# DA-1726, A Next Gen. Anti-Obesity Drug Candidate

차세대 비만치료제 후보물질, DA-1726

May 29, 2024

Head of Dong-A ST Research HQ

**Mi-Kyung Kim, PhD**

NeuroBo PHARMACEUTICALS

DONG-A ST

# Disclosure

- Dong-A ST Co., Ltd | Vice President, Stockholder
- NeuroBo Pharmaceuticals, Inc. | Consulting Chief Scientific Officer

# Evolution of GLP1 Analogs Therapeutics

**1900-1960**

1906 Intestinal extracts decrease glycosuria in diabetes
**1923 Discovery of glucagon**
**1929 Intestinal extracts lower blood glucose via "incretin"**
1964 Greater insulin rise when glucose is given orally vs. IV "incretin effects"

**1970-2000**

**1970 ID of first incretin, GIP** isolated from intestinal preparations
1973 GIP stimulates insulin secretion in humans
**1986 ID of GLP1 as 2nd incretin hormone**
1993 DPP4 cleaves incretin/Discovery of GLP1R agonist, **exendin-4**
1997 GLP1 decrease food intake and body composition

**2005-present**

**2005 Approval of exenatide (BID)** as T2D Tx
2006 Approval of DPP4 inhibitor, sitagliptin as T2D Tx
2009 Discovery of first dual agonists for GLP1R and GCGR
**2010 Approval of liragluglide (QD) as T2D Tx**
2013 Discovery of dual agonists for GLP1R and GIPR
**2014 Approval of dulaglutide (QW)** as T2D Tx
2015 Discovery of triple agonists for GLP1R, GCGR, and GIPR
2016 Approval of lixisenatide as T2D Tx
2018/**2019 Approval of semaglutide** (QW for sc, **QD for po**) for T2D
**2022 Approval of dual agonist tirzepatide** for T2D

- 2014 Approval of **high dose liraglutide (QD)**
- 2021 Approval of **high dose semaglutide (QW)**
- 2023 Approval of **dual agonist tirzepatide** for obesity

Science Translational Medicine, 2023, 15(723)
DOI: 10.1126/scitranslmed.adh4453

# Proglucagon-Derived Peptides

*Int J Mol Sci, 2019;20(14):3532*
*Front Endocrinol, 2021(12):689678. doi:10.3389/fendo.2021.689678*

