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.

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Background

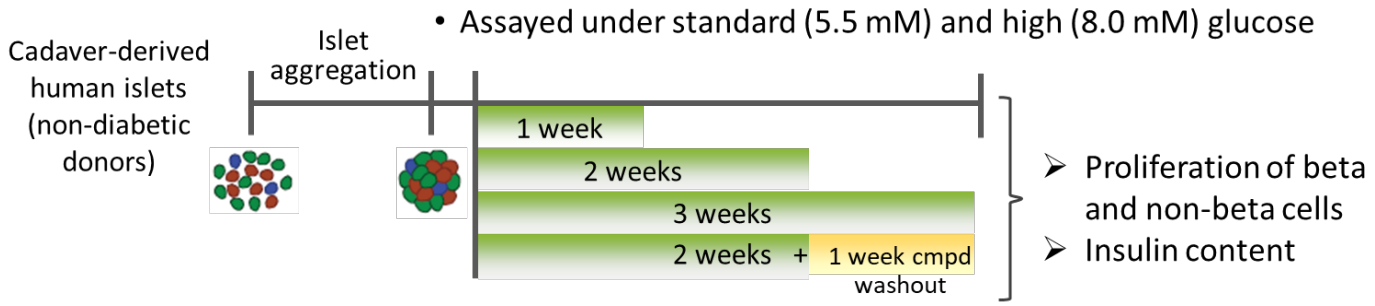
Icovamenib

- 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.

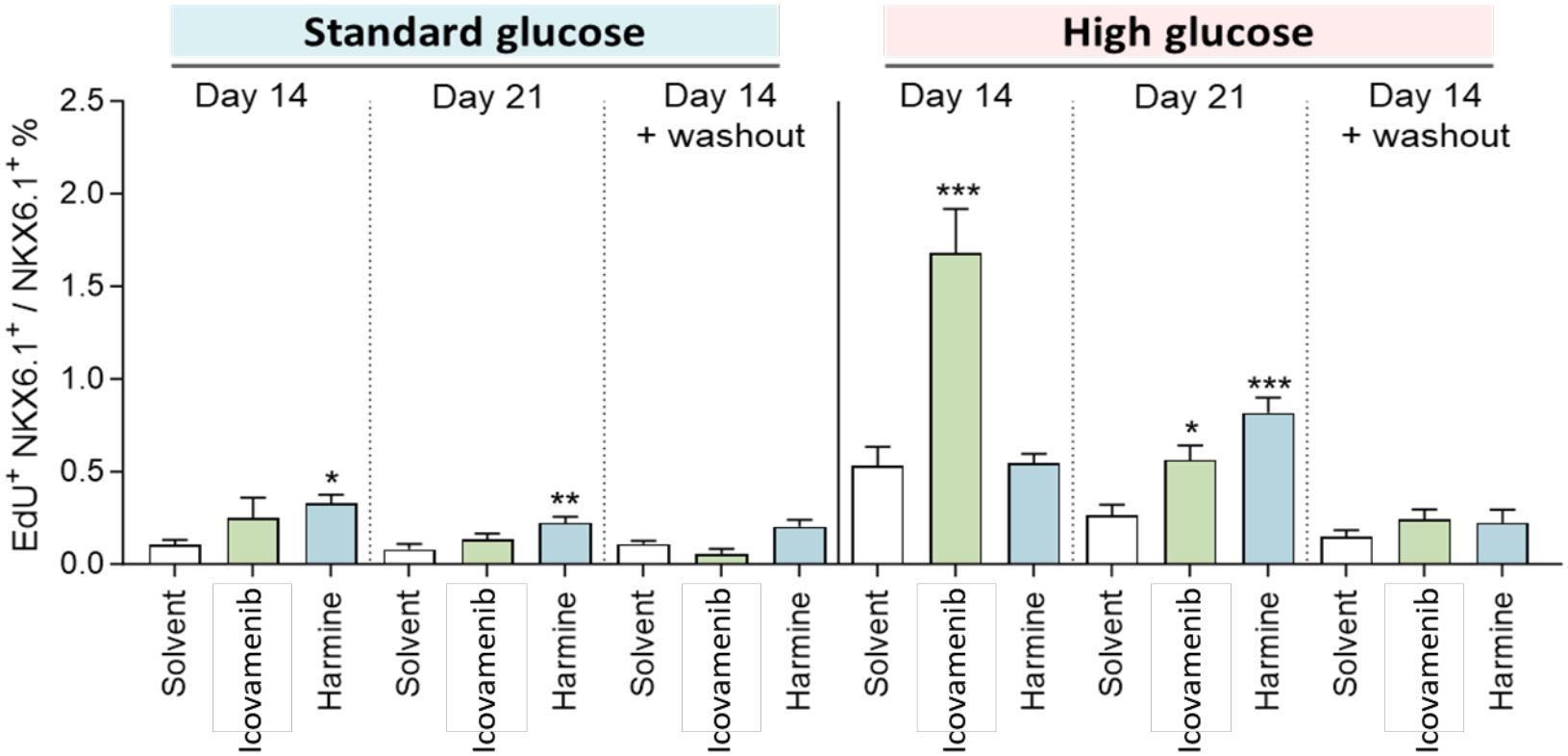
Icovamenib Promotes Selective Proliferation of Islet Beta Cells



