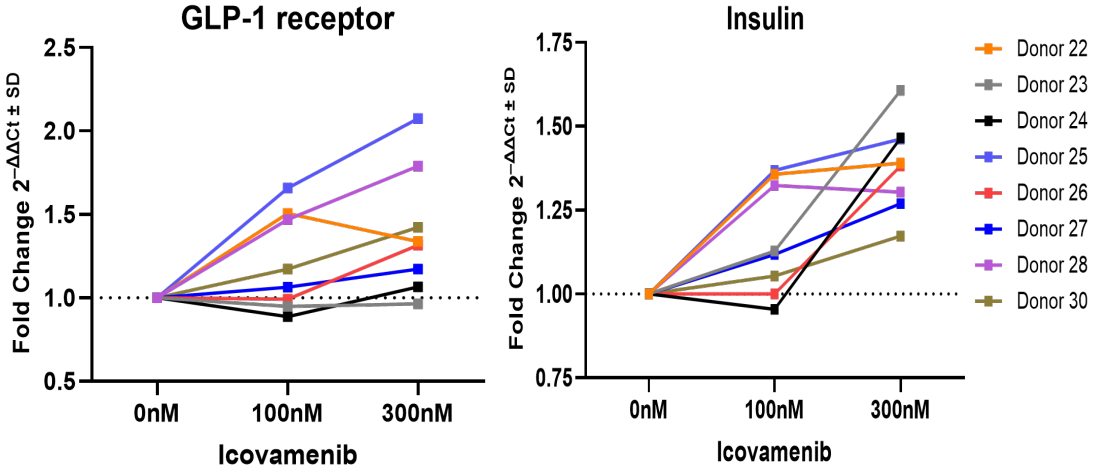


*normalized to vinculin/loading control

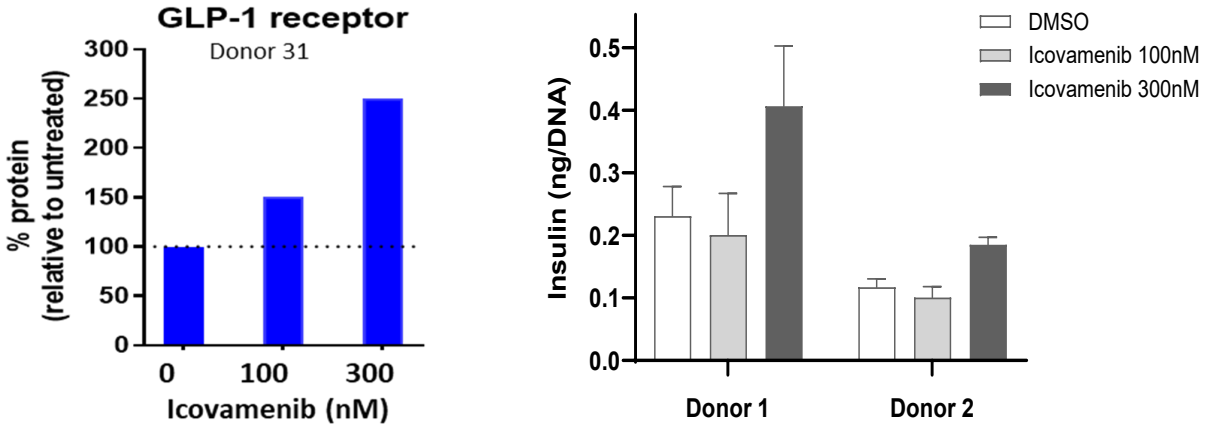
Icovamenib Enhances GLP-1 Receptor and Insulin Expression