GIP:
GLP-1: glucagon-like peptide-1
PC: Prohormone convertase

```
Glucagon HSQGTFTSDYSKYLDSRRAQDFVQWLMNT-OH
GIP      YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ-OH
GLP-1    HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG-OH
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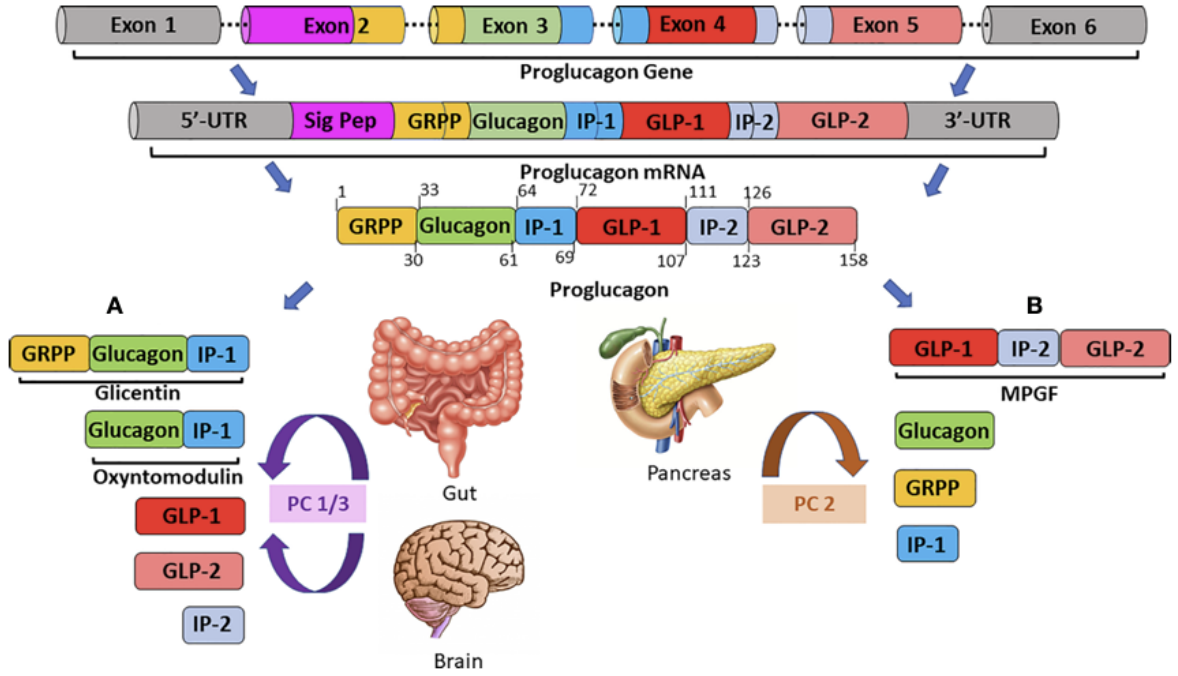
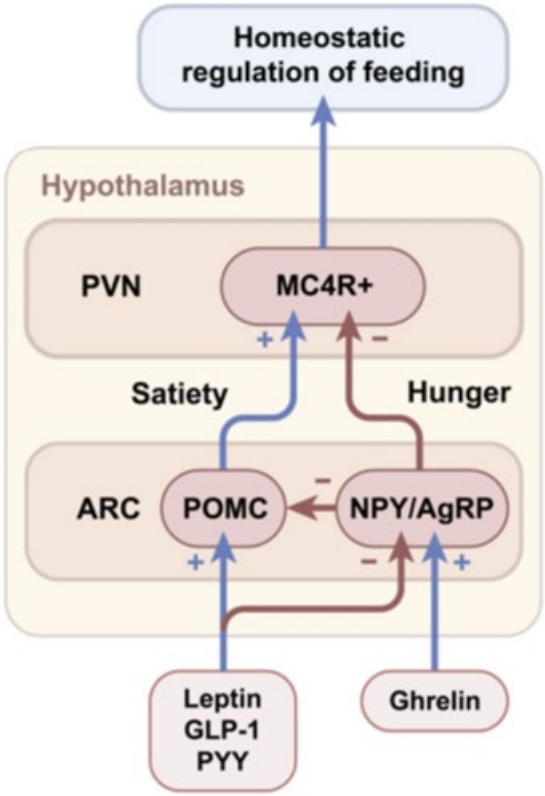
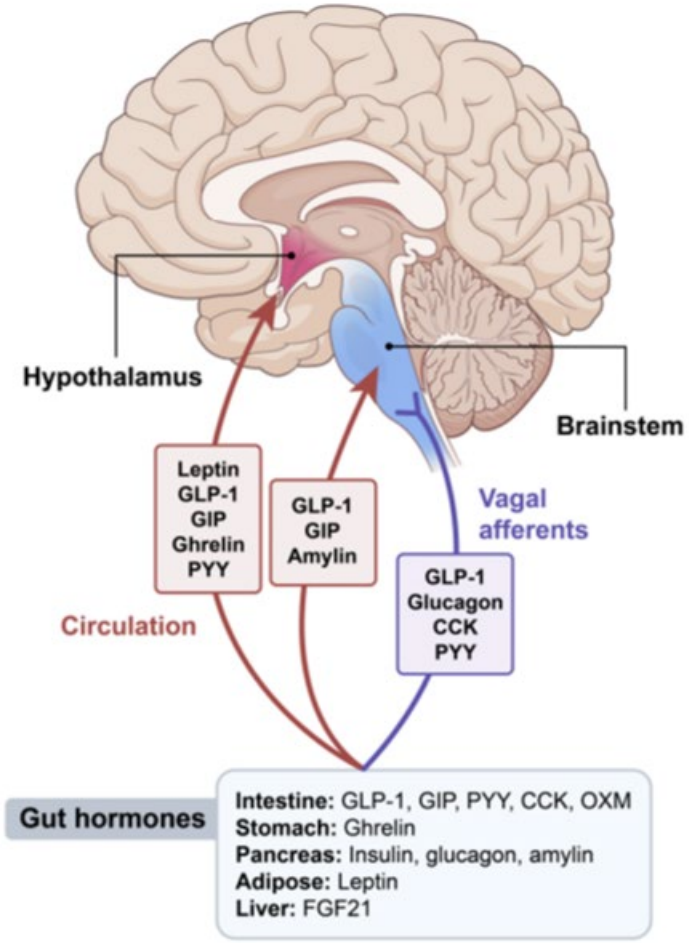



**FIGURE 1** | A schematic overview of tissue-specific proglucagon processing in the gut/brain **(A)** and in the pancreas **(B)**. The proglucagon gene, located on chromosome 2 and comprised of 6 exons, is transcribed to generate proglucagon messenger RNA (mRNA). Proglucagon mRNA is subsequently translated to yield the 158 residue, precursor protein, proglucagon. In enteroendocrine L-cells of the ileum and colon **(A)** proglucagon is processed by prohormone convertase 1/3 (PC1/3) to generate glicentin, oxyntomodulin, glucagon-like peptides-1 and -2 (GLP-1, GLP-2) and intervening peptide-2 (IP-2). Conversely, in