Donor characteristics:

	Age	BMI	HbA1c
Donor 1	19	23.2	5.8

Icovamenib: 0.3 µM
Harmine: 10 µM



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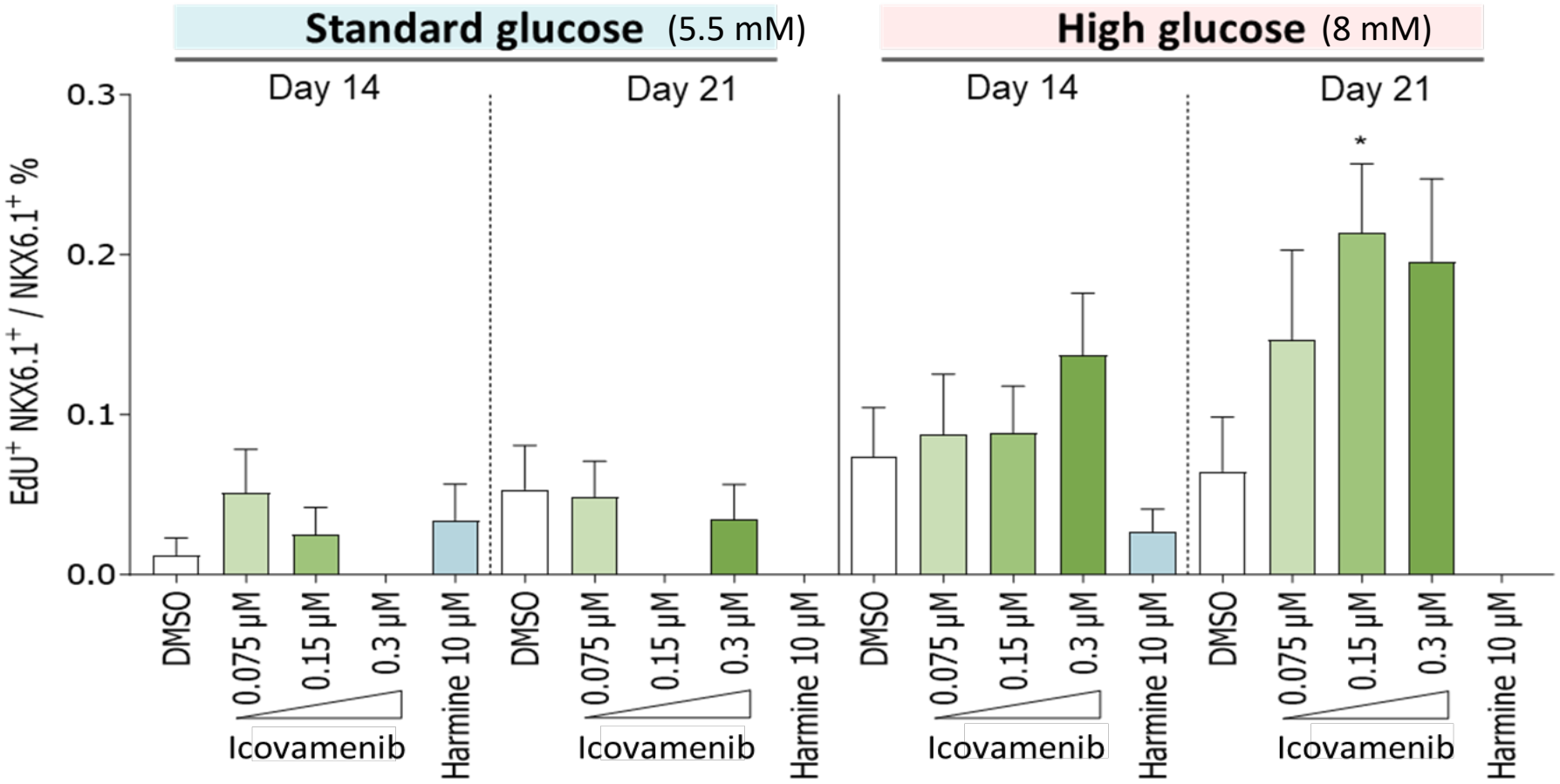
Icovamenib Promotes Selective Proliferation of Islet Beta Cells

Donor characteristics:

	Age	BMI	HbA1c
Donor 2	32	25	5.2



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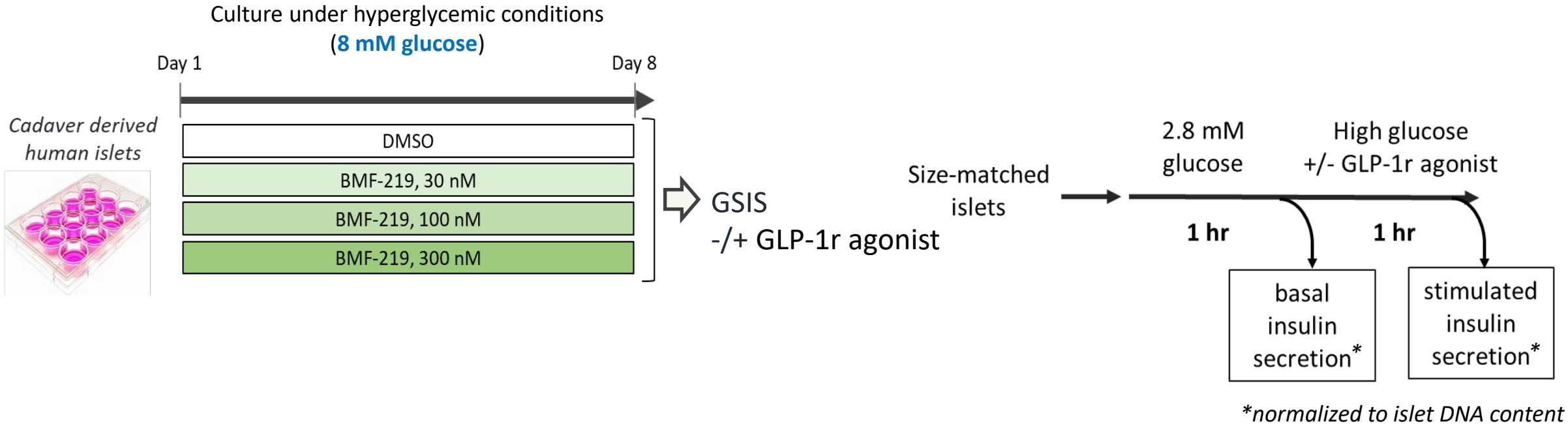
Combination Treatment with Icovamenib and GLP-1-based