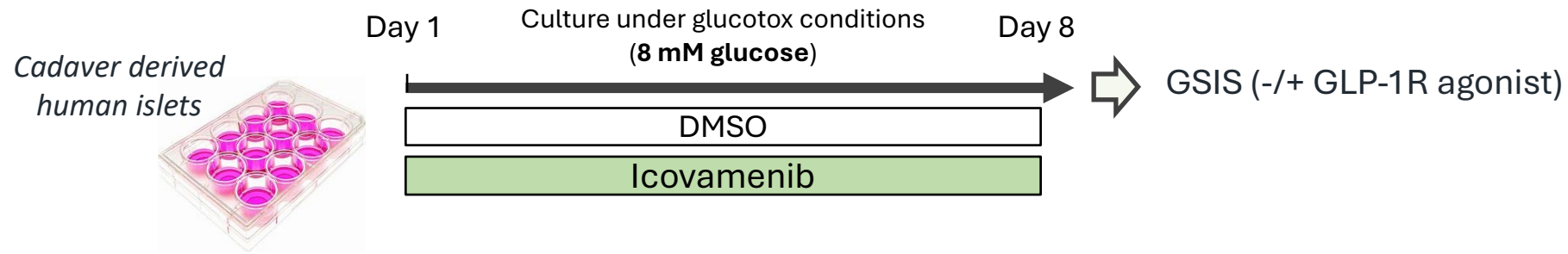
Increased gene expression



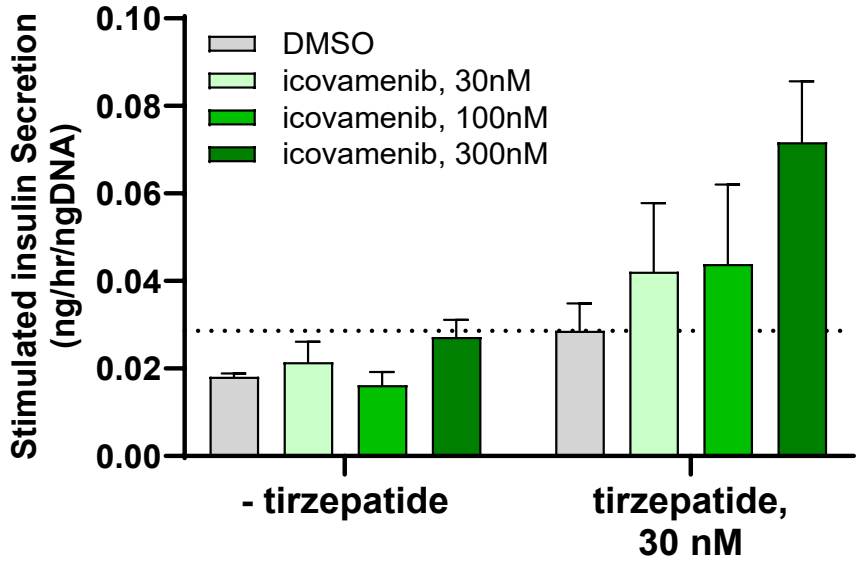
Increase in protein levels



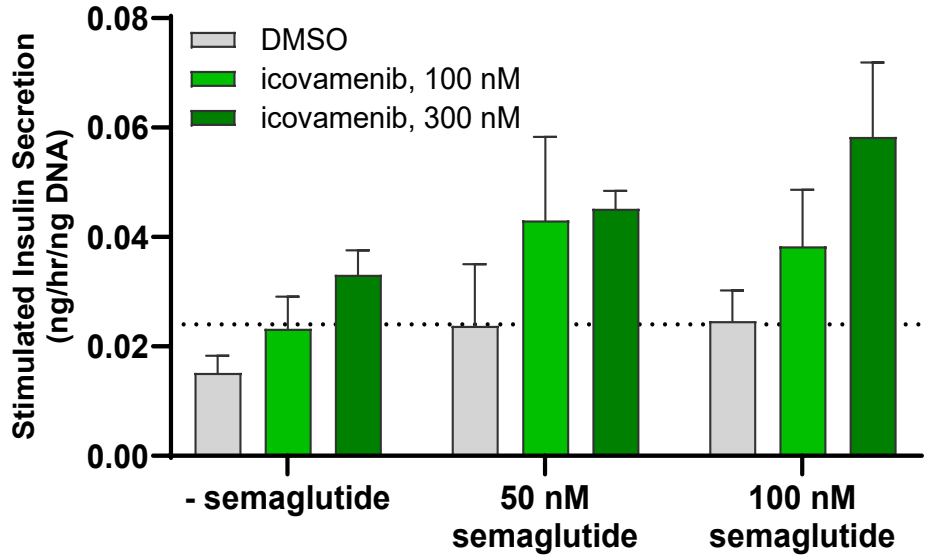
Icovamenib Enhances the Responsiveness of Human Islets to GLP-1 Therapeutic Agents