pancreatic alpha-cells **(B)**, post-translational modification by prohormone convertase 2 (PC2) is responsible for the generation of the major proglucagon fragment (MPGF), glucagon, glicentin-related pancreatic polypeptide (GRPP) and intervening peptide-1 (IP-1).

# Anorexic Effects Induced by Gut Hormones



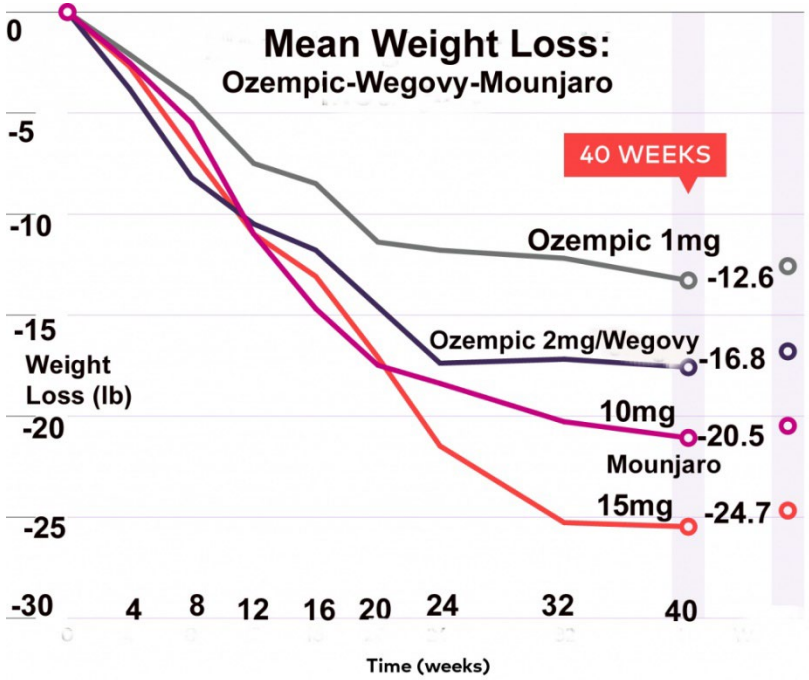




"Success with GLP-1 drug treatment means a *weight loss of more than 5% after 3 months* of treatment. However, in clinical practice, a weight loss of at least 10 to 15% or more is achieved to achieve more meaningful metabolic health."

*Int J Mol Sci, 2023;24:3384*

# Obesity Game Changer

- Obesity treatment market expected to rise rapidly
- Two lipidated long-acting peptide drugs:
  Wegovy™ vs. Mounjaro™
- Unmet needs: injection, muscle loss, yo-yo effect




| | Zepbound® (tirzepatide) | Wegovy® (semaglutide) |
|---|---|---|
| *Manufacturer* | Eli Lilly & Co. | Novo Nordisk |
| *FDA Approved* | Nov 2023 for Obesity | June 2021 for Obesity |
