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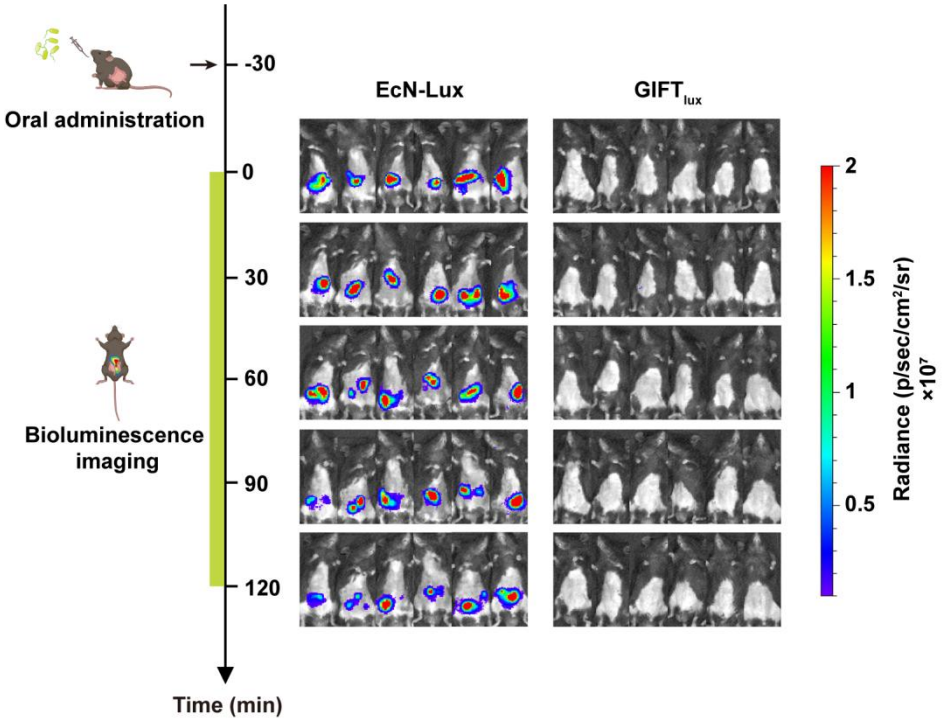
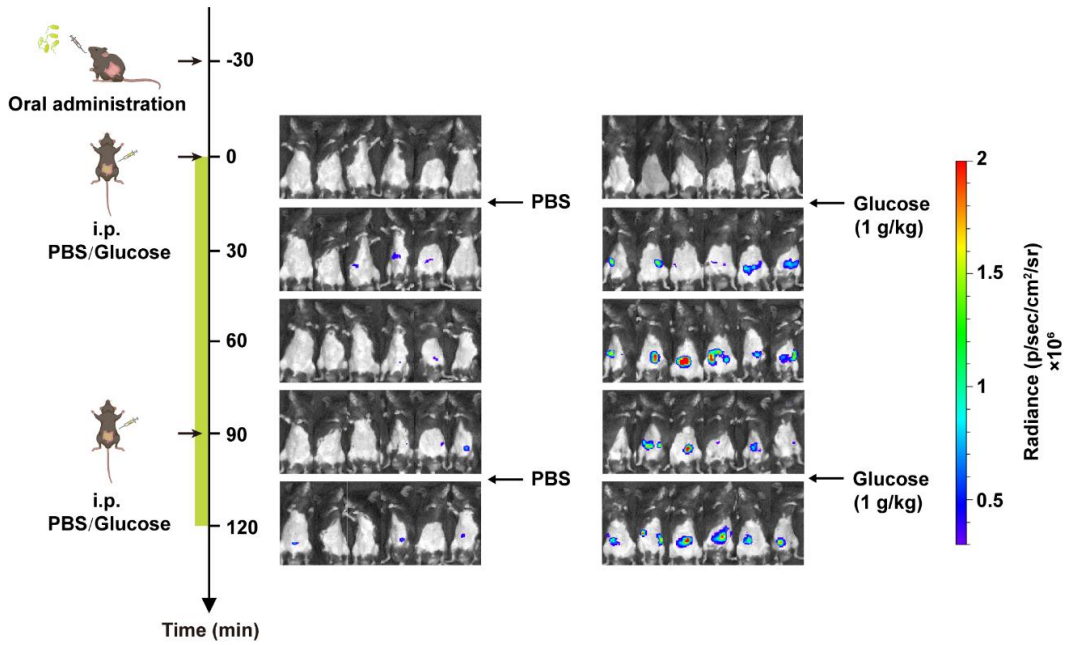
Supplementary information

Glucose-responsive probiotics for glycaemic modulation in mice and monkeys

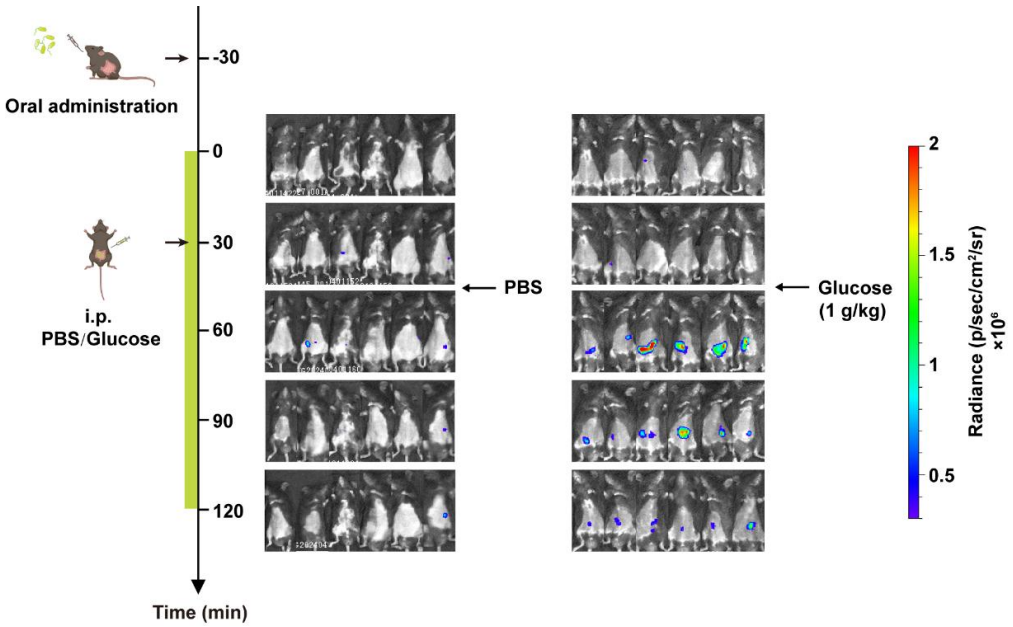
In the format provided by the authors and unedited



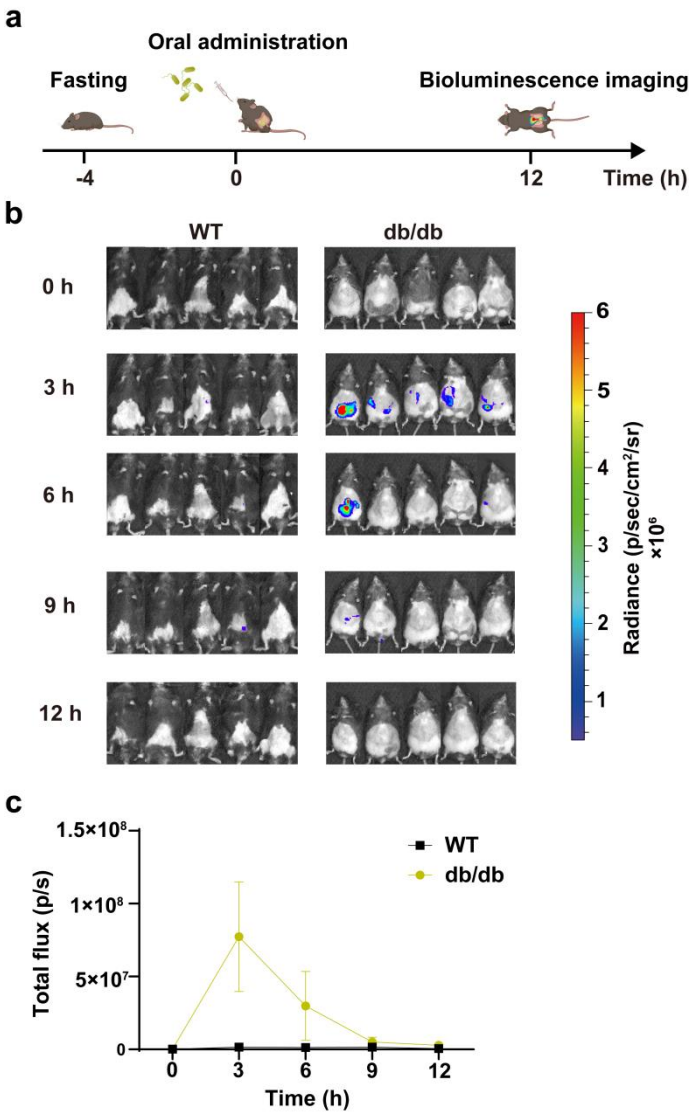
Supplementary Fig. 1. Constitutive and GIFT-mediated gene expression kinetics in wild-type mice. After a 4-hour fast, wild-type mice were orally administered either EcN constitutively expressing LuxCDABE (EcN-Lux) or $GIFT_{Lux}$ cells (10^9 CFU). Imaging was performed every 30 min using an *in vivo* imaging system.