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

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

Culture 7 days under hyperglycemic conditions

Day 1 (8 mM glucose) Day 8

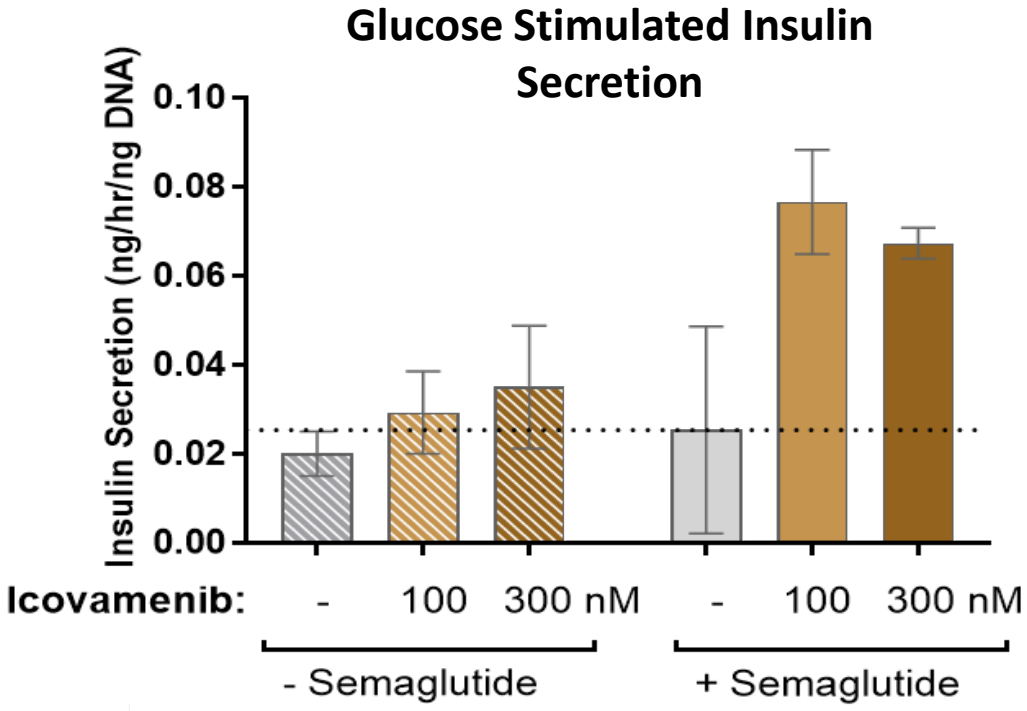
Cadaver derived human islets

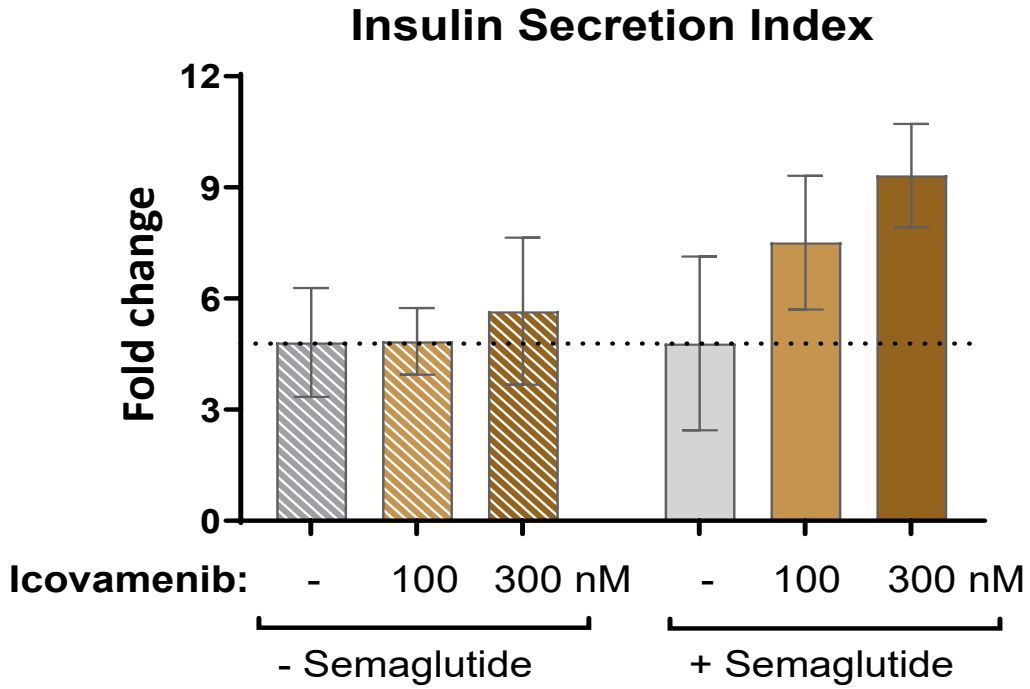
DMSO

BMF-219, 100 nM

BMF-219, 300 nM

GSIS -/+ **Semaglutide** (200nM)





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

Culture 7 days under hyperglycemic conditions
(8 mM glucose)