| *Delivery* | Once weekly injection | Once weekly injection |
| *Dose range* | 2.5 mg - 15.0 mg | 0.25 mg - 2.4 mg |
| *Targets* | GLP-1 and GIP | GLP-1 |
| *Most common side effects* | Nausea, diarrhea, constipation, vomiting | Nausea, diarrhea, vomiting, constipation |
| *Avg. weight loss in clinical trials* | 22.5% of body weight after 72 weeks (15 mg) [3] | 14.9% of body weight after 68 weeks (2.4 mg) [4] |

ONCE-WEEKLY wegovy® semaglutide injection 2.4 mg

RYBELSUS® semaglutide tablets 7mg | 14mg

once weekly mounjaro® (tirzepatide) injection 0.5 mL
2.5 mg | 5 mg | 7.5 mg | 10 mg | 12.5 mg | 15 mg

once weekly zepbound® (tirzepatide) injection 0.5 mL
2.5 mg | 5 mg | 7.5 mg | 10 mg | 12.5 mg | 15 mg

https://www.richardlipmanmd.com

# Anti-Obesity Pipeline (Phase 2 to Phase 3)

GLP1 analogue injection

- Beinaglutide (P3)
- Ecnoglutide (P3)
- Glutazumab (P3)
- GZR-18 (P2)
- TG-103 (P2)

GLP1+ injection

GLP1R/GCGR

- Survodutide (P3, BI)
- Mazdutide (P2, Lilly)
- Pegapamodutide (P2) → ???
- Pemvidutide (P2, Altimmune)

