# Combination of Icovamenib and GLP-1-based Therapeutic Agents Improves Beta Cell Function and Insulin Secretion

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All authors are employees of Biomea Fusion Inc.



# **Background**

## **Icovamenib**

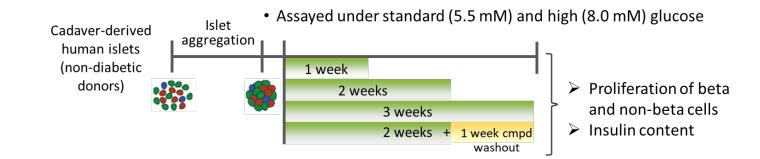
- Icovamenib is an oral, selective, covalent menin inhibitor that is currently in clinical development for the treatment of type 1 and type 2 diabetes
- In T2D patients, 4 weeks of daily icovamenib resulted in improved glycemic control at Week 26 (22 weeks after cessation of treatment with icovamenib) and was safe and generally well tolerated.
- In preclinical models of diabetes, icovamenib showed durable glycemic control following short-term treatment in ZDF and STZ rat models.

### Menin

- Scaffold protein that displays tissue-specific roles via regulating gene expression and specific cell signaling pathways, dependent on the menin-bound protein complexes.
- A key negative regulator of both beta-cell proliferation and mass.
- Shown to regulate GLP-1 receptor expression and the GLP-1 receptor pathway.