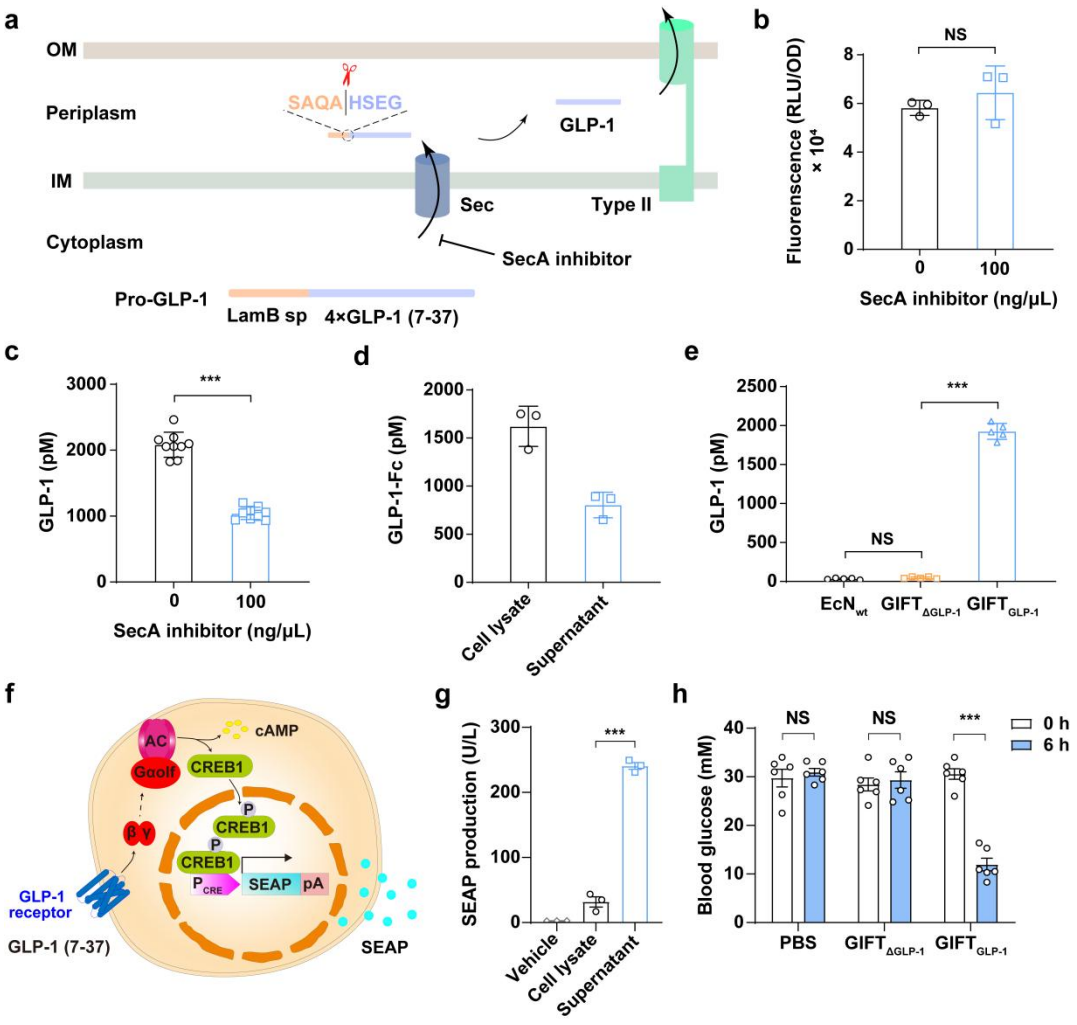
Supplementary Fig. 2. GIFT-mediated gene expression kinetics (ON-OFF-ON) in wild-type mice. After a 4-hour fast, wild-type mice were orally administered $GIFT_{Lux}$ cells (10^9 CFU) at -30 min, followed by intraperitoneal injection (i.p.) of PBS or glucose (1 g/kg) at 0 and 90 min. Imaging was performed every 30 min using an *in vivo* imaging system.



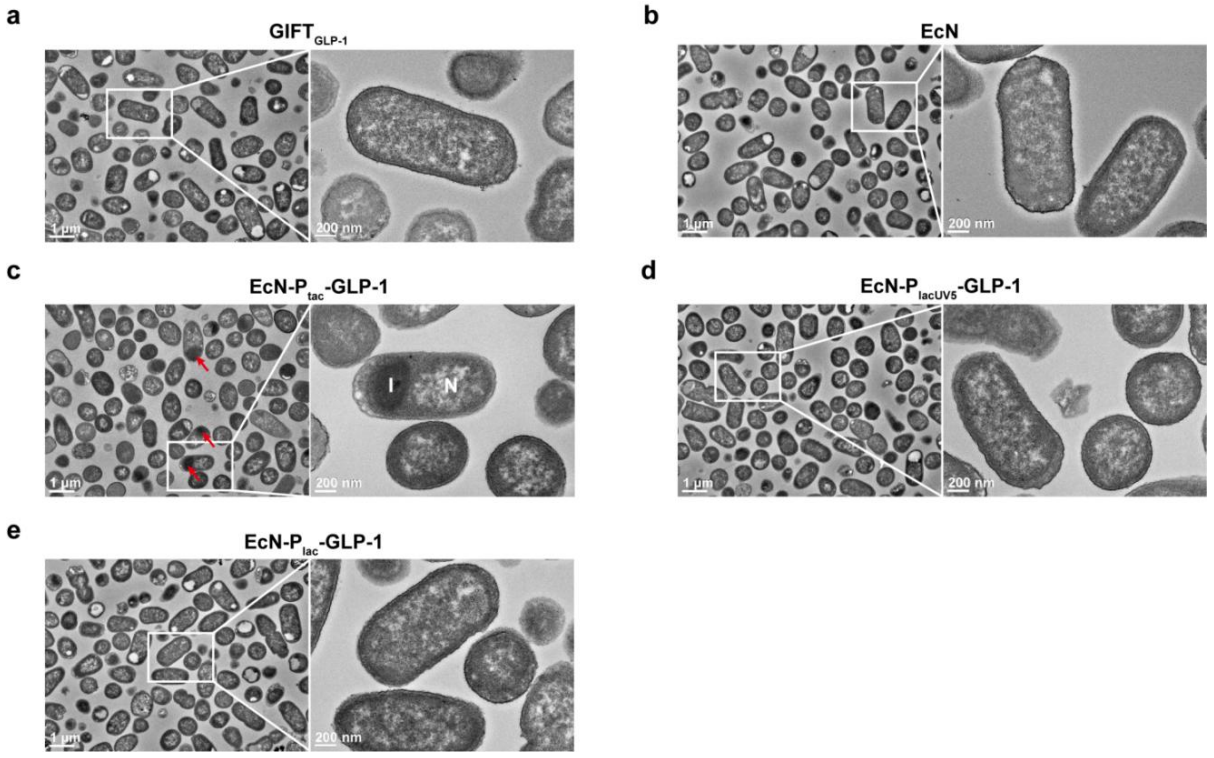
Supplementary Fig. 3. GIFT-mediated gene expression kinetics (OFF-ON-OFF) in wild-type mice. After a 4-hour fast, wild-type mice were orally administered $GIFT_{Lux}$ cells (10^9 CFU) at -30 min, followed by intraperitoneal injection (i.p.) of PBS or glucose (1 g/kg) at 30 min. Imaging was performed every 30 min using an *in vivo* imaging system.