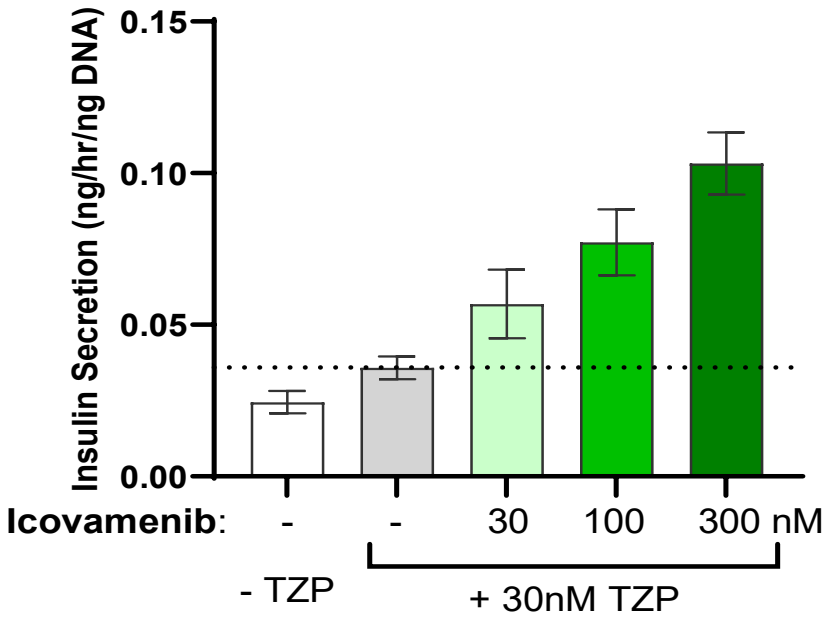
Day 1 — Day 8

Cadaver derived human islets

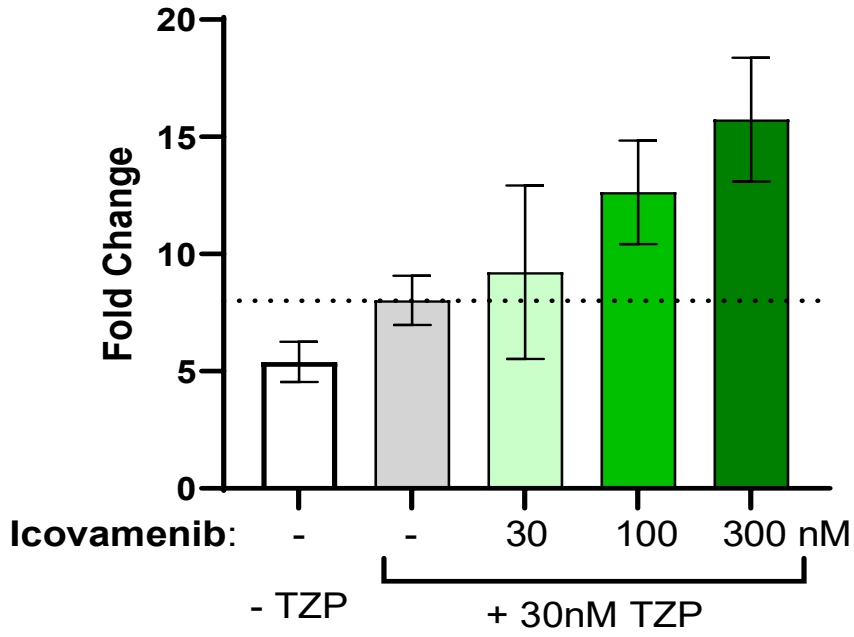
- DMSO
- BMF-219, 30 nM
- BMF-219, 100 nM
- BMF-219, 300 nM

GSIS -/+ **Tirzepatide** (30nM)

Glucose Stimulated Insulin Secretion