## **Icovamenib Promotes Selective Proliferation of Islet Beta Cells**

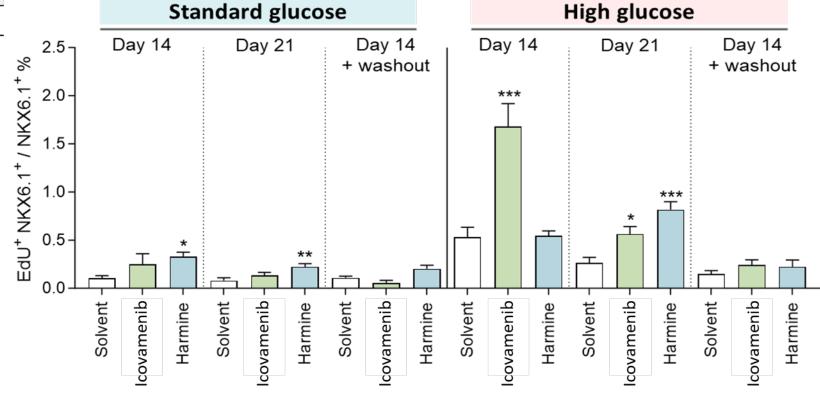


#### **Donor characteristics:**

	Age	ВМІ	HbA1c
Donor 1	19	23.2	5.8

Icovamenib: 0.3 μM

Harmine: 10 μM

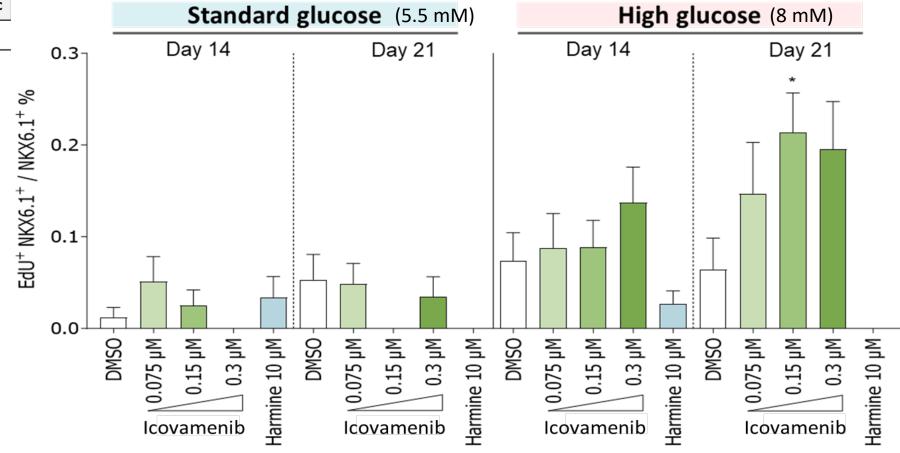




## **Icovamenib Promotes Selective Proliferation of Islet Beta Cells**

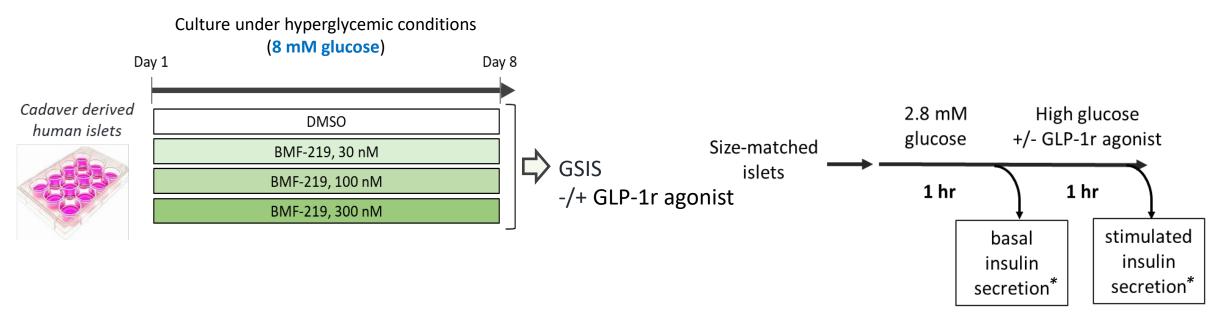
#### **Donor characteristics:**

	Age	ВМІ	HbA1c
Donor 2	32	25	5.2





## **Combination Treatment with Icovamenib and GLP-1-based**



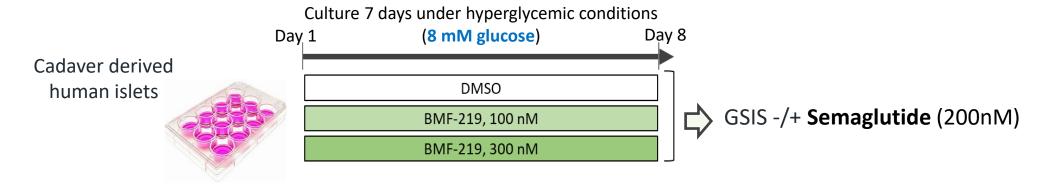
\*normalized to islet DNA content

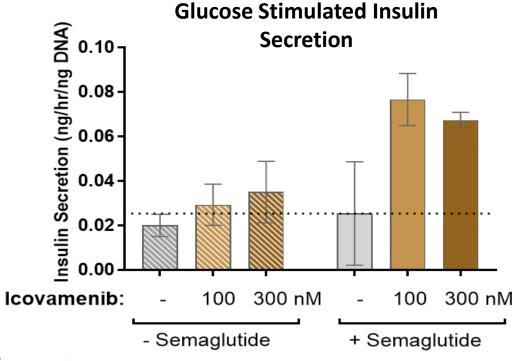
#### **Readouts:**

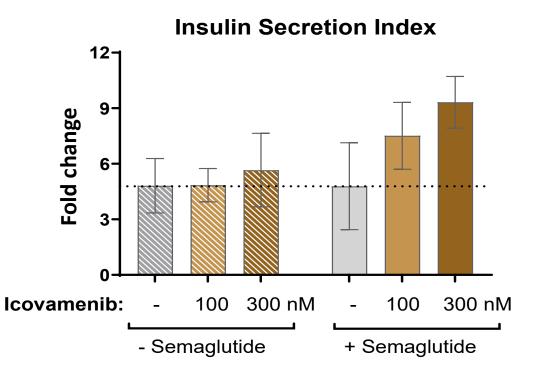
- Basal and glucose-stimulated insulin secretion (GSIS)
- Secretion Index = Stimulated secretion/ basal secretion
- Insulin and DNA content in islets