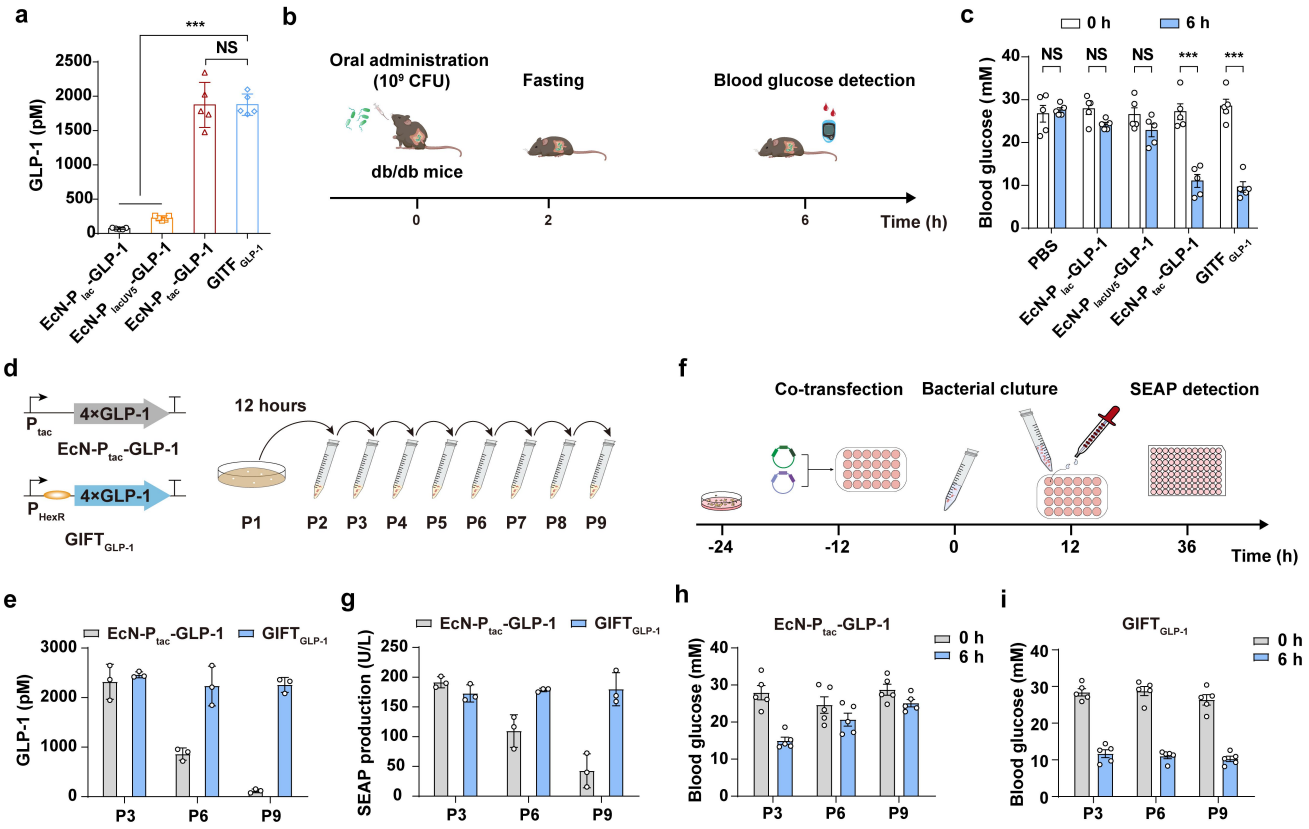
Supplementary Fig. 4. Time-dependent GIFT-mediated gene expression kinetics in wild-type and db/db mice. a, The time schedule for GIFT-mediated gene expression after oral delivery to mice. After fasting for 4 hours, wild-type (WT) and db/db mice were orally administered $GIFT_{Lux}$ cells (10^9 CFU). The imaging was performed every 3 hours using an *in vivo* imaging system. **b**, Detailed images of the bioluminescence in mice. **c**, Quantification of the bioluminescence signals in **b**. Data are expressed as means ± SEM; *n* = 5 mice.



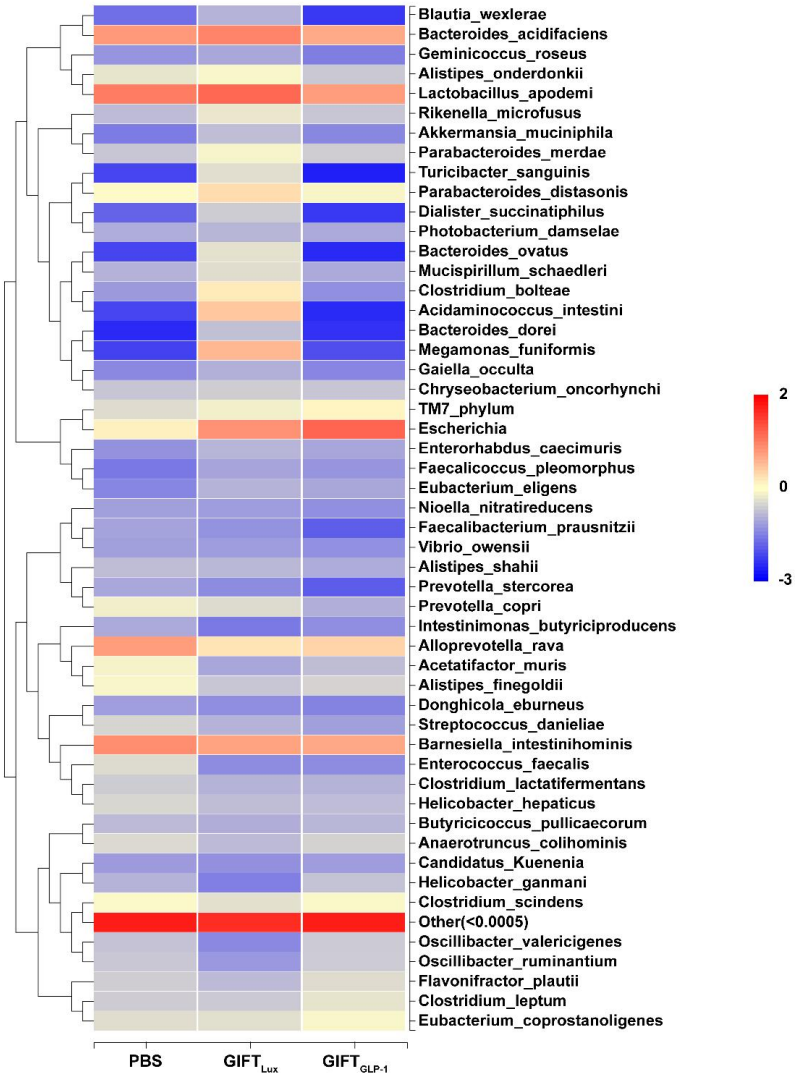
Supplementary Fig. 5. Effect of secretion signal peptide on GLP-1 secretion. a, Schematic illustration of GLP-1 secretion by $GIFT_{GLP\text{-}1}$ cells mediated by the LamB signal peptide. Upon glucose induction, $GIFT_{GLP\text{-}1}$ cells express a Pro-GLP-1 construct [LamB-4×GLP-1 (7-37)], which is translocated across the inner membrane (IM) via the Sec-dependent secretion pathway—a process that can be inhibited by SecA inhibitors. Within the periplasm, the LamB signal peptide (sp) is cleaved, and the mature GLP-1 fragment (residues 7-37) is subsequently transported across the outer membrane (OM) via the type II secretion system into the extracellular environment. **b**, **c**, Effect of SecA inhibition on protein expression (**b**) and GLP-1 secretion (**c**) by $GIFT_{GFP}$/$GIFT_{GLP\text{-}1}$ cells. **d**, Quantification of GLP-1-Fc [GLP-1 (7-37) fused to human IgG] levels in the supernatant and cell lysate of $GIFT_{GLP\text{-}1\text{-}Fc}$ (GIFT-medaited GLP-1-Fc secretion) cells. **e**, GLP-1 levels in the culture supernatant of wild-type EcN (EcN_{wt}) and GIFT cells expressing GLP-1 with ($GIFT_{GLP\text{-}1}$) or without ($GIFT_{\Delta GLP\text{-}1}$) the LamB secretion signal peptide. **f**, Schematic illustrating the detection of biologically active GLP-1 in culture supernatants or cell lysates from $GIFT_{GLP\text{-}1}$. **g**, SEAP production of HEK-293T cells treated with the culture supernatant or cell lysate of $GIFT_{GLP\text{-}1}$. **h**, Blood glucose levels of db/db mice treated with PBS, $GIFT_{GLP\text{-}1}$, or $GIFT_{\Delta GLP\text{-}1}$. Data in **b-e**, **g** are expressed as means ± SD; n = 3 independent experiments in **b**, **d**, and **g**, n = 9 independent experiments in **c**, n = 5 independent experiments in **e**. Data in **h** are expressed as means ± SEM; n = 6 mice. P-values were calculated using a two-tailed unpaired t-test (**b**, **c**), one-way ANOVA (**e**, **g**), or two-way ANOVA (**h**). NS, not significant; ***$P < 0.001$. Detailed statistics are provided in Supplementary Table 16.



