

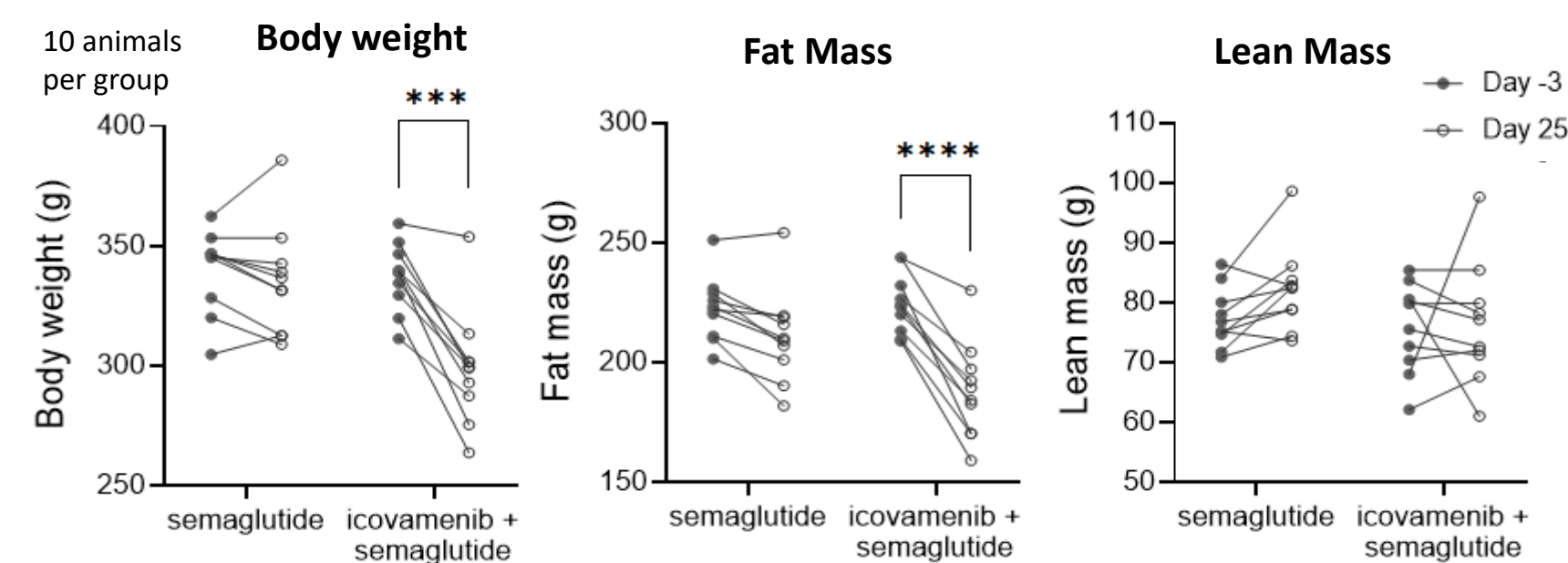
## Background

- Icovamenib is an investigational, menin-targeted small-molecule oral drug candidate, currently in phase II clinical development for the treatment of type 1 diabetes (T1D) and type 2 diabetes (T2D).
- In T2D patients failing standard of care, a 12-week course of icovamenib resulted in durable HbA1c reduction and C-peptide increase through 52 weeks<sup>1</sup>.
- Findings from non-clinical studies including studies in rodent models and ex vivo human islets indicate that icovamenib promotes glucose lowering through at least two distinct mechanisms: 1) increasing beta cell numbers and/or mass, and 2) enhancing the incretin effect (via increasing GLP-1 receptor and insulin expression).
- Menin interacts with transcription factors and chromatin-modifying complexes to modulate gene transcription, signaling pathways and cellular processes involved in glycemic control as well as metabolism.