GLP1R/GIPR

- Tirzepatide (Launched, Lilly)
- AMG-133 (P2, Amgen) → GIPR ant
- CT-868 (P2, Carmot)
- HRS-9531 (P2, Jiangu Hengrui; CN)
- VK-2735 (P2, Viking)

GLP1R/GIPR/GCGR

- Retatrutide (P3, Lilly)
- HM-15275 (P1, Hanmi)

GLP1+Amylin analoges combo

- Cagrilintide/Semaglutide (P3, NN)

GLP1/GLP1+ Oral formulation

- Semaglutide oral (P3)

Non-peptide GLP1RA

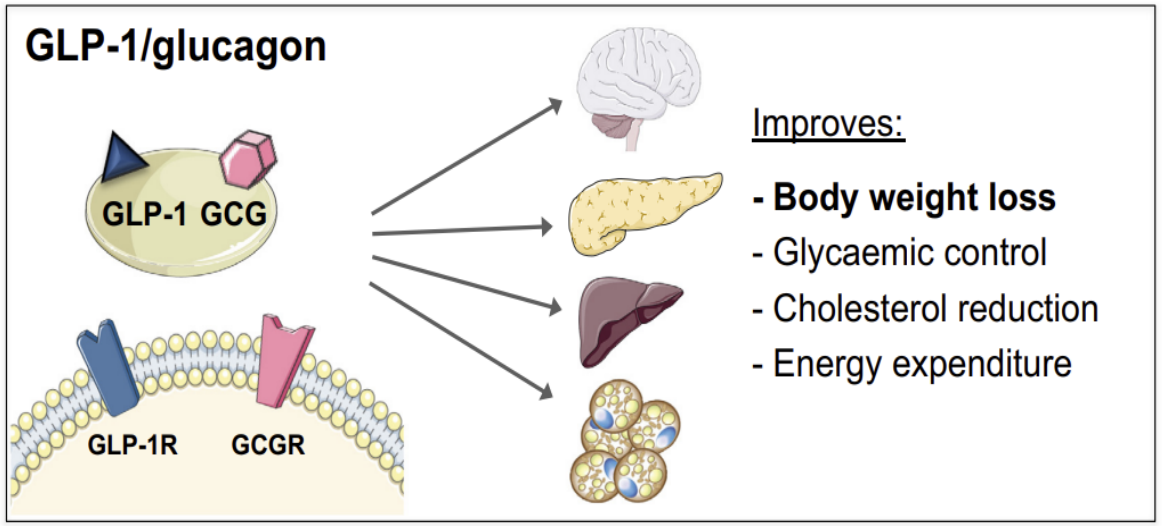
- Orforglipron (P3, Lilly) → -14.7% BWL, -2.1%P HbA1c reduction in P2
- Danuglipron (P2, Pfizer; BID) → discontinued IR and switched to SR Rx
- Lotiglipron (P2, Pfizer; QD) → discontinued due to DILI (Jun 2023)
- GSBR-1290 (P2, Structure Therapeutics)

# Next-Generation Anti-Obesity Drugs

*To lead additive BWL via enhancing basal metabolic rate*

**"New Long-Acting and Dual GLP1R/GCGR Agonists and a Novel Appetite-Regulating Drug Expected to Drive Obesity Market Growth During the Next Decade"**

*(Source: GlobalData Report_Obesity: Competitive Landscape to 2026_Oct 2018)*



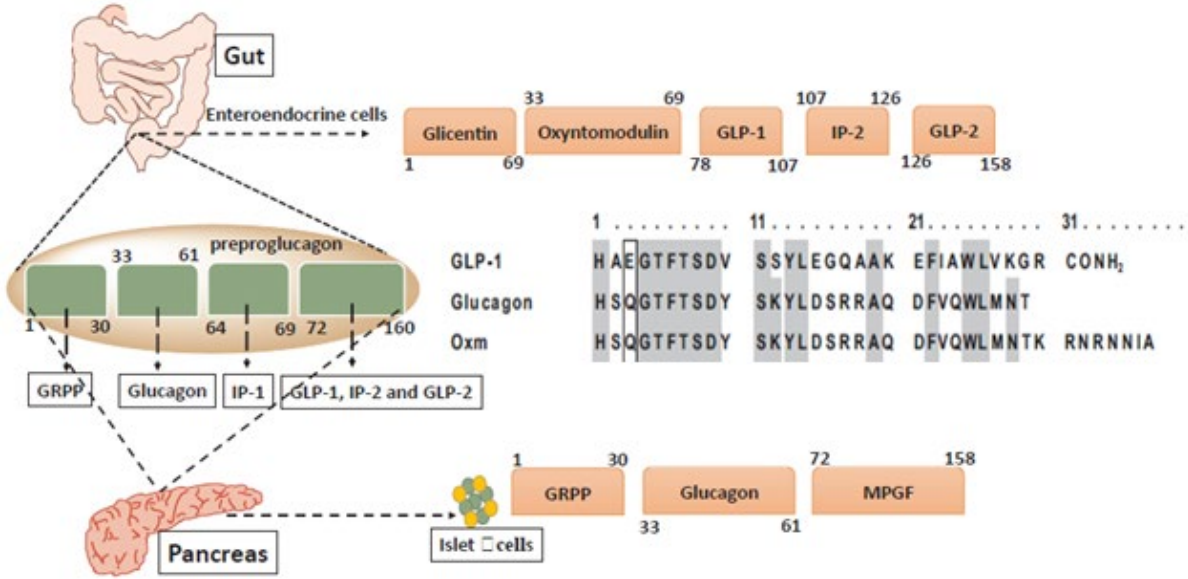