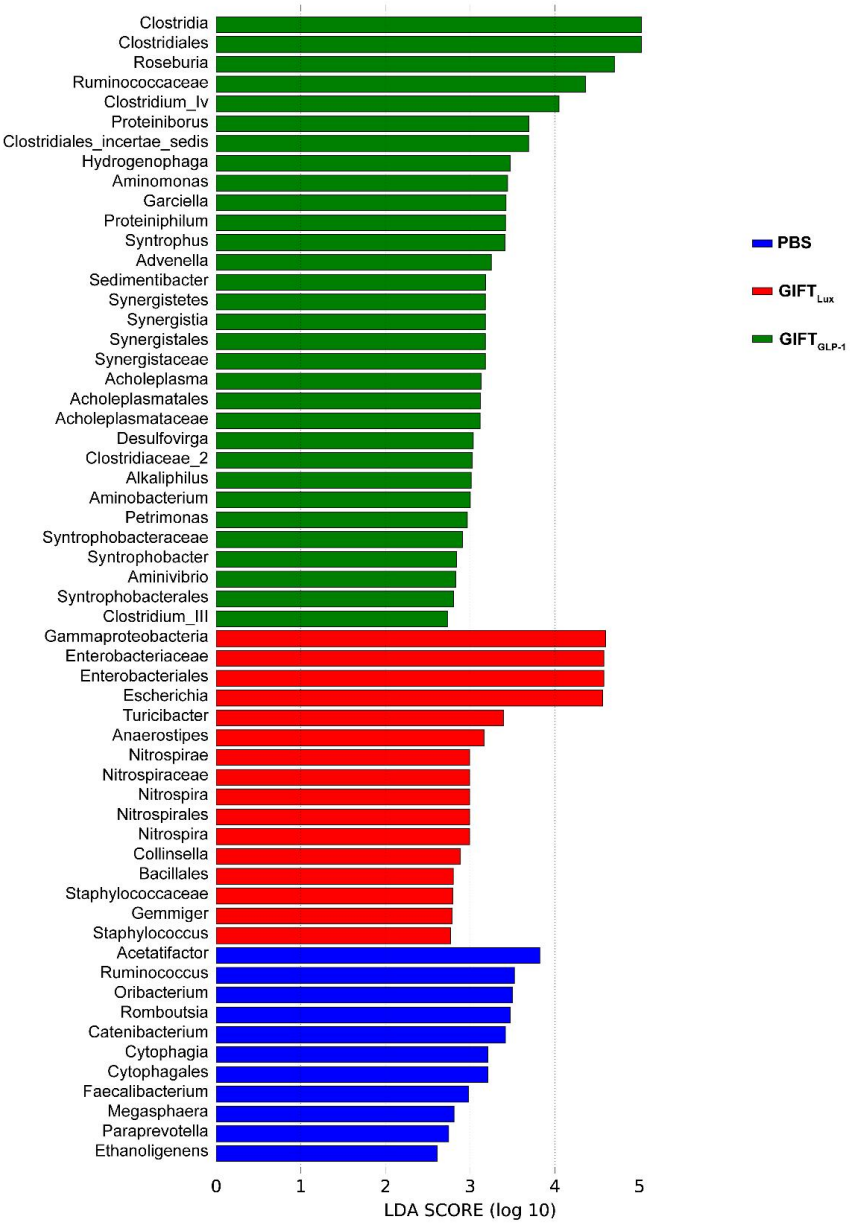
Supplementary Fig. 6. Transmission electron microscopy (TEM) images showing inclusion body formation in engineered EcN cells. $GIFT_{GLP-1}$ (**a**), EcN (**b**), and EcN transformed with constitutive GLP-1 expression plasmids driven by P_{tac} (**c**), P_{lacUV5} (**d**), or P_{lac} (**e**) were cultured for 12 h before TEM analysis. Red arrows indicate the location of inclusion bodies. Inclusion bodies (I) and the nuclear region (N) are indicated. The images are representative of three independent experiments with similar results.



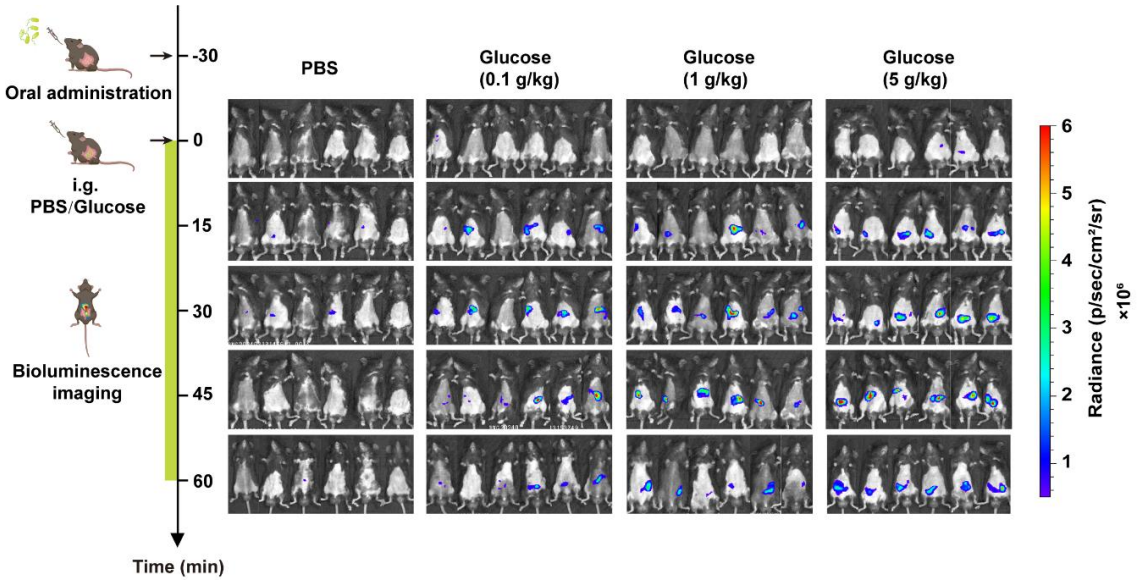
Supplementary Fig. 7. A comparison between glucose-responsive regulation and constitutive expression of GLP-1. a, GLP-1 concentrations in the culture supernatant of either $GIFT_{GLP-1}$ cells or constitutive GLP-1 constructs driven by different promoters. Cells were induced with 15 mM glucose for 12 hours, and GLP-1 levels were measured by ELISA. **b**, Time schedule for oral administration of $GIFT_{GLP-1}$ or constitutive GLP-1 expression cells for glycemic control in db/db mice. **c**, Blood glucose levels (fasting for 4 hours). **d**, Schematic of the time schedule for sub-culturing the engineered strains. $GIFT_{GLP-1}$ cells and EcN transformed with a plasmid for constitutive GLP-1 expression driven by a P_{tac} promoter (EcN-P_{tac}-GLP-1) were cultured in LB medium, with a 1% inoculum sub-cultured every 12 hours. **e**, ELISA for GLP-1 secreted by EcN-P_{tac}-GLP-1 and $GIFT_{GLP-1}$ cells across different generations. **f**, Schematic of the time schedule for detection of the biological activity of GLP-1 produced by EcN-P_{tac}-GLP-1 and $GIFT_{GLP-1}$ cells. EcN-P_{tac}-GLP-1 cells and $GIFT_{GLP-1}$ cells from the 3rd, 6th, and 9th subcultures were inducted with 15 mM glucose for 8 hours, and the culture supernatant was supplemented to HEK-293T cells expressing the GLP-1 receptor (GLP1R) and a SEAP reporter driven by a P_{CRE} promoter. **g**, SEAP production of HEK-293T cells treated with the culture supernatant of EcN-P_{tac}-GLP-1 and $GIFT_{GLP-1}$ cells. **h**, **i**, Blood glucose levels of db/db mice treated with EcN-P_{tac}-GLP-1 cells (**h**) and $GIFT_{GLP-1}$ cells (**i**) from the 3rd, 6th, and 9th subcultures. Data in **a, e,** and **g** are expressed as means ± SD; *n* = 5 independent experiments in **a**, *n* = 3 independent experiments in **e** and **g**. Data in **b, h,** and **i** are expressed as means ± SEM; *n* = 5 mice. *P*-values were calculated using one-way ANOVA followed by Tukey's multiple comparisons test (**a**) or two-way ANOVA followed by Sidak's multiple comparisons test (**c**). NS, not significant; ***$P < 0.001$. Detailed statistics are provided in Supplementary Table 16.



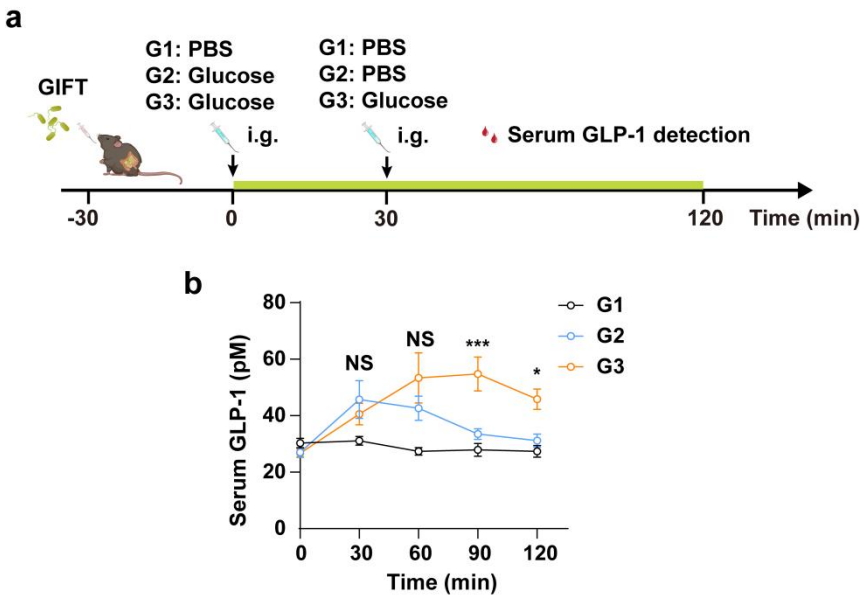
Supplementary Fig. 8. Gut microbiota composition in db/db mice undergoing different treatments. db/db mice were administered PBS, $GIFT_{Lux}$, or $GIFT_{GLP\text{-}1}$ daily for 30 days. Fecal samples were collected 6 days after the final gavage for microbiome analysis. Taxonomic profiles are shown at the species level. Species with a relative abundance ≥0.5% in at least one sample are displayed individually, whereas species with lower abundance were grouped by phylum and labeled as “Others”. Heatmap colors represent Z-score–normalized, log-transformed relative abundances of each species across samples, with values ranging from −3 to 2, indicating the deviation (in standard deviations) of a species’ abundance in a given sample from its mean abundance across all samples. Hierarchical clustering along the vertical axis reflects similarities in species-level microbial community composition among samples.