Icovamenib in combination with tirzepatide

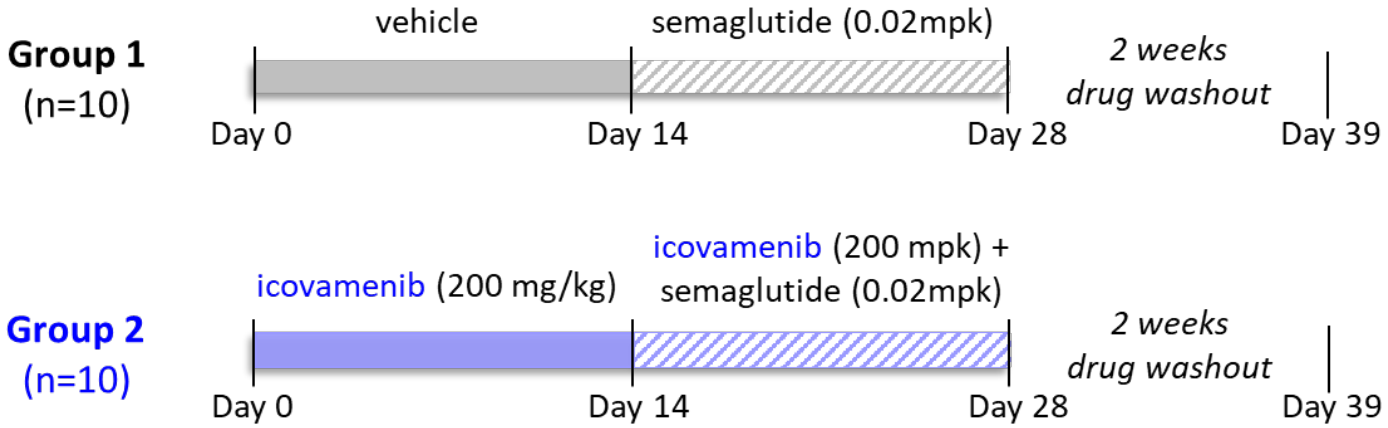


Icovamenib in combination with semaglutide



Icovamenin + Semaglutide Combination Treatment in ZDF Rats

male ZDF rats
12 to 13 weeks age



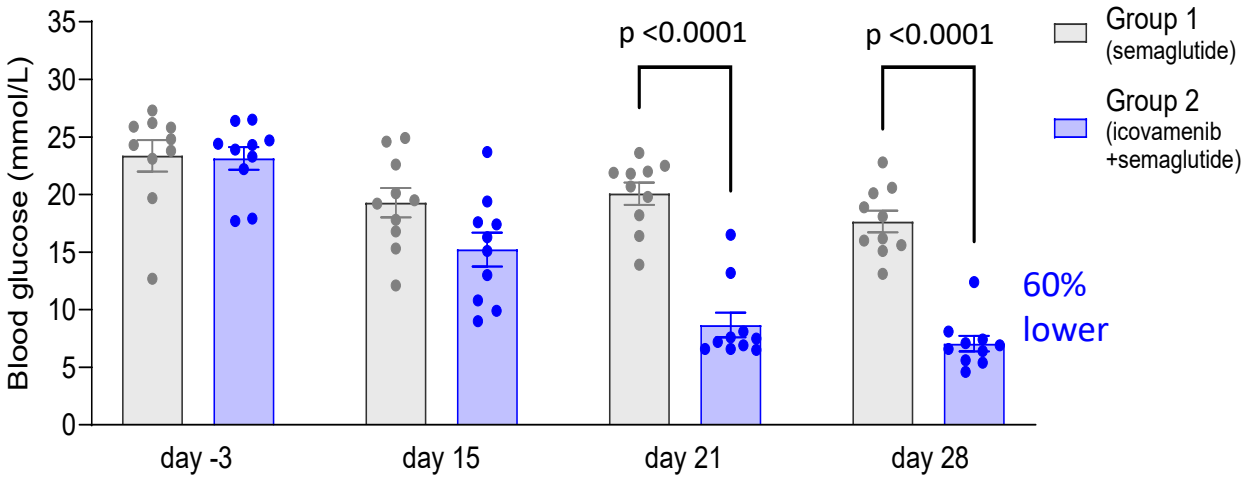
Icovamenib: p.o, QD
Semaglutide: sc, QD

Readouts at multiple time points:

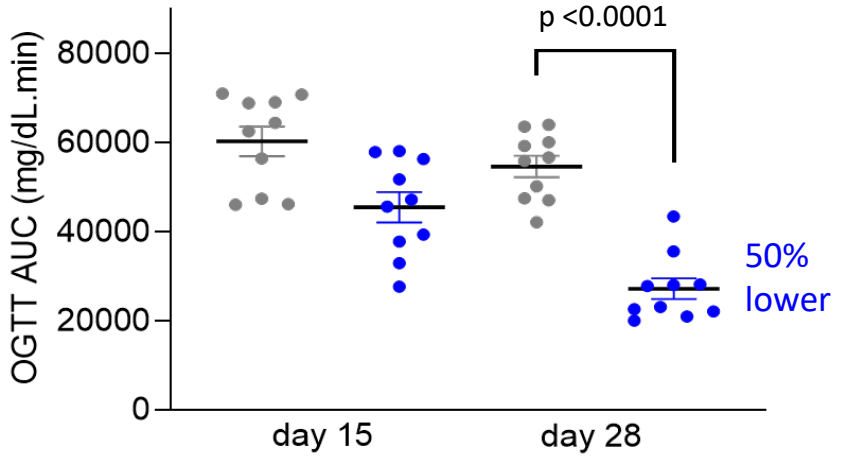
- Glycemic control:
  - Fasting blood glucose and insulin
  - HbA1c
  - oral glucose tolerance test (OGTT)
  - C-peptide index
  - beta cell function (HOMA-B)
  - insulin resistance (HOMA-IR)
- Food & water consumption
- Body weight
- Body composition by Minispec analysis

Combination Treatment of Icovamenib and Low-Dose Semaglutide Improves Glycemic Parameters