*Journal of Internal Medicine, 2018, 284; 581–602*

- Need to be optimized to maximize weight loss, without disrupting glucose homeostasis, while minimizing GI adverse events
- Additional benefits of glucagon to reduce hepatic lipid synthesis and promote lipid oxidation for the treatment of NASH

# GLP1/Glucagon (GCG) Receptor Dual Agonist

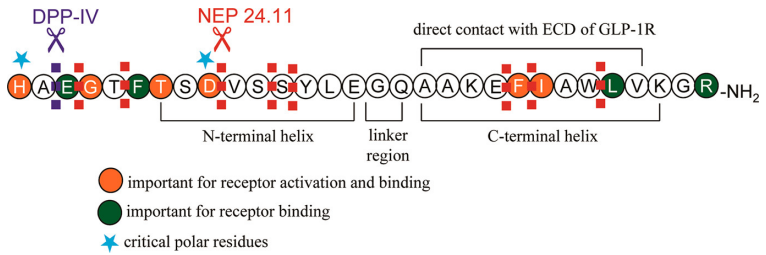
*Oxyntomodulin as an endogenous dual agonist*

- Secreted from intestinal L cells after meal ingestion
- Glucagon + N-terminal octapeptide (37-residue)
- Dual weak, but full agonist of GLP-1 receptor and glucagon receptor
- Rapidly degraded by DPP4 enzyme ($T_{1/2}$ ≈ 12 min)
- Reduces food intake + Increases energy expenditure



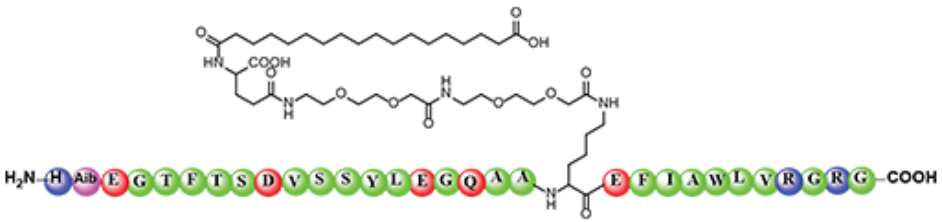

## In the case of Semaglutide

**GLP1 ($t_{1/2}$,1~2 min)**




- *Peptide substitution*
- *Lipidation*

**Semaglutide ($t_{1/2}$, ~6.7 days in humans)**

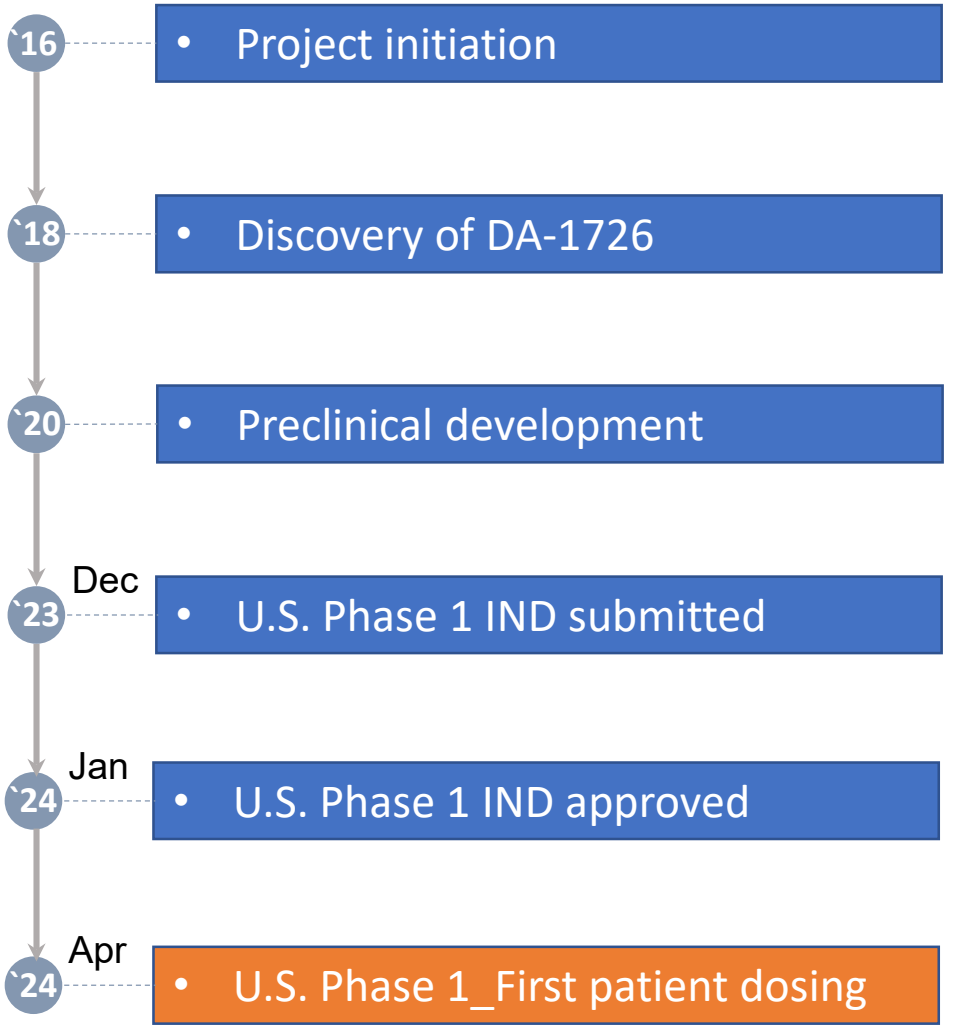


J Med Chem, 2015:58(3):1020–1037

# Dong-A's Clinical Candidate

- DA-1726