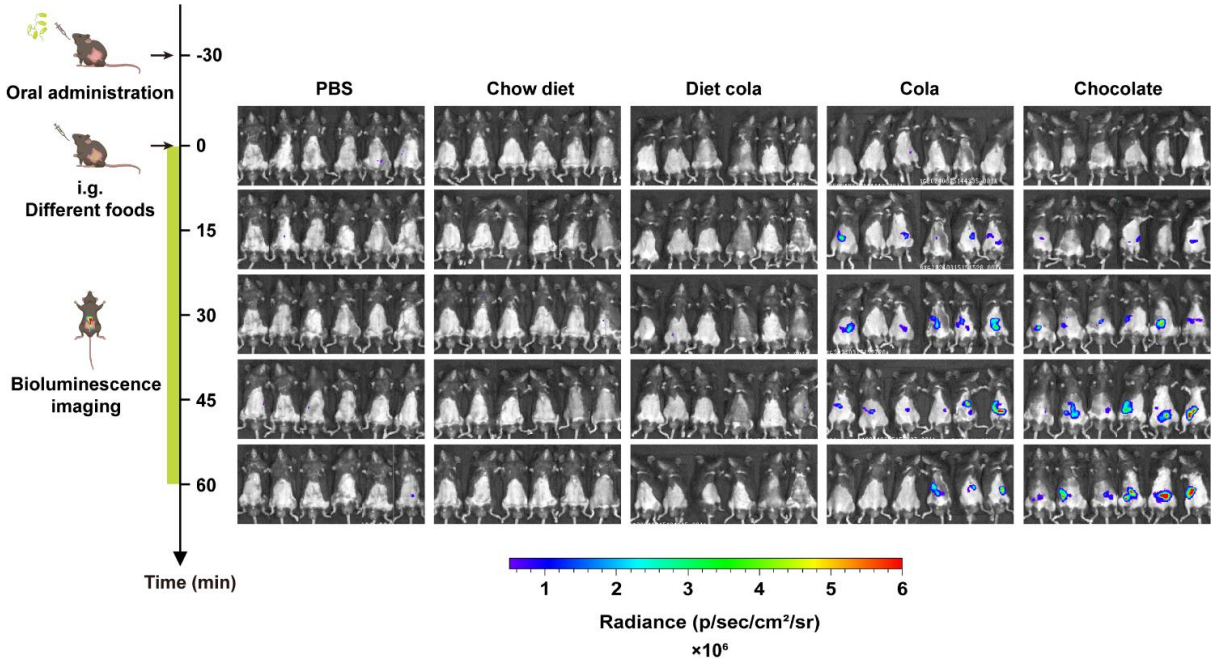
Supplementary Fig. 9. Linear discriminant analysis effect size (LEfSe) difference analysis among db/db mice undergoing different treatments. db/db mice were treated with PBS, $GIFT_{Lux}$, or $GIFT_{GLP\text{-}1}$ daily for 30 days. Fecal samples were collected 6 days after the final gavage and subjected to microbiome analysis. Bars represent the linear discriminant analysis (LDA) scores (log_{10}), indicating the effect size of each taxon contributing to differences among treatment groups. Only taxa with an LDA score ≥2 were considered discriminative and are shown.



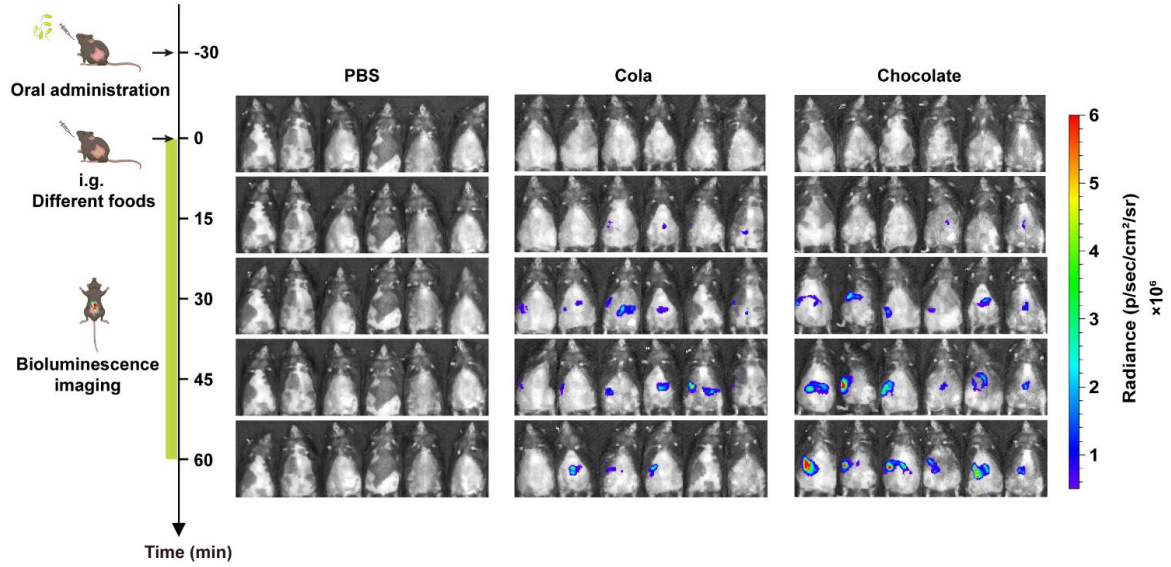
Supplementary Fig. 10. Effects of intragastric administration of varying concentrations of glucose on blood glucose levels and GIFT-mediated gene expression dynamics in wild-type mice. Wild-type mice were orally administered $GIFT_{Lux}$ cells (10^9 CFU). Thirty minutes post-gavage, the mice were intragastric (i.g.) administration of glucose at concentrations of 0, 0.1, 1, and 5 g/kg. Imaging was performed every 15 min using an *in vivo* imaging system.



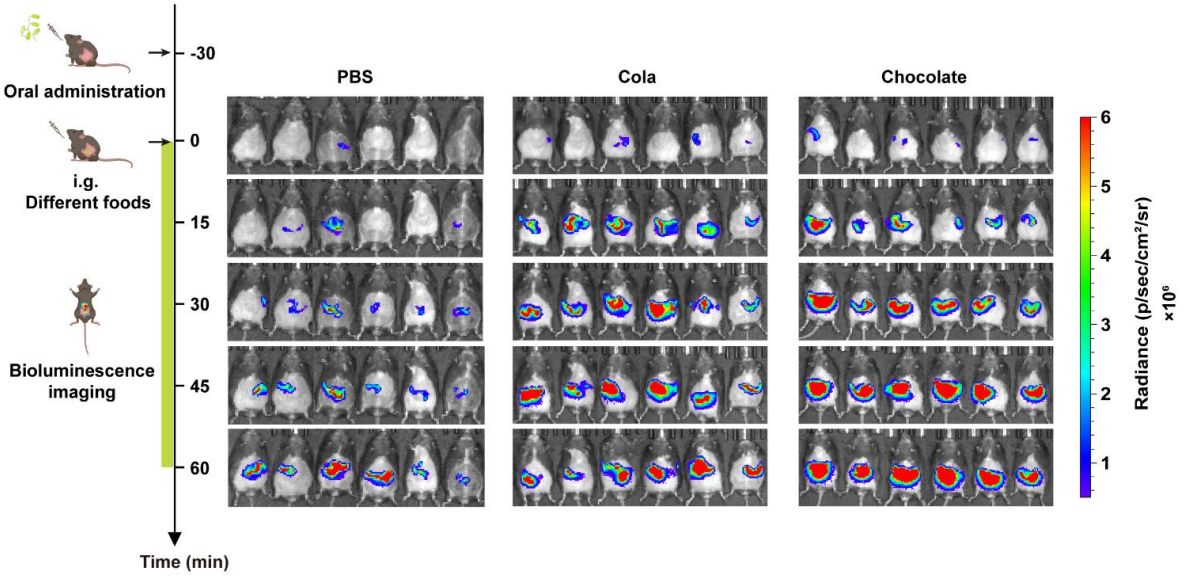
Supplementary Fig. 11. GIFT-mediated GLP-1 secretion kinetics in wild-type mice following oral glucose administration. a, Time schedule for GIFT-mediated GLP-1 secretion in wild-type mice following oral glucose administration. After a 4-hour fast, wild-type mice were orally administered $GIFT_{GLP\text{-}1}$ cells (10^9 CFU) and randomly divided into three groups. Thirty minutes later (defined as 0 min), mice in group 1 (G1) received an intragastric (i.g.) administration of PBS, while mice in group 2 (G2) and group 3 (G3) received oral glucose (5 g/kg). At 30 min, G1 and G2 received PBS, while G3 was given a second oral glucose dose (5 g/kg). Serum GLP-1 levels were measured by ELISA every 30 min from 0-120 min. **b**, Serum GLP-1 levels of mice in different group. Data are expressed as means ± SEM; *n* = 5 mice. *P*-values were calculated using two-way ANOVA followed by Tukey's multiple comparisons test, with comparisons between G2 and G3. NS, not significant; **P* < 0.05, ****P* < 0.001. Detailed statistics are provided in Supplementary Table 16.