Fasting Blood Glucose†

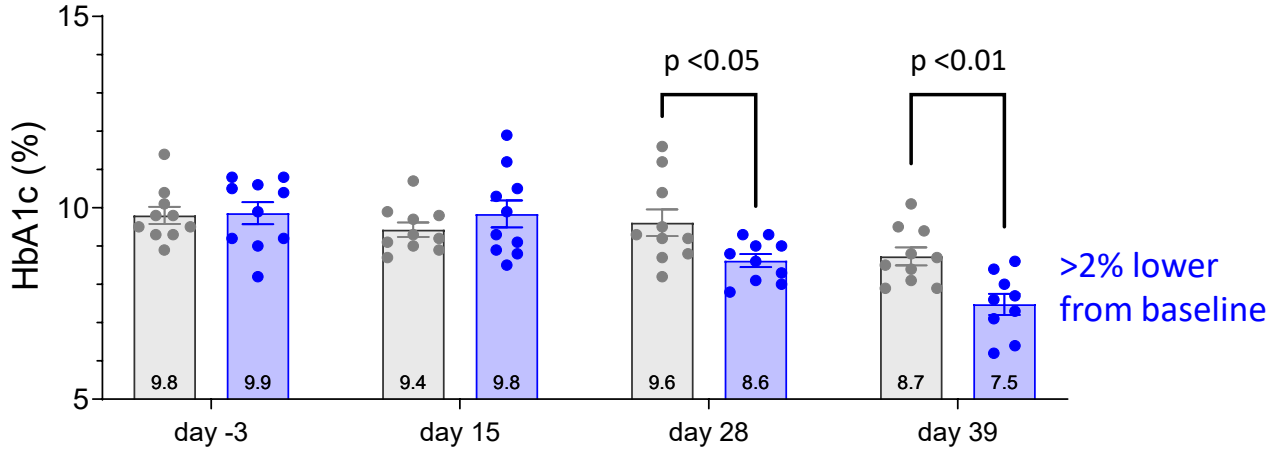


Glucose AUC during Oral Glucose Tolerance Test

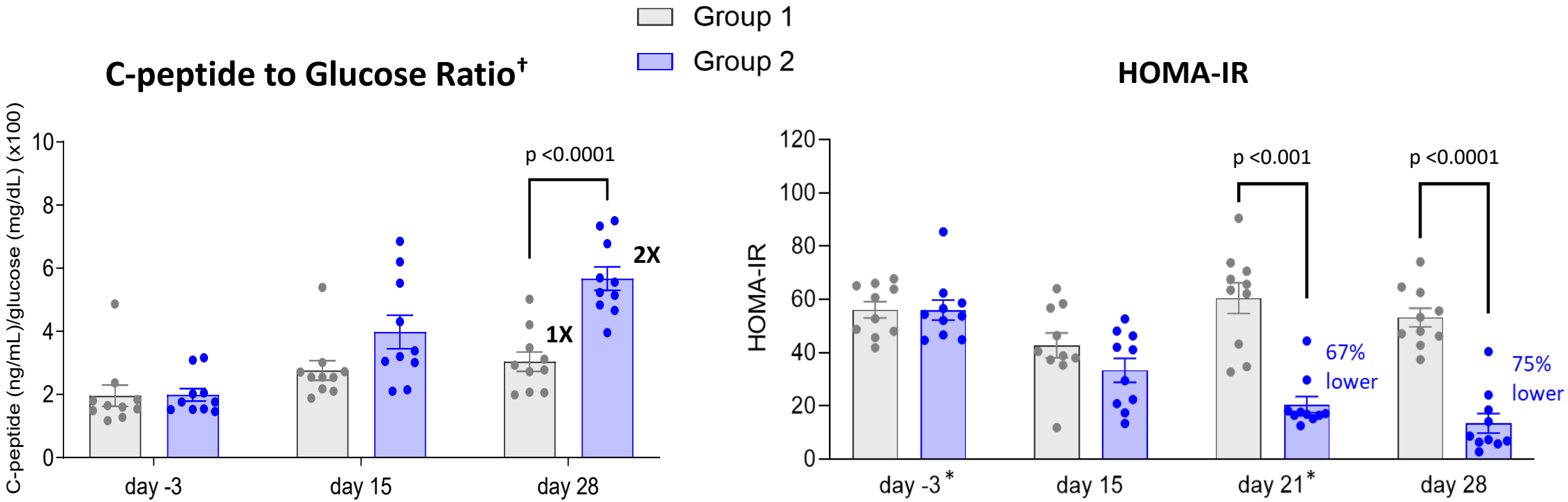


Plots represent mean ± SEM
Dots represent data for individual animal
† *6hr fasting on days -3 and 21, overnight fasting on days 15 and 28.*