Insulin Secretion Index



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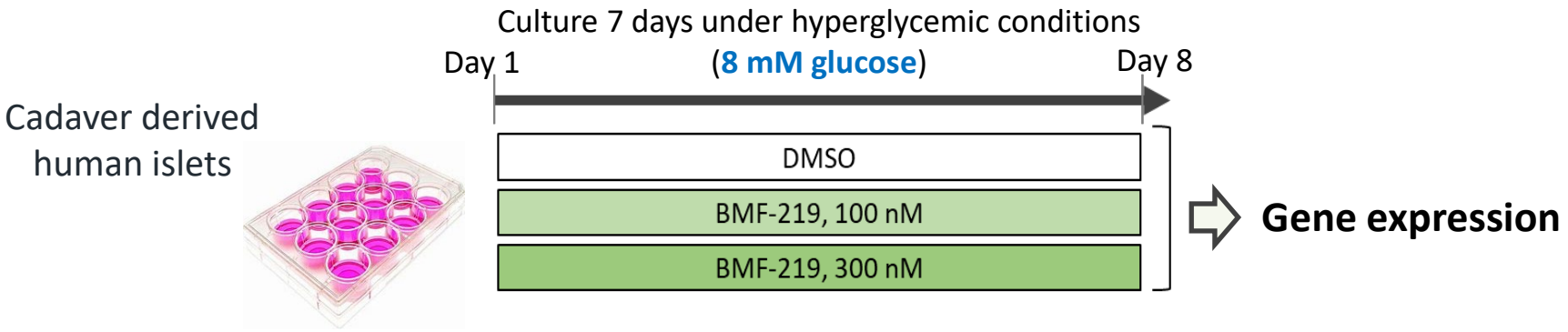
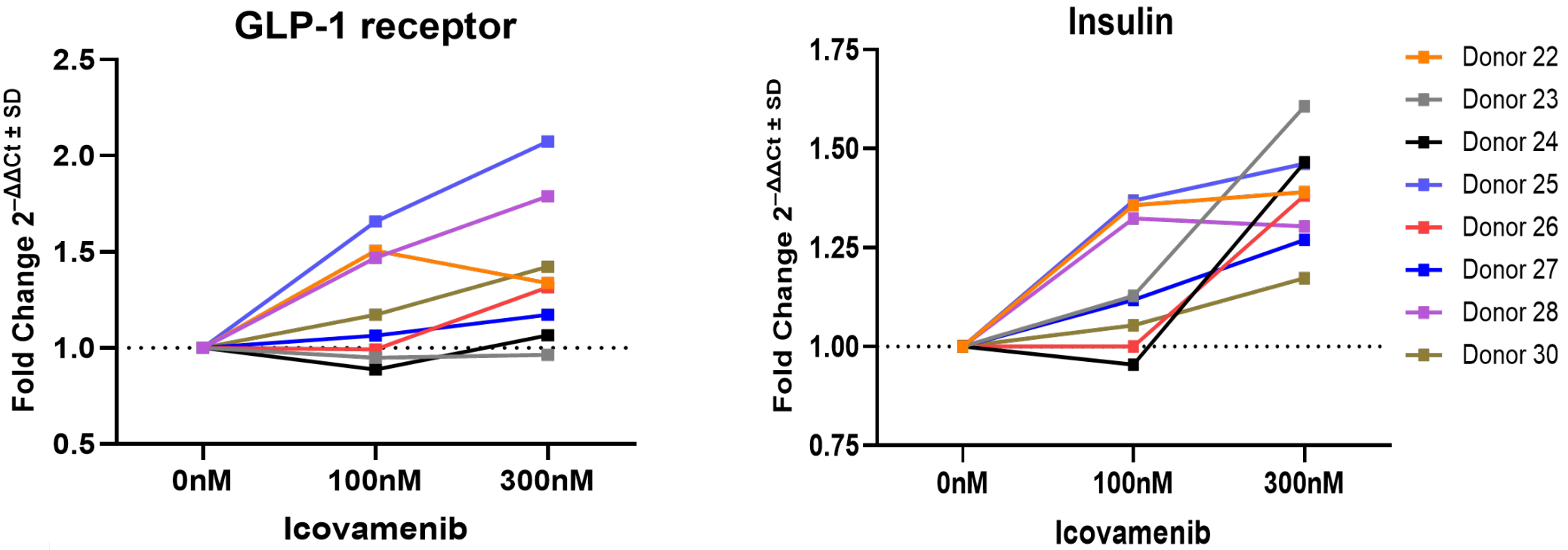
Icovamenib enhances GLP-1 receptor and insulin transcript levels