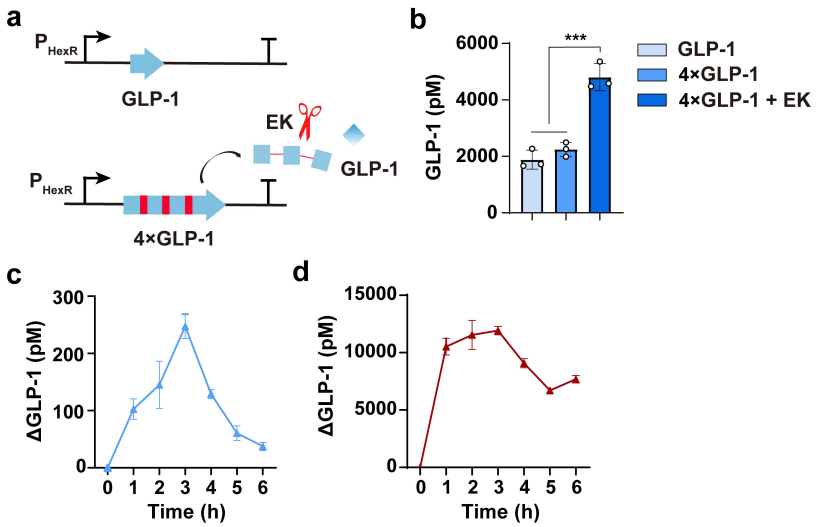
Supplementary Fig. 12. Effects of different sugary foods on blood glucose levels and GIFT-mediated gene expression dynamics in wild-type mice. Wild-type mice were orally administered $GIFT_{Lux}$ cells (10^9 CFU). Thirty minutes post-gavage, the mice were either given a chow diet or administered intragastrically (i.g.) with PBS, diet cola, cola, or chocolate. Imaging was performed every 15 min using an *in vivo* imaging system.



Supplementary Fig. 13. Effects of different sugary foods on GIFT-mediated gene expression dynamics in DIO mice. DIO mice were orally administered $GIFT_{Lux}$ cells (10^9 CFU). Thirty minutes post-gavage, the mice were administered intragastrically (i.g.) with PBS, cola, or chocolate. Imaging was performed every 15 min using an *in vivo* imaging system.



Supplementary Fig. 14. Effects of different sugary foods on GIFT-mediated gene expression dynamics in db/db mice. db/db mice were orally administered $GIFT_{Lux}$ cells (10^9 CFU). Thirty minutes post-gavage, the mice were administered intragastrically (i.g.) with PBS, cola, or chocolate. Imaging was performed every 15 min using an *in vivo* imaging system.



Supplementary Fig. 15. Design of a construct for GLP-1 tetra-copolymer expression in GIFT cells and measurement of serum GLP-1 levels in db/db mice. a, Schematic of the genetic configurations for GLP-1 and tetrameric GLP-1 (4×GLP-1) expression systems. The 4×GLP-1 is linked via enterokinase (EK) cleavage sites. **b**, Quantification of GLP-1 levels in the culture supernatant from $GIFT_{GLP\text{-}1}$ cells expressing either GLP-1 or 4×GLP-1. Cells (10^9 CFU) were induced with 15 mM glucose for 12 hours, followed by incubation of the supernatant with enterokinase for 12 hours to activate tetrameric GLP-1. GLP-1 content was then measured using an ELISA kit. **c**, **d**, Increased serum GLP-1 levels in db/db mice following oral administration of $GIFT_{GLP\text{-}1}$ cells (**c**) or semaglutide injection (**d**). $GIFT_{GLP\text{-}1}$ cells (10^9 CFU) or semaglutide (0.12 mg/kg) were administered to db/db mice, and serum GLP-1 levels were monitored for 6 hours. The increase in GLP-1 relative to baseline (0 hours) was calculated. Data in **b** are expressed as means ± SD; *n* = 3 independent experiments. Data in **c** and **d** are expressed as means ± SEM; *n* = 5 mice. *P*-values in **b** were calculated using one-way ANOVA followed by Tukey's multiple comparisons test. ***$P < 0.001$. Detailed statistics are provided in Supplementary Table 16.

Supplementary Table 1. Complete blood count (CBC) in db/db mice 12 hours after oral gavage of $GIFT_{GLP-1}$ cells (10^9 CFU/mouse) or injection of semaglutide (1 mg/kg).

Index	Wild-type mice	db/db mice		
		Untreated	Semaglutide	$GIFT_{GLP-1}$
WBC (10^3/μL)	5.78±0.77	4.31±0.66	3.29±0.25	5.27±0.91
RBC (10^6/μL)	10.67±0.16	12.04±0.47	12.50±0.17	12.14±0.32
HGB (g/dL)	16.05±0.22	17.87±0.48	19.20±0.43	17.72±0.36
HCT (%)	51.94±0.57	56.58±1.48	57.88±0.80	56.10±1.44
MCV (fL)	48.69±0.34	47.20±1.29	46.32±0.62	46.27±1.23
MCH (pg)	15.03±0.06	14.92±0.37	15.33±0.20	14.62±0.22
MCHC (g/dL)	30.90±0.14	31.62±0.61	33.18±0.76	31.62±0.46
RDW-SD (fL)	29.69±0.87	24.45±1.72	21.37±0.70	25.55±0.70
RDW-CV (%)	21.07±0.19	19.40±1.21	16.43±1.53	18.07±1.05
PDW (fL)	7.20±0.06	6.87±0.29	6.03±0.34	6.27±0.32
MPV (fL)	6.51±0.04	6.38±0.12	6.37±0.11	6.55±0.15
P-LCR (%)	4.25±0.15	2.82±0.64	2.85±0.14	3.3±0.58
PCT (%)	0.99±0.04	1.01±0.07	0.87±0.07	1.00±0.04
NEUT (10^3/μL)	0.93±0.29	1.52±0.54	1.02±0.13	2.38±0.29
LYMPH (10^3/μL)	4.93±0.66	2.60±0.20	2.13±0.24	2.59±0.65
MONO (10^3/μL)	0.19±0.04	0.13±0.05	0.11±0.02	0.23±0.05
EO (10^3/μL)	0.04±0.01	0.05±0.01	0.04±0.01	0.07±0.03
BASO (10^3/μL)	0.01±0.00	0.00±0.00	0.00±0.00	0.01±0.00
NEUT (%)	13.74±2.77	31.40±6.12	31.28±4.01	35.03±5.26
LYMPH (%)	82.49±3.01	64.90±6.62	64.10±3.88	59.70±6.00
MONO (%)	3.03±0.42	2.55±0.54	3.45±1.01	4.18±0.66
EO (%)	0.69±0.08	1.13±0.28	1.17±0.19	1.18±0.37
BASO (%)	0.10±0.04	0.02±0.02	0.00±0.00	0.08±0.04
RET (%)	4.78±0.34	2.73±0.24	2.45±0.25	2.74±0.42
RET (10^6/μL)	0.51±0.03	0.33±0.02	0.31±0.03	0.33±0.05
IRF (%)	56.27±0.71	49.57±2.39	46.58±2.41	44.27±3.56
LFR (%)	43.73±0.71	50.43±2.39	53.42±2.41	55.73±3.56
MFR (%)	19.88±0.79	15.47±0.49	15.90±0.30	15.02±0.39
HFR (%)	36.39±1.31	34.10±2.73	30.68±2.59	29.25±3.42
PLT-I (10^3/μL)	1516.00±64.39	1583.67±88.16	1372.00±118.75	1535.00±59.80
PLT-O (10^3/μL)	1029.70±39.57	1293.67±88.08	1205.83±80.48	1257.33±49.60
RBC-O (10^6/μL)	9.69±0.13	11.54±0.51	11.90±0.50	11.73±0.48

The wild-type mice group data were obtained from 8-week-old male C57BL/6J mice.

Abbreviations: **WBC**, white cell count; **RBC**, red cell count; **HGB**, hemoglobin; **HCT**, hemoglobin; **MCV**, mean corpusular volume; **MCH**, mean corpusular volume; **MCHC**, mean corpusular volume; **RDW**, mean corpusular volume; **PDW**, mean platelet volume; **MPV**, mean platelet volume; **P-LCR**, platelet -larger cell ratio; **PCT**, mean platelet volume; **NEU**, neutrophils; **LYM**, lymphocytes; **MON**,

monocytes; **EOS**, eosinophils; **BAS**, basophils; **RET**, reticulocyte; **IRF**, immature reticulocyte fraction; **LFR**, low fluorescence reticulocyte; **MFR**, medium fluorescence reticulocyte; **HFR**, high fluorescence reticulocyte; **PLT-I**, impedance platelet count; **PLT-O**, optical platelet count; **RBC-O**, optical red cell count.

Supplementary Table 2. Complete blood count (CBC) in db/db mice at 24 hours after oral gavage of $GIFT_{GLP-1}$ cells (10^9 CFU/mouse) or injection of semaglutide (1 mg/kg).