HbA1c

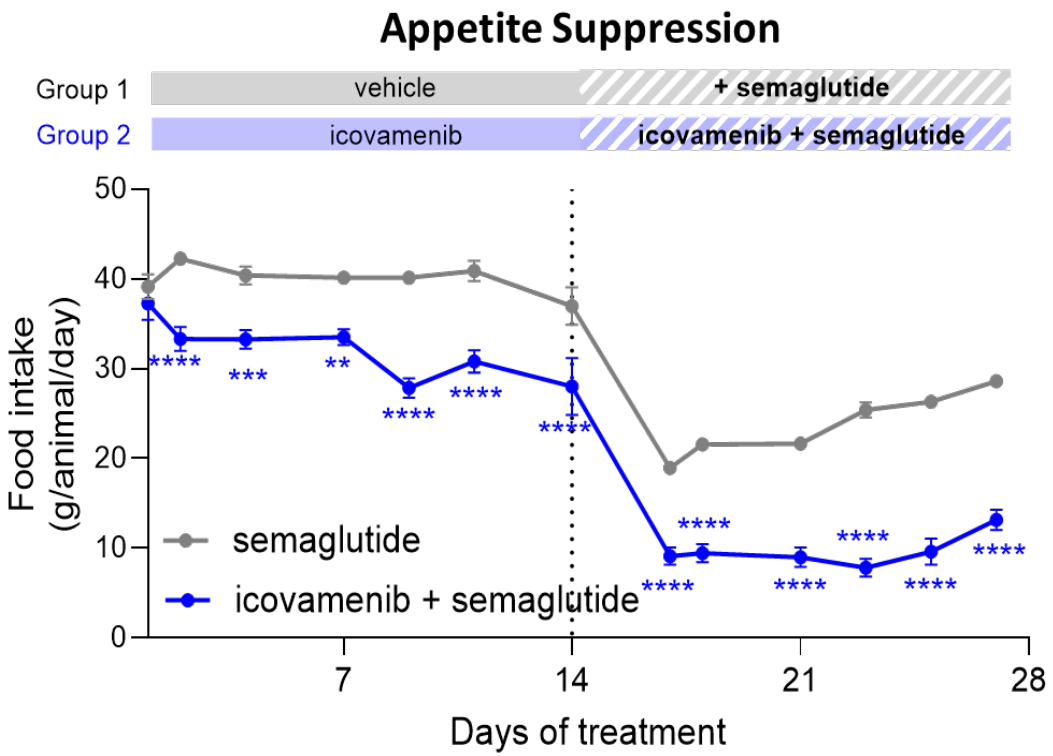


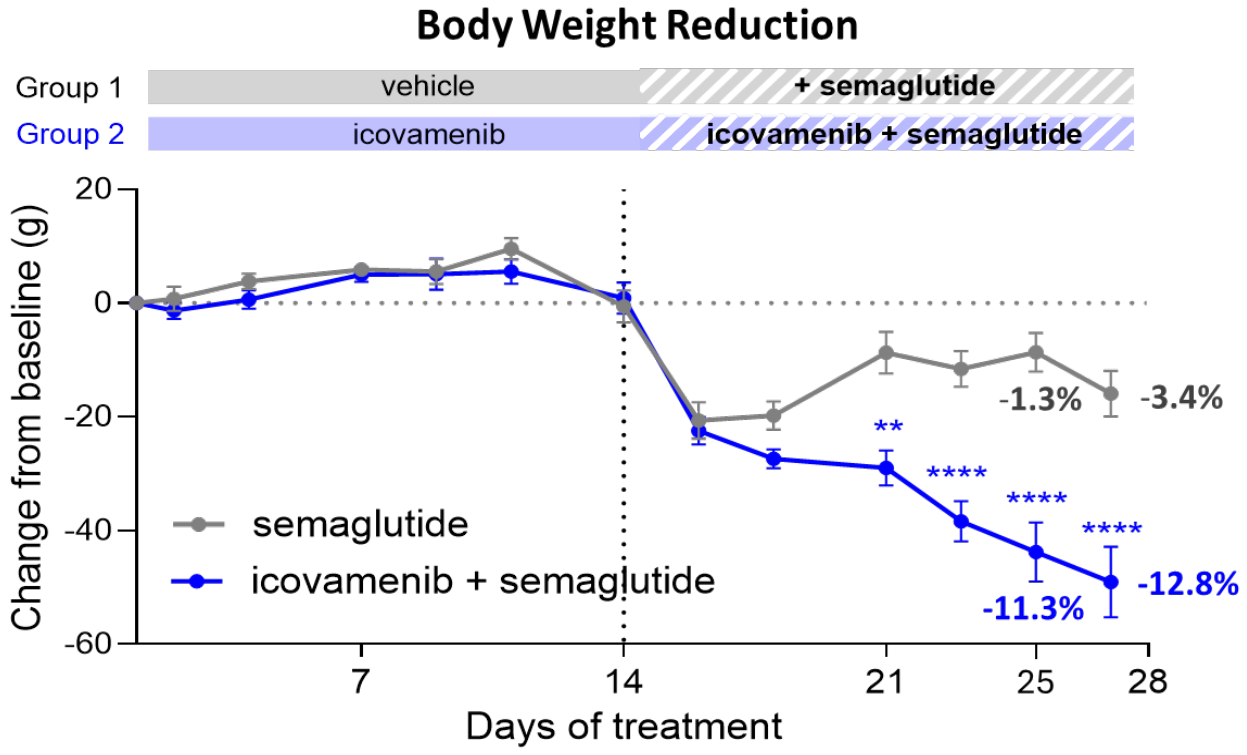
Combination Treatment of Icovamenib and Low-Dose Semaglutide Improves Beta Cell Health and Insulin Sensitivity



Plots represent mean ± SEM
Dots represent data for individual animal
† *6hr fasting on days -3 and 21, overnight fasting on days 15 and 28.*