## Rationale

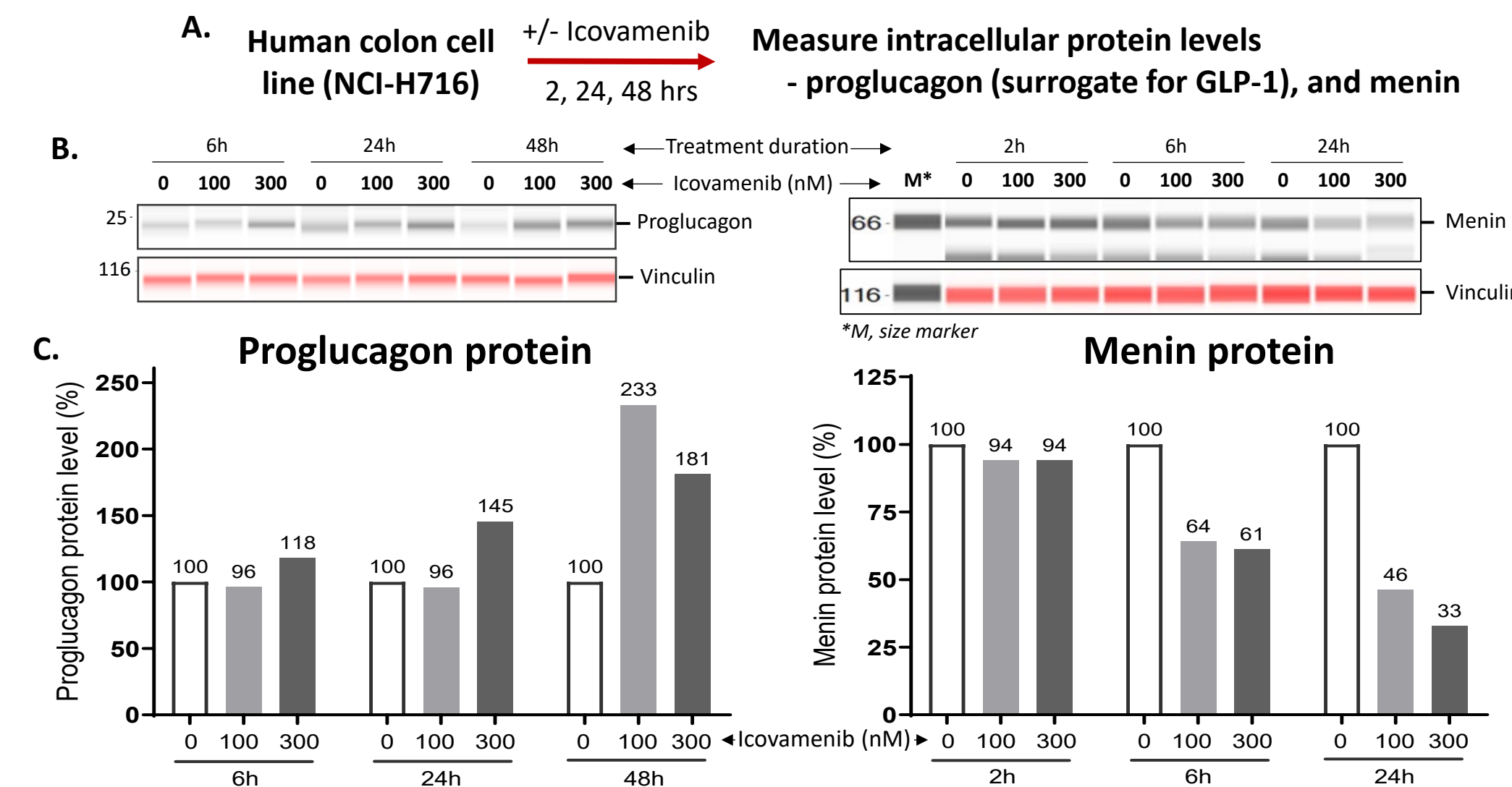
- Menin is a negative regulator of GIP (via inhibition of PI3K/AKT signaling), GLP-1 (via  $\beta$ -catenin), and GLP-1 receptor (via PRMT5) expression<sup>2, 3, 4</sup>.
- Menin modulates signaling pathways critical for muscle health. Menin-depleted mice display increased intercostal muscle mass and enhanced myogenesis<sup>5</sup>.
- In STZ and ZDF rat models, icovamenib treatment induced modest appetite suppression and body weight reductions along with reductions in plasma triglyceride levels<sup>6,7</sup>.
- In ZDF rats, the combination of icovamenib and low dose semaglutide induced greater body weight reduction driven by fat mass loss with preservation of lean mass<sup>8</sup>.

### Combination Treatment of Icovamenib and Low Dose Semaglutide in ZDF Rats Induced Greater Body Weight Reduction, Driven by Fat Loss With Preservation of Lean Mass<sup>7</sup>