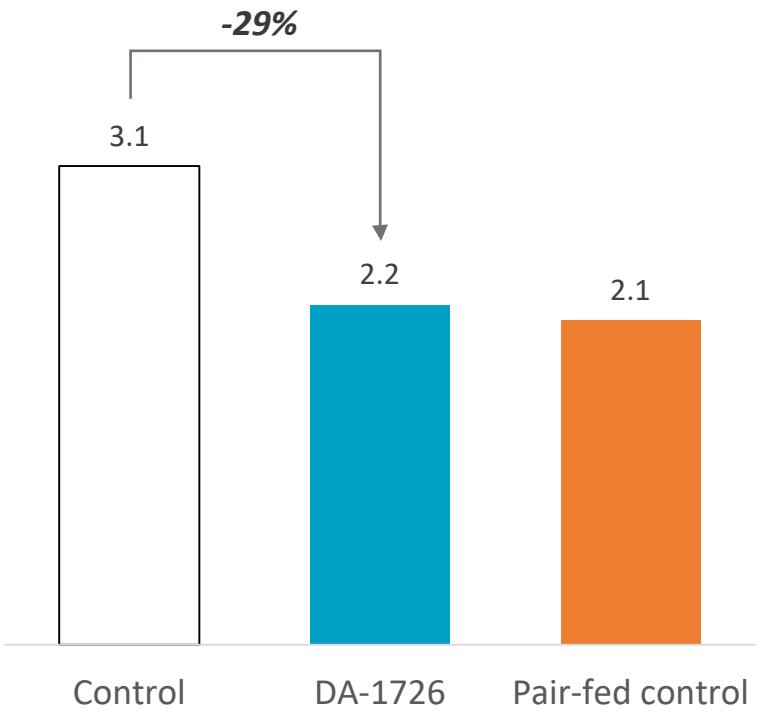
- 37 amino-acid-long *synthetic peptide* drug candidate
- Prolonged half-life *enabling once weekly s.c. injection*
- *Well-balanced activity* between GLP1 and GCG receptors
- BWL effects through *reducing food intake* and *enhancing peripheral metabolism*



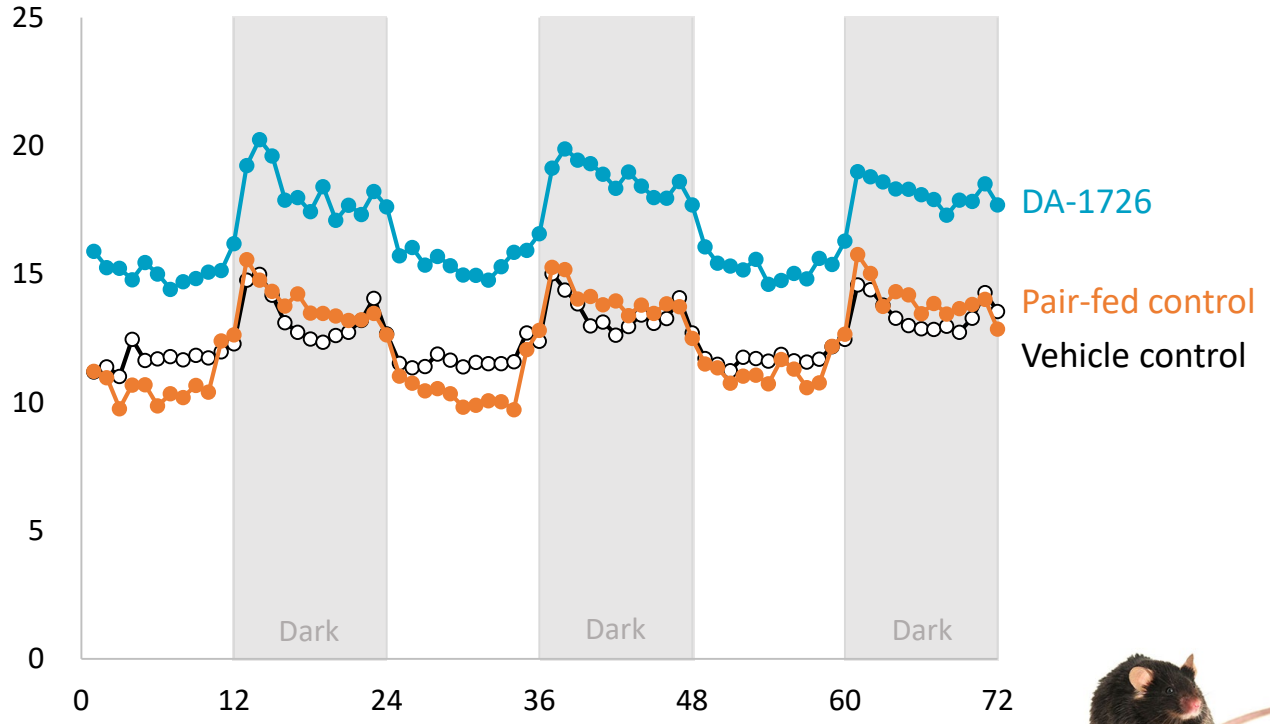
# Mode of Action for Weight Loss Effects

*DA-1726* ***reduces diet consumption*** *and* ***enhances basal metabolic rate***

Daily food intake
(g/mouse)



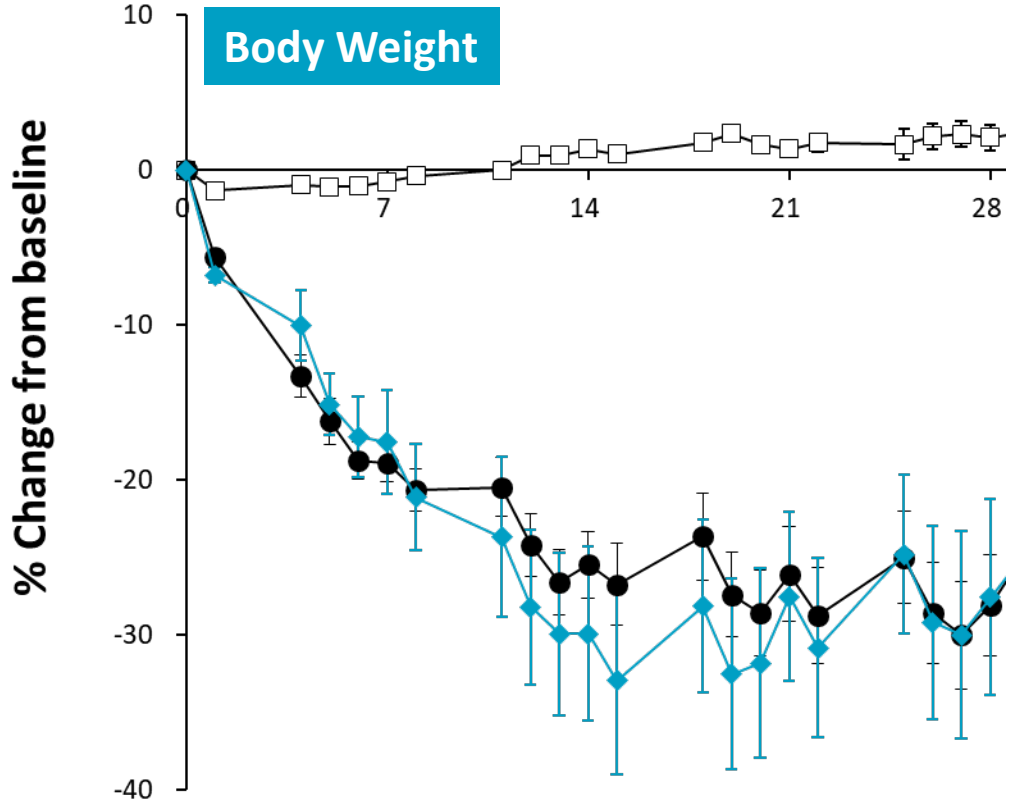

Energy expenditure
(kcal/kg/hr)




Kim TH et al., 82nd Scientific Sessions of ADA, Jun 3-7, 2022, New Orleans, LA (1403-P)

# Strong Competitiveness in BWL Effect

*BWL efficacy comparable to **Tirzepatide** (FiC GLP1/GIP receptors dual agonist)*




Vehicle control

Tirzepatide 100 nmol/kg/BIW

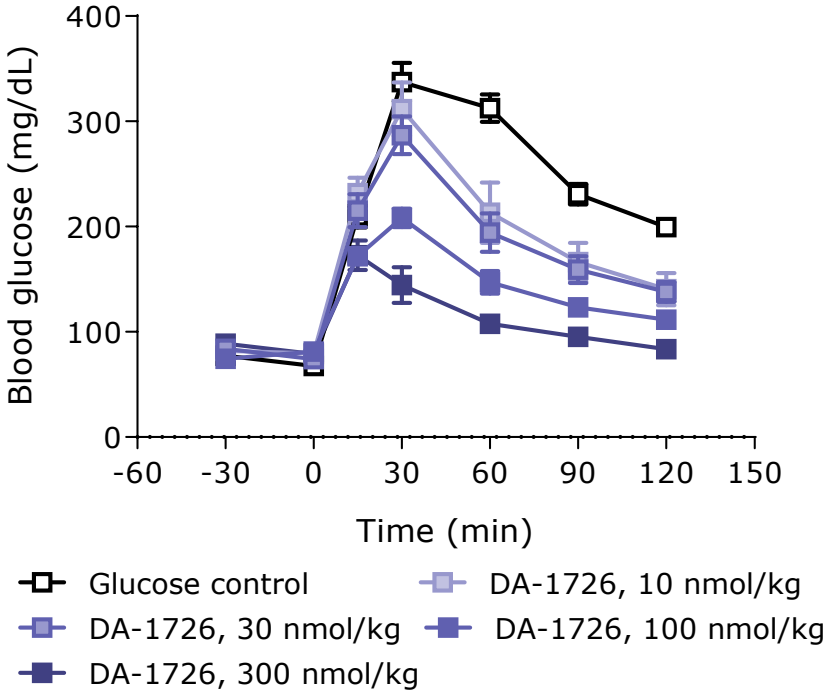
DA-1726 200 nmol/kg/BIW

Kim TH et al., 83rd Scientific Sessions of ADA, Jun 23-26, 2023, San Diego, CA (1668-P)

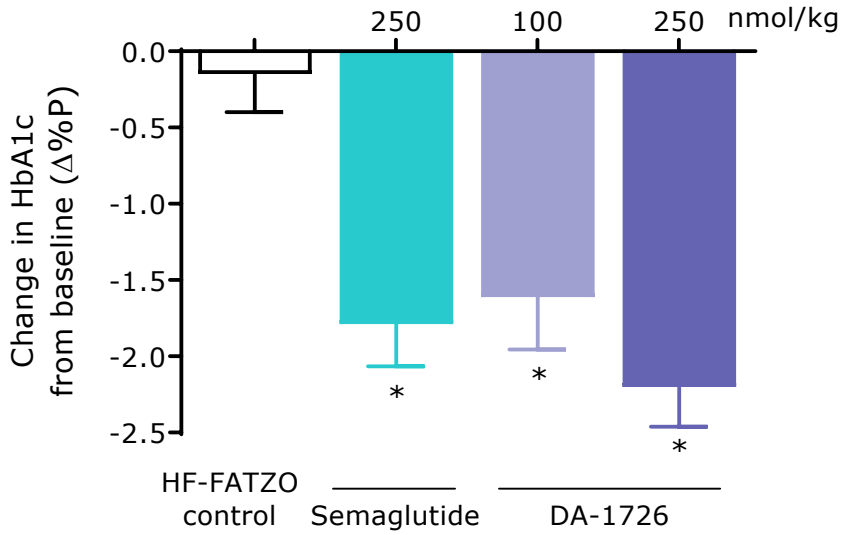