Index	Wild-type mice	db/db mice		
		Untreated	Semaglutide	$GIFT_{GLP-1}$
WBC (10^3/μL)	5.78±0.77	4.98±1.01	4.04±0.41	4.74±0.35
RBC (10^6/μL)	10.67±0.16	10.08±0.34	12.47±0.30	10.83±0.31
HGB (g/dL)	16.05±0.22	15.58±0.55	18.70±0.32	16.08±0.42
HCT (%)	51.94±0.57	49.63±1.69	56.83±1.02	51.42±1.31
MCV (fL)	48.69±0.34	49.25±0.48	45.60±0.30	47.50±0.28
MCH (pg)	15.03±0.06	15.47±0.19	15.00±0.14	14.87±0.12
MCHC (g/dL)	30.90±0.14	31.37±0.18	32.92±0.22	31.30±0.11
RDW-SD (fL)	29.69±0.87	23.87±0.35	22.15±0.41	22.15±0.24
RDW-CV (%)	21.07±0.19	15.37±0.95	16.98±1.38	16.28±0.85
PDW (fL)	7.20±0.06	6.32±0.33	6.17±0.36	6.27±0.19
MPV (fL)	6.51±0.04	6.87±0.11	6.42±0.13	6.48±0.09
P-LCR (%)	4.25±0.15	4.38±0.57	2.30±0.32	2.73±0.38
PCT (%)	0.99±0.04	0.88±0.04	1.07±0.10	0.98±0.02
NEU (10^3/μL)	0.93±0.29	0.97±0.24	1.28±0.18	0.75±0.06
LYM (10^3/μL)	4.93±0.66	3.62±0.70	2.57±0.40	3.79±0.37
MON (10^3/μL)	0.19±0.04	0.27±0.13	0.17±0.05	0.14±0.03
EOS (10^3/μL)	0.04±0.01	0.12±0.04	0.02±0.01	0.05±0.02
BAS (10^3/μL)	0.01±0.00	0.00±0.00	0.00±0.00	0.00±0.00
NEU (%)	13.74±2.77	18.95±3.09	33.25±6.48	16.43±2.13
LYM (%)	82.49±3.01	73.37±3.99	62.3±6.39	79.42±2.18
MON (%)	3.03±0.42	4.30±1.35	3.95±0.84	2.92±0.57
EOS (%)	0.69±0.08	3.32±1.83	0.40±0.14	1.18±0.37
BAS (%)	0.10±0.04	0.07±0.07	0.10±0.07	0.05±0.05
RET (%)	4.78±0.34	3.68±0.27	2.39±0.14	2.74±0.31
RET (10^6/μL)	0.51±0.03	0.37±0.03	0.30±0.01	0.29±0.03
IRF (%)	56.27±0.71	58.13±1.66	44.50±2.46	51.68±2.58
LFR (%)	43.73±0.71	41.87±1.66	55.50±2.46	48.32±2.58
MFR (%)	19.88±0.79	13.95±0.60	15.45±0.25	15.03±0.59
HFR (%)	36.39±1.31	44.18±2.21	29.05±2.65	36.65±2.31
PLT-I (10^3/μL)	1516.00±64.39	1280.33±66.99	1679.00±169.04	1514.67±35.56
PLT-O (10^3/μL)	1029.70±39.57	986.33±110.71	1412.17±102.37	1248.83±37.91
RBC-O (10^6/μL)	9.69±0.13	9.94±0.41	12.20±0.40	10.37±0.40

The wild-type mice group data were obtained from 8-week-old male C57BL/6J mice.

Supplementary Table 3. Blood glucose levels in db/db mice at various time points after insulin glargine injection (7 U/kg).

Mouse ID	Blood glucose levels (mM)					
	0 hours	2 hours	4 hours	6 hours	8 hours	10 hours
Mouse 1	26.6	7.2	9.4	11.0	16.1	21.4
Mouse 2	15.8	4.9	5.1	4.2	6.8	10.6
Mouse 3	32.0	6.7	4.9	5.8	9.6	9.9
Mouse 4	26.2	10.1	5.7	7.2	15.0	20.5
Mouse 5	16.5	7.4	5.1	6.7	27.3	33.0
Mouse 6	32.7	10.7	7.1	11.6	17.5	21.6
Mouse 7	21.2	6.6	5.4	5.1	7.0	19.4
Mouse 8	26.4	7.6	5.2	4.2	3.3 ↓	10.7
Mouse 9	21.7	8.6	5.3	7.3	9.3	16.7
Mouse 10	26.4	8.5	7.1	12.8	28.8	33.0
Mouse 11	29.2	6.8	5.0	5.2	5.2	5.2
Mouse 12	29.2	6.8	5.0	5.2	5.2	5.2
Mouse 13	28.1	5.9	3.7 ↓	4.8	5.1	5.8
Mouse 14	25.9	8.4	5.2	4.1	6.0	4.4
Mouse 15	25.5	5.3	4.5	3.3 ↓	2.8 ↓	3.6 ↓

Insulin glargine (7 U/kg) was intramuscularly injected into db/db mice at 0 hours, and blood glucose levels were measured every 2 hours from 0 to 10 hours. Blood glucose levels below 3.9 mM were defined as hypoglycemia and are indicated by ↓.

Supplementary Table 4. Blood glucose levels in db/db mice at various time points after semaglutide injection (1 mg/kg).

Mouse ID	Blood glucose levels (mM)					
	0 hours	2 hours	4 hours	6 hours	8 hours	10 hours
Mouse 1	24.2	12.6	13.8	11.4	11.9	12.9
Mouse 2	18.1	8.3	6.5	4.4	4.9	4.8
Mouse 3	30.2	13.4	13.4	15.9	12.6	14.9
Mouse 4	19.9	6.5	4.3	4.8	6.0	4.7
Mouse 5	17.7	10.4	9.2	9.8	11.2	11.6
Mouse 6	28.9	17.9	14.7	14.8	14.4	19.1
Mouse 7	34.0	19.5	15.6	10.9	10.4	10.7
Mouse 8	34.0	18.4	11.8	15.8	11.1	13.7
Mouse 9	34.0	17.7	16.2	14.8	16.6	15.0
Mouse 10	24.2	12.6	13.8	11.4	11.9	12.9
Mouse 11	18.1	8.3	6.5	4.4	4.9	4.8
Mouse 12	30.2	13.4	13.4	15.9	12.6	14.9
Mouse 13	19.9	6.5	4.3	4.8	6.0	4.7
Mouse 14	32.1	18.1	15.7	20.4	18.1	15.3
Mouse 15	17.7	10.4	9.2	9.8	11.2	11.6

Semaglutide (1 mg/kg) was subcutaneously injected into db/db mice at 0 hours, and blood glucose levels were measured every 2 hours from 0 to 10 hours. Blood glucose levels below 3.9 mM were defined as hypoglycemia and are indicated by ↓.

Supplementary Table 5. Blood glucose levels in db/db mice at various time points after semaglutide injection (0.12 mg/kg).

Mouse ID	Blood glucose levels (mM)					
	0 hours	2 hours	4 hours	6 hours	8 hours	10 hours
Mouse 1	22.3	11.3	10.4	8.2	9.9	6.9
Mouse 2	21.9	18.6	13.1	13.6	9.3	8.4
Mouse 3	29.8	16.6	17.8	18.6	20.3	20.5
Mouse 4	23.7	8.6	7.3	7.8	6.6	8.6
Mouse 5	24.4	11.9	11.3	9.9	8.5	10.8
Mouse 6	33.2	17.8	18.9	22.1	20.6	21.9
Mouse 7	23.4	11.3	8.6	8.2	8.2	9.3
Mouse 8	30.4	21.7	20.3	24.2	19.6	20.1
Mouse 9	19.4	15.9	11.8	9.9	8.3	7.8
Mouse 10	32.8	12.7	12.9	11.4	12.1	13.1
Mouse 11	27.3	18.1	16.1	14	8.3	9.9
Mouse 12	10.6	5.6	5.4	7.4	6.2	10.6
Mouse 13	12.8	6.9	6.6	6.6	7.9	8.2
Mouse 14	31.3	12.7	14.0	12	10.4	14.1
Mouse 15	27.9	13.9	9.1	10.4	8.8	9.7

Semaglutide (0.12 mg/kg) was subcutaneously injected into db/db mice at 0 hours, and blood glucose levels were measured every 2 hours from 0 to 10 hours. Blood glucose levels below 3.9 mM were defined as hypoglycemia and are indicated by ↓.

Supplementary Table 6. Blood glucose levels in db/db mice at various time points after injection of semaglutide (1 mg/kg) and insulin glargine (7 U/kg).

Mouse ID	Blood glucose levels (mM)						
	-2 hours	0 hours	2 hours	4 hours	6 hours	8 hours	10 hours
Mouse 1	28.9	12.3	6.7	3.3 ↓	3.6 ↓	2.3 ↓	2.3 ↓
Mouse 2	24.0	6.0	3.3 ↓	3.3 ↓	2.8 ↓	2.9 ↓	2.7 ↓
Mouse 3	30.1	11.3	5.6 ↓	4.1	3.3 ↓	3.2 ↓	2.1 ↓
Mouse 4	29.4	7.2	3.2 ↓	2.8 ↓	2.1 ↓	2.1 ↓	1.8 ↓
Mouse 5	28.3	10.4	3.3 ↓	2.9 ↓	3.1 ↓	2.5 ↓	3.5 ↓
Mouse 6	24.5	16.7	12.3	4.7	4.2	5.3	4.7
Mouse 7	20.9	7.2	4.7	3.8 ↓	3.8 ↓	6.2	4.1
Mouse 8	34.0	17.0	6.9	5.3	4.1	6.1	3.9
Mouse 9	34.0	14.9	9.6	7.4	5.3	6.4	6.3
Mouse 10	32.1	15.4	9.1	9.4	6.2	6.5	6.6
Mouse 11	33.5	14.2	6.1	4.3	3.4 ↓	3.6 ↓	3.6 ↓
Mouse 12	30.8	11.9	5.9	4.2	5.0	5.2	7.2
Mouse 13	30.7	19.7	5.9	5.2	3.7 ↓	3.9	4.1
Mouse 14	25.6	10.3	6.1	4.2	3.6 ↓	3.9	4.8
Mouse 15	20.5	15.4	5.8	4.3	3.4 ↓	4.3	4.5

Semaglutide (1 mg/kg) was subcutaneously injected into db/db mice at -2 hours, followed by intramuscular insulin glargine injection (7 U/kg) at 0 hours. Blood glucose levels were measured every 2 hours from 0 to 10 hours. Blood glucose levels below 3.9 mM were defined as hypoglycemia and are indicated by ↓.