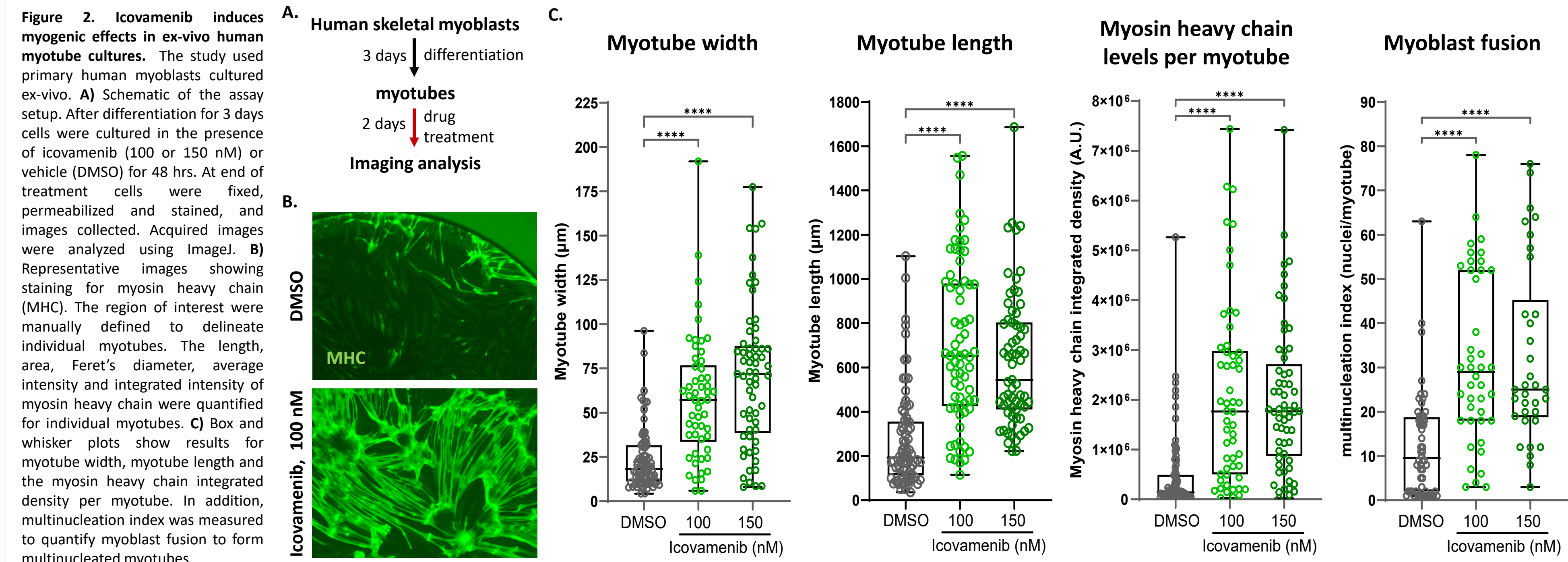
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## Figure 1: Icovamenib Enhanced GLP-1 Expression



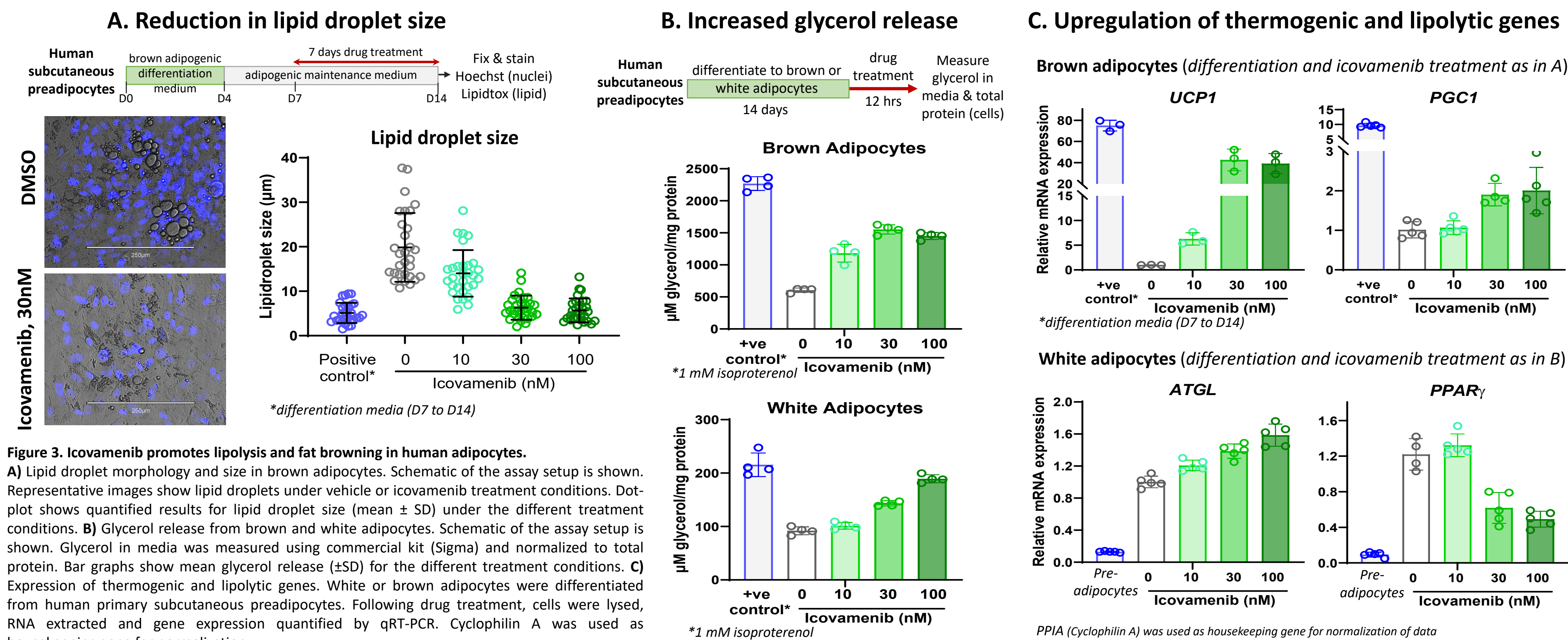
**Figure 1. Icovamenib increases intracellular proglucagon expression in the human colon cell line NCI-H716.** The human colon cell line NCI-H716 retains enteroendocrine characteristics and serves as an intestinal L cell model for studying GLP-1 expression and secretion. A) Schematic of the assay setup. Cells were cultured in the presence of icovamenib (100 nM or 300 nM) or vehicle and harvested at the specified time-points. Cell lysates were analyzed for proglucagon (surrogate for GLP-1) and menin protein levels by automated Western using JESS (ProteinSimple). B) Results from a representative experiment are shown. Vinculin served as the loading control. C) Bar charts depict the quantified results for intracellular levels of proglucagon (left) and menin (right) protein. The % protein in the icovamenib-treated samples are plotted relative to the protein level in the vehicle (DMSO)-treated samples.