## Combination treatment: Icovamenib enhances responsiveness of islets to GLP-1r agonist

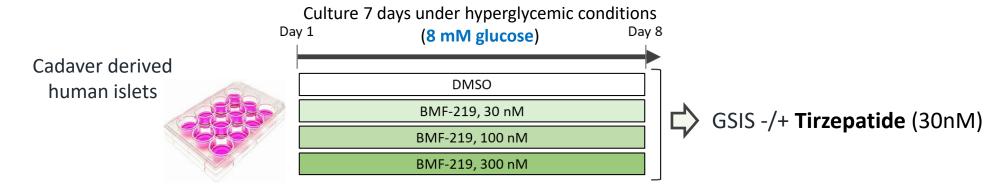




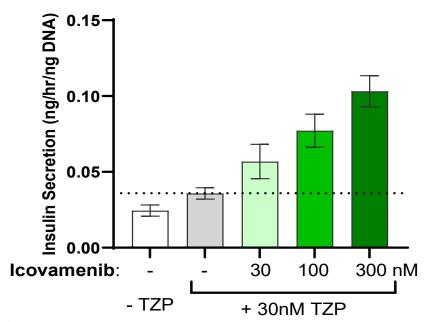




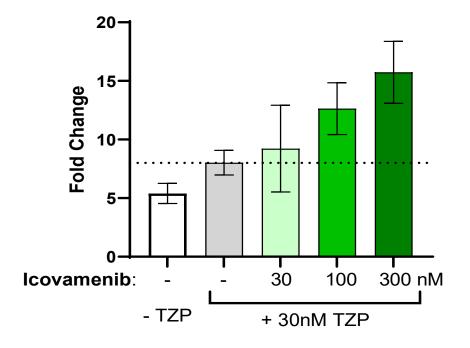
## Combination treatment: Icovamenib enhances responsiveness of islets to GLP-1r agonist



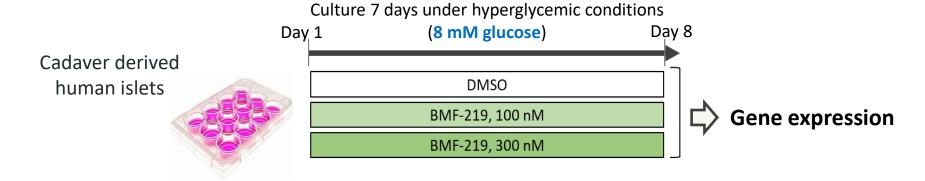
#### **Glucose Stimulated Insulin Secretion**