Combining Icovamenib with Low-Dose Semaglutide Enhances Appetite Suppression and Body Weight Reduction



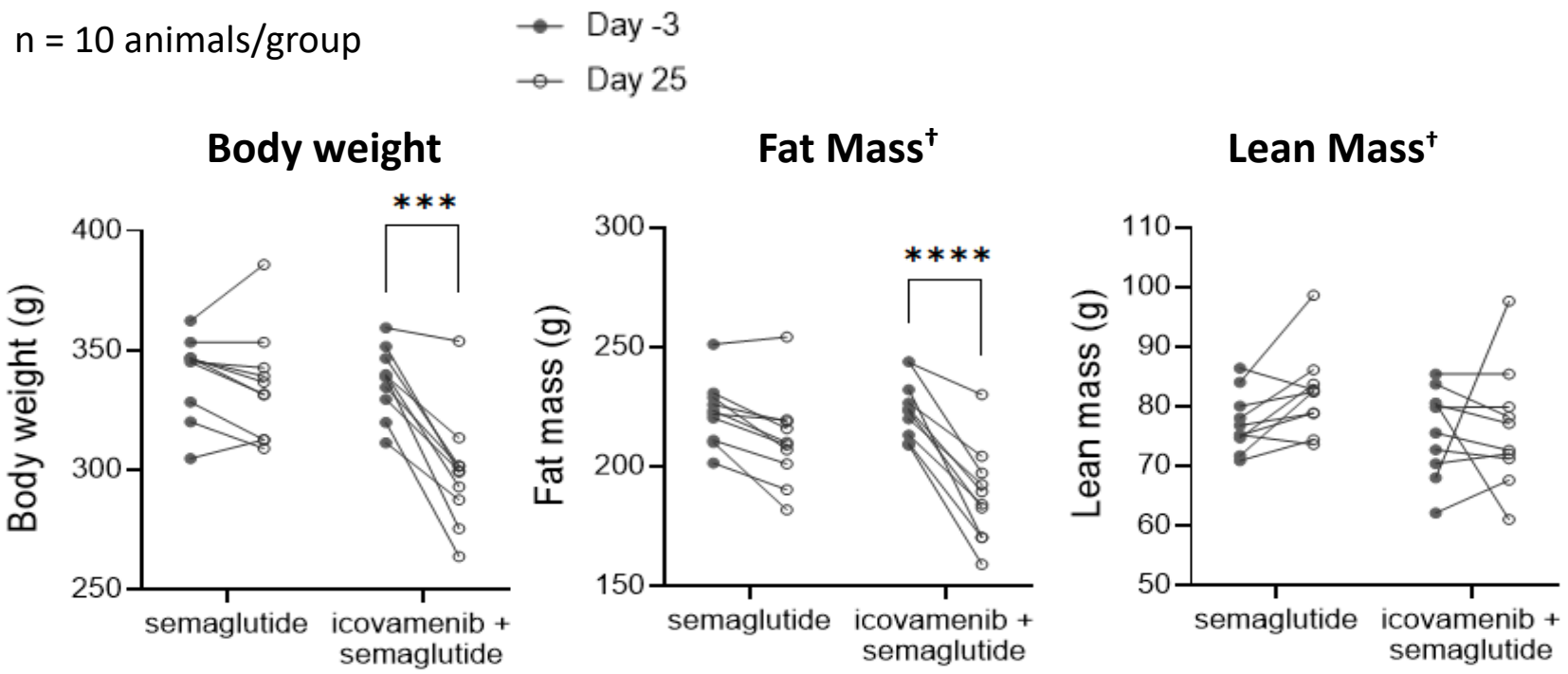


Plots show mean ± SEM

** p<0.01, *** p<0.001, **** p<0.0001

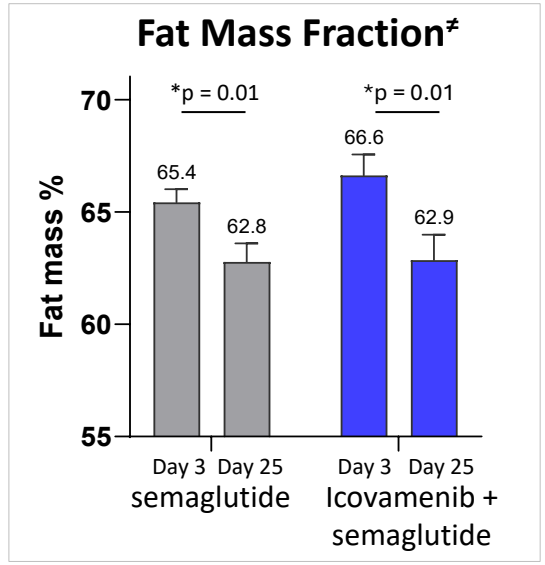
Combination Therapy Drives Body Weight Reduction Almost Exclusively by Fat Mass Loss with Preservation of Lean Mass

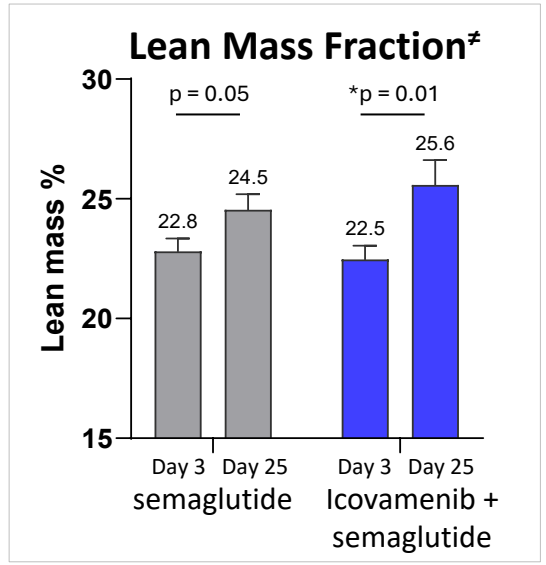
n = 10 animals/group



† Minispec analysis

Plots show individual animal data
*** p<0.001, **** p<0.0001





≠ percentage of body weight
Plots show mean ± SEM

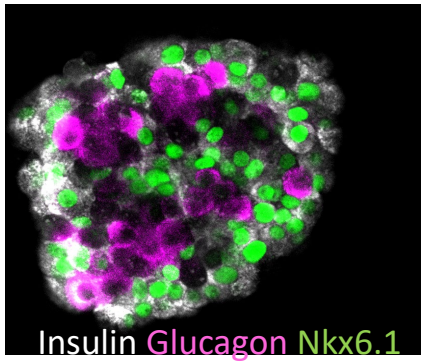
Summary and Conclusions

- Icovamenib downmodulates menin levels in *ex vivo* human islets. Effect is reversed upon drug washout
- Icovamenib enhanced the responsiveness of human islets to GLP-1 RA therapies. This enhancement was associated with increased GLP-1 receptor and insulin expression
- Icovamenib enhanced the efficacy of low dose semaglutide in the ZDF rat model of T2D. Combination treatment was superior to low dose semaglutide:
  - Superior appetite suppression and 10% greater body weight reduction
  - Body weight reduction exclusively from fat mass loss with preservation of lean mass
  - Superior glycemic control vs semaglutide alone
    - 60% lower fasting blood glucose and 50% lower glucose OGTT AUC
    - Greater reduction in HbA1c (>2% by Day 39)
    - Significant increase in C-peptide index
    - Greater improvement in insulin sensitivity

Summary and Conclusions

- Preliminary results suggest icovamenib may promote muscle health and protects against atrophy (ADA 2025)
- Overall results demonstrate the enhanced efficacy of the combination of icovamenib and low dose semaglutide (vs semaglutide alone), potentially allowing lower doses of GLP-1-based therapies to achieve the glycemic and weight loss targets and improve tolerability of these agents.

Acknowledgements



- **Priyanka Somanath, PhD**
- **Tracy Zhang, PhD**
- **Kung-Hsien Ho, PhD**
- **Dina Mousavi, MS**
- **Nida Tanataweethum, PhD**

- **Juan Pablo Frias, MD**

Physiogenex, Claire Bigot, PhD and Francios Briand, PhD

Rohit N. Kulkarni, MD, PhD - Biomea SAB member
Professor of Medicine
Joslin Clinic, Harvard Medical School