# Sustained Glucose-Lowering Effect

*Obesity and hyperglycemia can be controlled **simultaneously** unlike other previous clinical candidate*

## OGTT - Postprandial Effect




## Hemoglobin A1c

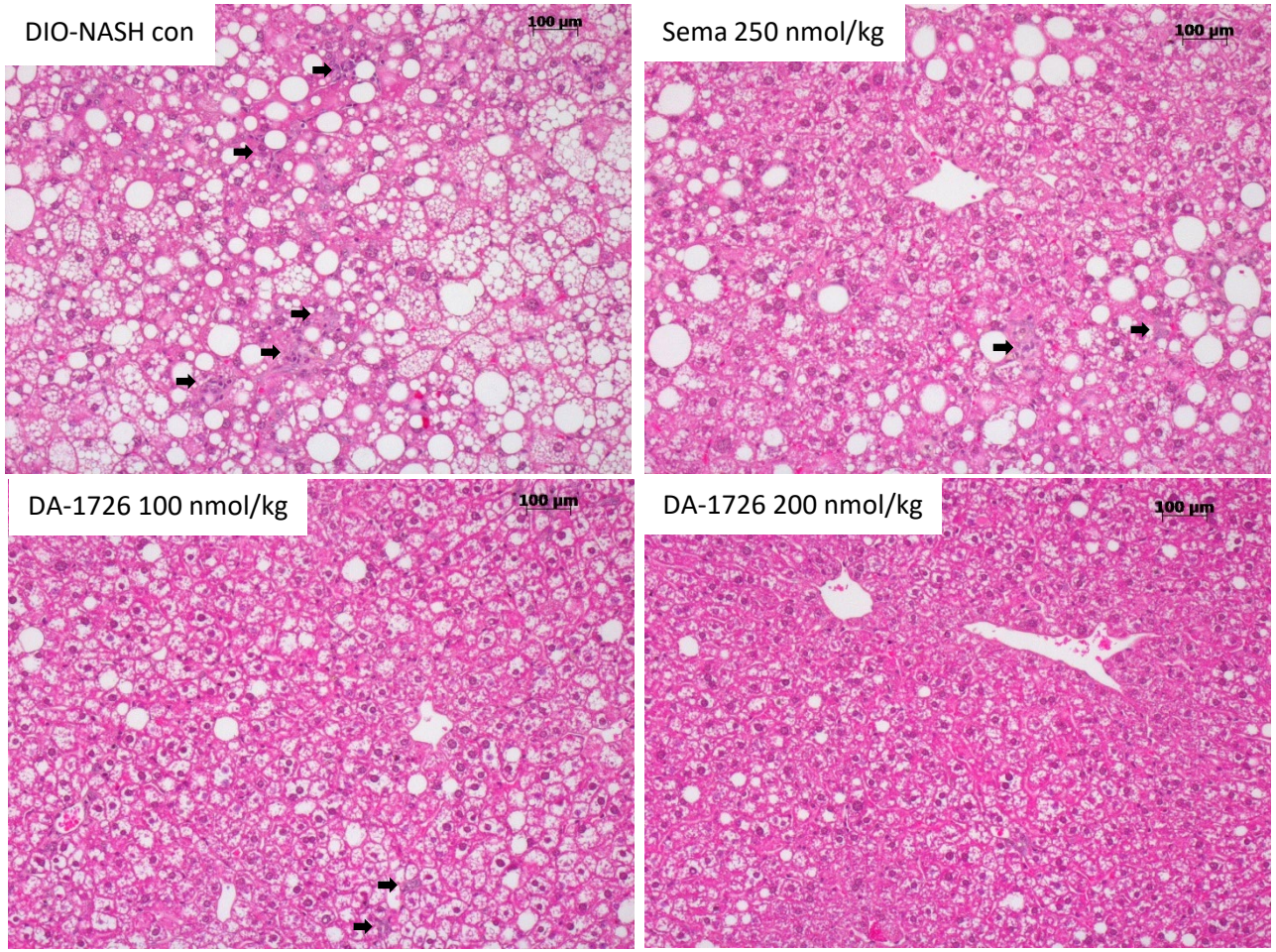



Mean±SEM, *P<0.05 vs. HF-FATZO control, One-way ANOVA

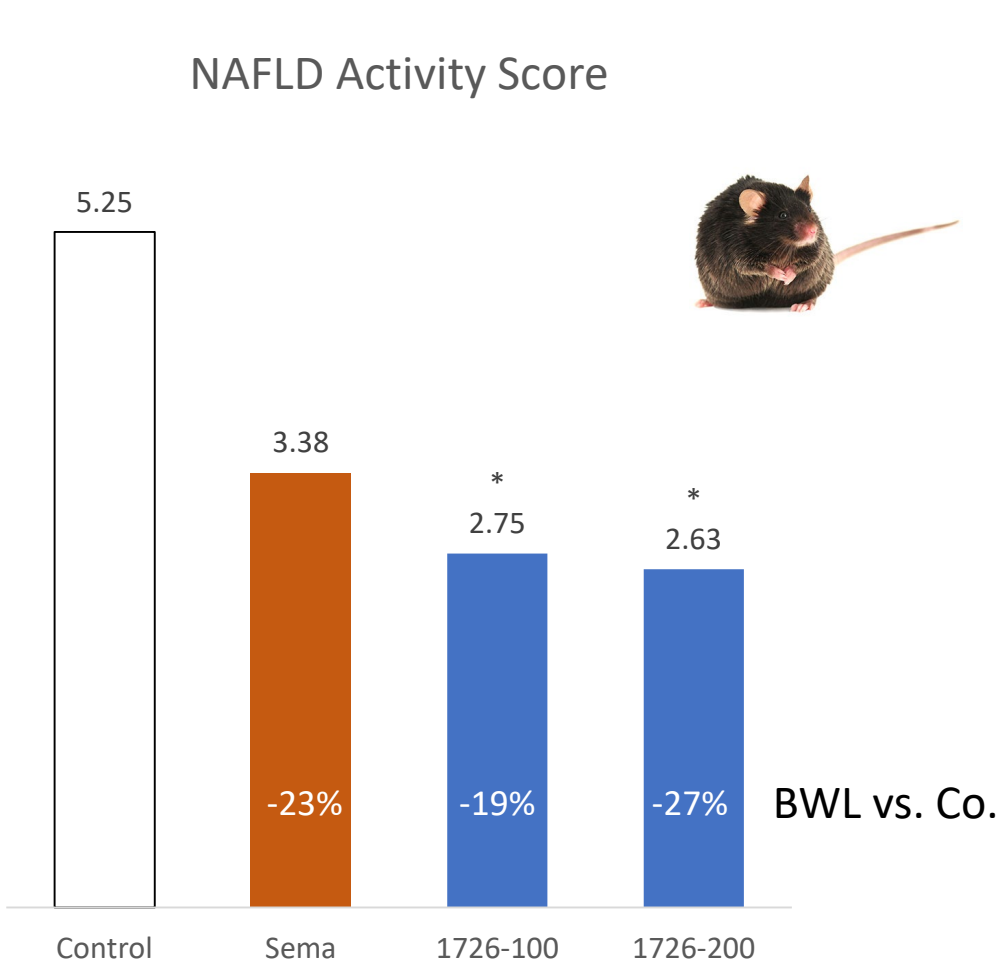
Kim TH et al., 82nd Scientific Sessions of ADA, Jun 3-7, 2022, New Orleans, LA (1403-P)

# Potential Anti-MASH Effect

*Higher anti-MASH effect compared to **Semaglutide** after 8-week treatment in DIO-MASH mice*




Arrow: inflammation foci




Chae YN et al., 82nd Scientific Sessions of ADA, Jun 3-7, 2022, New Orleans, LA (1333-P)

# A Next Generation Anti-Obesity Drug Candidate, DA-1726

**Strong body weight loss effect comparable to Tirzepatide**

**Well-balanced activity between GLP-1 and GCG receptors**

: Little risk in hypoglycemia and hyperglycemia

: Body weight loss effect along with strong glucose-lowering effect

**Best-in-class potential drug candidate under Phase 1 development**