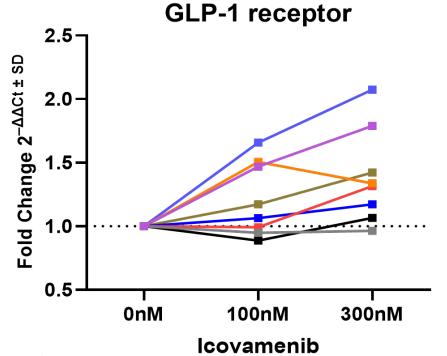


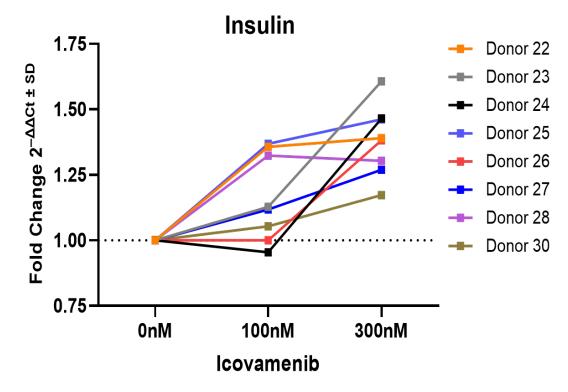
#### **Insulin Secretion Index**



## Icovamenib enhances GLP-1 receptor and insulin transcript levels

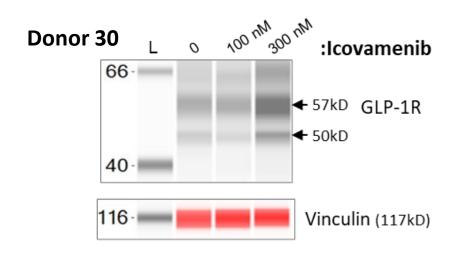


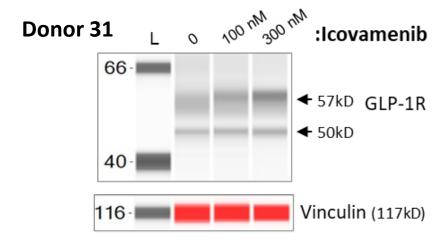


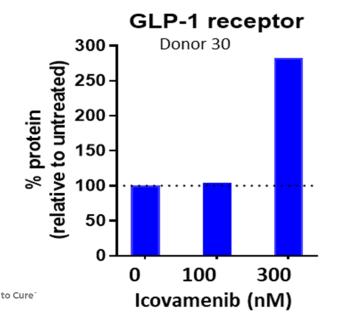


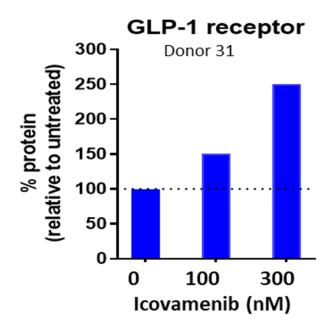


## Icovamenib treatment increases GLP-1 receptor protein expression



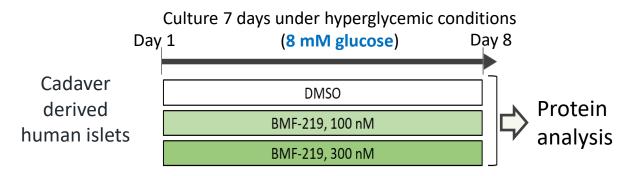




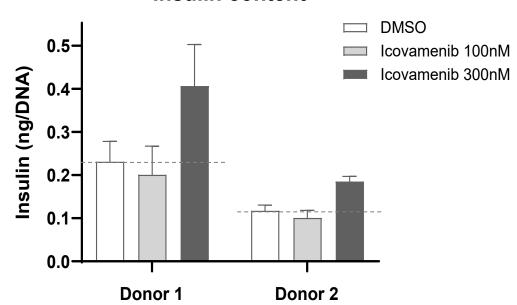




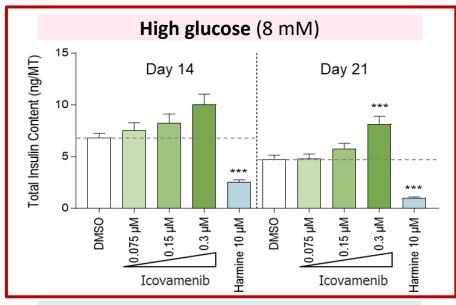
## Icovamenib treatment increases cellular insulin expression



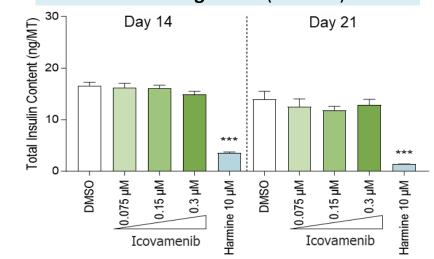
#### **Insulin content**



#### **Human islet microtissues**



#### Standard glucose (5.5 mM)





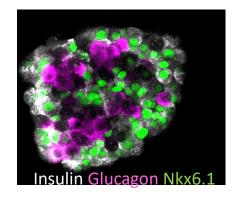
# **Summary and Conclusions**

- Icovamenib promotes controlled proliferation of beta cells in human islet microtissues ex vivo, in a glucose- and dose- dependent manner.
- In combination studies with GLP-1 receptor agonists, icovamenib enhanced the responsiveness of human islets to semaglutide and tirzepatide.
- Icovamenib-induced enhancement in beta cell function was associated with an increase in the expression levels of the GLP-1 receptor as well as insulin, at the transcript and protein levels.
- Icovamenib induced dose dependent increase in Ki-67 expression, consistent with it's ability to promote beta cell proliferation (data not shown).
- The overall results demonstrate synergy of the combination therapy. Additionally, the increase in beta cell mass and improved beta cell function induced by icovamenib may allow lower doses of GLP-1-based therapies to achieve glycemic targets, potentially improving tolerability of these agents.



## **Acknowledgements**

- Tracy Zhang, PhD
- Kung-Hsien Ho, PhD
- Dina Mousavi, MS



- Juan Pablo Frias, MD CMO and Head of Diabetes
- Thomas Butler, MS, MBA, CEO and Founder

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