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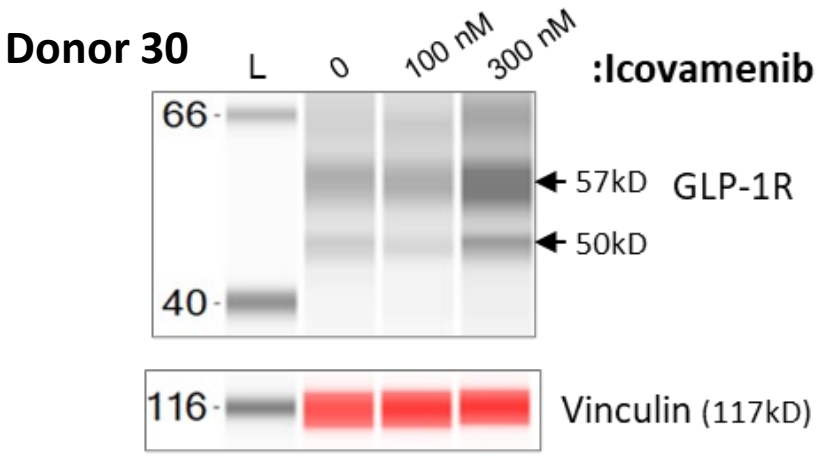
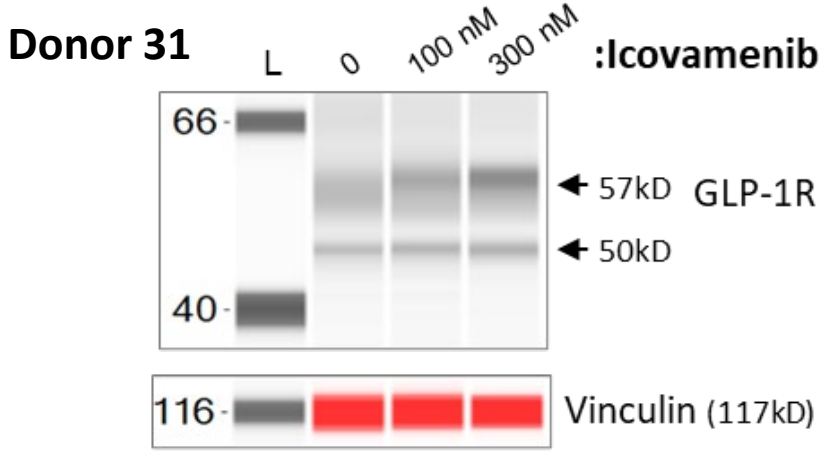
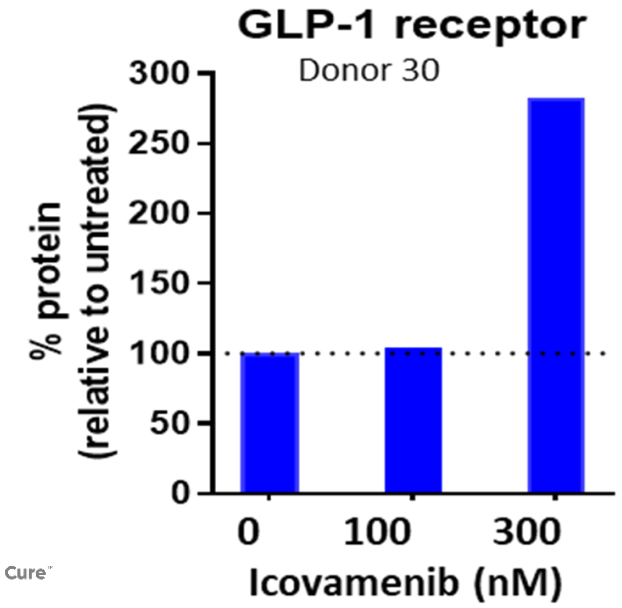
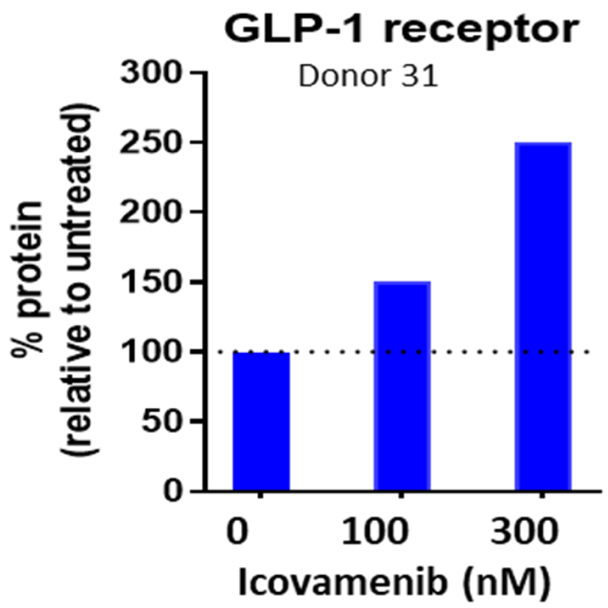
Icovamenib treatment increases GLP-1 receptor protein expression