## Figure 2: Icovamenib Induced Myogenic Effects in Human Skeletal Myoblast-derived Myotubes



**Figure 2. Icovamenib induces myogenic effects in ex-vivo human myotube cultures.** The study used primary human myoblasts cultured ex-vivo. A) Schematic of the assay setup. After differentiation for 3 days cells were cultured in the presence of icovamenib (100 or 150 nM) or vehicle (DMSO) for 48 hrs. At end of treatment cells were fixed, permeabilized and stained, and images collected. Acquired images were analyzed using ImageJ. B) Representative images showing staining for myosin heavy chain (MHC). The region of interest were manually defined to delineate individual myotubes. The length, area, Feret's diameter, average intensity and integrated intensity of myosin heavy chain were quantified for individual myotubes. C) Box and whisker plots show results for myotube width, myotube length and the myosin heavy chain integrated density per myotube. In addition, multinucleation index was measured to quantify myoblast fusion to form multinucleated myotubes.

## Figure 3: Icovamenib Promoted Lipolysis and Fat Browning in Human Adipose Tissue



**Figure 3. Icovamenib promotes lipolysis and fat browning in human adipocytes.** A) Lipid droplet morphology and size in brown adipocytes. Schematic of the assay setup is shown. Representative images show lipid droplets under vehicle or icovamenib treatment conditions. Dot-plot shows quantified results for lipid droplet size (mean  $\pm$  SD) under the different treatment conditions. B) Glycerol release from brown and white adipocytes. Schematic of the assay setup is shown. Glycerol in media was measured using commercial kit (Sigma) and normalized to total protein. Bar graphs show mean glycerol release ( $\pm$ SD) for the different treatment conditions. C) Expression of thermogenic and lipolytic genes. White or brown adipocytes were differentiated from human primary subcutaneous preadipocytes. Following drug treatment, cells were lysed, RNA extracted and gene expression quantified by qRT-PCR. Cyclophilin A was used as housekeeping gene for normalization.

## Conclusions

- The overall findings provide insights into icovamenib's potential to activate mechanisms that support metabolic health, including enhancing glycemic control, fat reduction and muscle preservation.
- Icovamenib induced dose-dependent increase in GLP-1 expression in the human colon cell line as well as GLP-1 receptor expression in human islets<sup>9</sup>, properties that can promote incretin effects.
  - In primary human skeletal myoblast-derived myotubes, icovamenib induced myogenic effects evidenced by:
    - dose-dependent increase in myotube width and length
    - upregulation of myosin heavy chain protein levels, and
    - increased myoblast fusion to form multinucleated myotubes
  - Icovamenib promoted adipocyte browning and lipolysis evidenced by:
    - reduction in lipid droplet size
    - increased glycerol release, and
    - modulation of UCP1, PGC1, ATGL and PPAR $\gamma$ , key molecular regulators in triglyceride hydrolysis and energy metabolism
  - Collectively these findings suggest that icovamenib activates complimentary biological pathways promoting metabolic health and support icovamenib's potential for treating obesity in addition to diabetes. These observations warrant further evaluation of icovamenib as part of combination therapy approaches with GLP-based agents.