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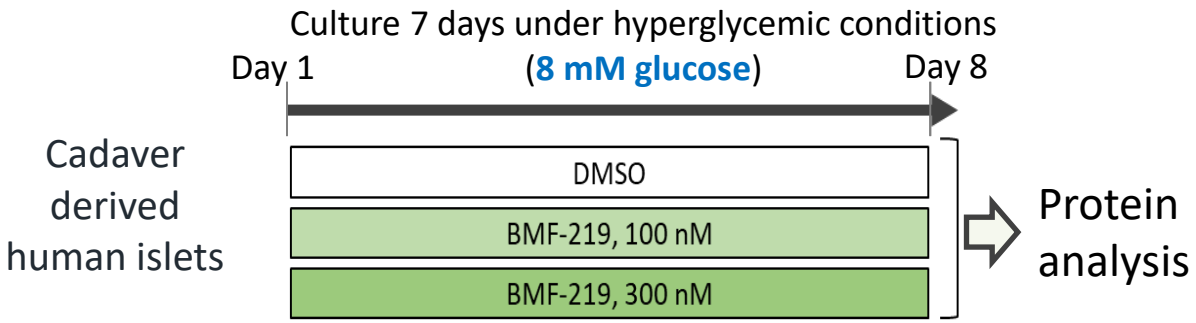
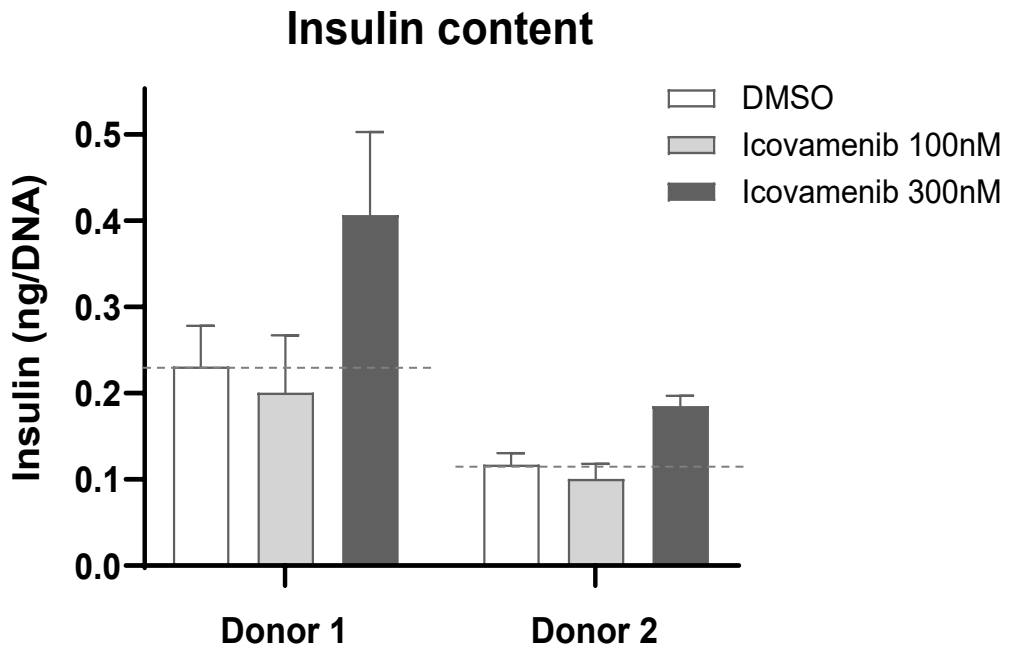
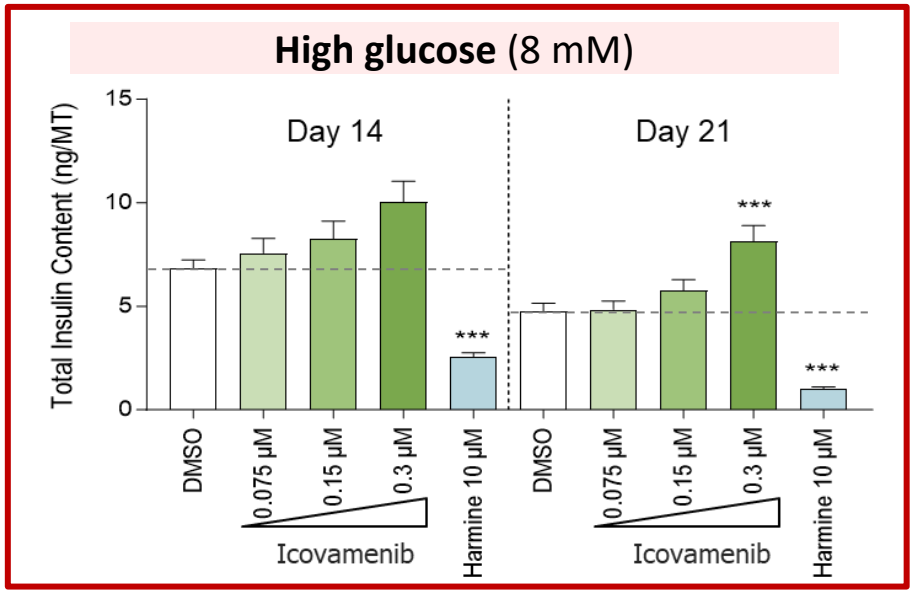
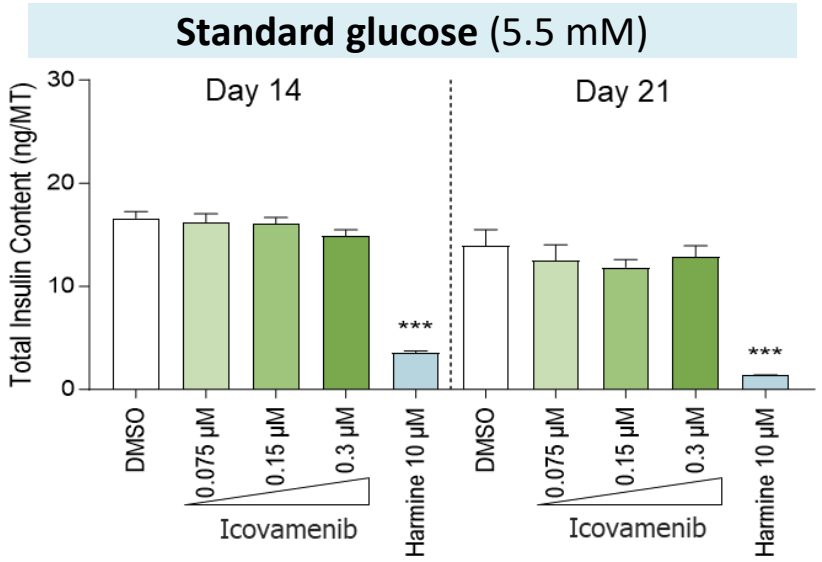
Icovamenib treatment increases cellular insulin expression





Human islet microtissues





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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

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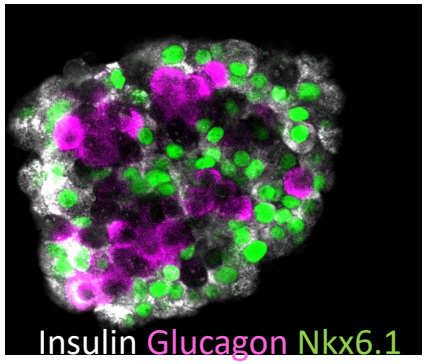

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Thank you

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