Supplementary Table 7. Blood glucose levels in db/db mice at various time points after injecting semaglutide (0.12 mg/kg) and insulin glargine (7 U/kg).

Mouse ID	Blood glucose levels (mM)						
	-2 hours	0 hours	2 hours	4 hours	6 hours	8 hours	10 hours
Mouse 1	13.4	5.0	3.3 ↓	4.8	5.5	6.0	7.1
Mouse 2	27.9	11.8	3.7 ↓	5.0	7.7	6.9	7.8
Mouse 3	13.6	5.5	4.8	5.3	5.2	5.2	6.4
Mouse 4	14.2	4.2	5.6	5.2	7.1	7.8	7.2
Mouse 5	28.3	8.5	4.7	6.2	6.4	6.5	9.4
Mouse 6	27.6	15.2	5.3	4.3	9.3	7.2	10.4
Mouse 7	18.2	6.7	4.4	5.6	6.7	7.7	6.4
Mouse 8	19.7	8.8	3.2 ↓	5.3	7.7	6.2	5.5
Mouse 9	13.2	6.4	4.9	5.1	4.7	5.7	4.9
Mouse 10	28.4	6.9	3.1 ↓	6.2	5.1	5.4	5.3
Mouse 11	32.7	6.4	3.8 ↓	3.6 ↓	4.5	5.0	4.7
Mouse 12	13.4	7.3	4.2	4.3	5.7	5.3	4.8
Mouse 13	15.9	6.1	4.7	5.6	4.5	5.9	4.9
Mouse 14	34.0	7.8	4.7	5.1	5.1	7.3	4.7
Mouse 15	20.7	5.9	2.7 ↓	4.1	8.5	5.7	6.1

Semaglutide (0.12 mg/kg) was subcutaneously injected into db/db mice at -2 hours, followed by intramuscular insulin glargine injection (7 U/kg) at 0 hours. Blood glucose levels were measured every 2 hours from 0 to 10 hours. Blood glucose levels below 3.9 mM were defined as hypoglycemia and are indicated by ↓.

Supplementary Table 8. Blood glucose levels in db/db mice at various time points after oral gavage of $GIFT_{GLP\text{-}1}$ cells (10^9 CFU/mouse).

Mouse ID	Blood glucose levels (mM)					
	0 hours	2 hours	4 hours	6 hours	8 hours	10 hours
Mouse 1	18.3	16.6	11.7	11.4	10.6	6.8
Mouse 2	23.6	15.6	10.6	11.8	12.7	13.1
Mouse 3	21.8	12.4	10.3	10.0	10.6	5.8
Mouse 4	31.6	16.5	15.9	15.5	11.6	6.4
Mouse 5	17.7	12.8	10.7	9.3	6.6	5.8
Mouse 6	28.5	20.6	19.3	16.2	14.7	8.1
Mouse 7	24.2	20.1	17.7	15.7	16.3	11.9
Mouse 8	21.8	21.4	15.7	9.5	12.1	12.6
Mouse 9	18.8	7.0	6.2	6.9	6.6	5.1
Mouse 10	18.2	16.3	17.7	15.1	14.6	12.3
Mouse 11	22.3	12.8	12.9	11.2	9.7	9.5
Mouse 12	16.4	11.9	9.8	7.6	8.3	8.2
Mouse 13	30.7	21.6	12.8	11.3	10.6	12.2
Mouse 14	19.9	12.2	13.2	8.0	7.8	14.7
Mouse 15	14.2	12.6	12.1	8.8	8.8	8.0

$GIFT_{GLP\text{-}1}$ cells (10^9 CFU) were administrated to db/db mice via oral gavage, and blood glucose levels were measured every 2 hours from 0 to 10 hours. Blood glucose levels below 3.9 mM were defined as hypoglycemia and are indicated by ↓.

Supplementary Table 9. Blood glucose levels in db/db mice at various time points after oral gavage of GIFT$_{GLP-1}$ cells (10^9 CFU/mouse) and insulin glargine injection (7 U/kg).

Mouse ID	Blood glucose levels (mM)						
	-2 hours	0 hours	2 hours	4 hours	6 hours	8 hours	10 hours
Mouse 1	23.6	21.2	5.6	4.9	27.5	29.7	18.1
Mouse 2	16.5	15.5	4.8	6.4	13.7	13.1	10.1
Mouse 3	19.1	14.8	4.4	5.3	8.8	20.4	15.1
Mouse 4	26.4	18.1	4.3	4.0	15.1	15.5	13.0
Mouse 5	24.8	17.8	4.0	4.1	10.6	15.3	13.1
Mouse 6	24.0	22.9	4.7	5.5	9.7	17.7	12.1
Mouse 7	26.3	19.7	5.7	6.4	7.4	15.4	20.4
Mouse 8	25.6	13.1	4.8	7.1	12.1	13.7	7.4
Mouse 9	18.1	15.4	4.7	4.4	10.1	15.8	13.7
Mouse 10	18.5	10.6	3.7 ↓	3.8 ↓	5.1	5.1	4.6
Mouse 11	16.9	7.5	3.6 ↓	6.4	4.9	5.1	6.0
Mouse 12	16.4	16.1	3.7 ↓	3.4 ↓	8.2	8.9	14.3
Mouse 13	27.2	22.2	6.0	5.5	12.4	25.3	31.9
Mouse 14	20.7	13.1	5.3	6.3	13.2	21.2	20.2
Mouse 15	17.1	9.2	4.1	3.9	9.1	9.2	8.6

GIFT$_{GLP-1}$ cells (10^9 CFU) were administered to db/db mice via oral gavage at -2 hours, followed by intramuscular insulin glargine injection (7 U/kg) at 0 hours. Blood glucose levels were measured every 2 hours from 0 to 10 hours. Blood glucose levels below 3.9 mM were defined as hypoglycemia and are indicated by ↓.

Supplementary Table 10. Complete blood count (CBC) in db/db mice after oral gavage of $GIFT_{GLP-1}$ cells (10^9 CFU/mouse/day) or injection of semaglutide (0.12 mg/kg/week) for two months.

Index	Wild-type mice	db/db mice		
		Untreated	Semaglutide	$GIFT_{GLP-1}$
WBC (10^3/μL)	5.78±0.77	5.07±1.06	4.18±0.86	5.97±1.09
RBC (10^6/μL)	10.67±0.16	12.35±0.74	12.79±0.89	12.86±0.98
HGB (g/dL)	16.05±0.22	17.58±1.04	18.83±1.40	18.88±1.45
HCT (%)	51.94±0.57	55.55±1.80	61.81±5.08	59.08±4.50
MCV (fL)	48.69±0.34	45.03±1.63	48.31±1.55	45.93±1.34
MCH (pg)	15.03±0.06	14.23±0.18	14.71±0.45	14.68±0.36
MCHC (g/dL)	30.90±0.14	31.63±1.19	30.48±0.40	31.95±0.38
RDW-SD (fL)	29.69±0.87	33.68±2.70	35.08±2.62	32.33±2.22
RDW-CV (%)	21.07±0.19	21.93±2.06	18.26±0.80	17.61±0.73
PDW (fL)	7.20±0.06	7.25±0.64	6.30±0.62	6.16±0.77
MPV (fL)	6.51±0.04	6.8±0.22	7.33±0.18	7.25±0.24
P-LCR (%)	4.25±0.15	3.93±0.90	5.90±0.92	4.76±1.19
PCT (%)	0.99±0.04	1.11±0.36	1.73±0.25	1.11±0.34
NEU (10^3/μL)	0.93±0.29	2.88±0.95	2.16±0.44	2.34±0.36
LYM(10^3/μL)	4.93±0.66	1.93±0.43	1.81±0.66	3.34±0.58
MON (10^3/μL)	0.19±0.04	0.21±0.07	0.11±0.04	0.24±0.14
EOS (10^3/μL)	0.04±0.01	0.04±0.02	0.09±0.19	0.03±0.03
NEU (%)	13.74±2.77	56.10±8.91	52.88±12.9	39.40±2.01
LYM (%)	82.49±3.01	38.93±9.00	42.28±11.39	56.06±1.67
MON (%)	3.03±0.42	4.10±1.26	2.56±0.94	3.91±1.78
EOS (%)	0.69±0.08	0.81±0.51	2.11±4.45	0.51±0.49
BAS (%)	0.10±0.04	0.05±0.08	0.15±0.12	0.10±0.08
RET (%)	4.78±0.34	3.62±0.80	3.25±0.54	2.79±0.52
RET (10^6/μL)	0.51±0.03	0.44±0.10	0.41±0.08	0.36±0.07
IRF (%)	56.27±0.71	53.98±3.78	60.51±4.35	53.73±5.42
LFR (%)	43.73±0.71	46.01±3.78	39.48±4.35	46.26±5.42
MFR (%)	19.88±0.79	14.73±1.99	12.36±1.20	14.86±1.45
HFR (%)	36.39±1.31	39.25±2.80	48.15±5.04	38.86±5.10
RET-He (pg)	16.67±0.24	16.7±0.35	17.81±0.84	16.83±0.25
IPF (%)	0.08±0.08	0.23±0.08	0.85±0.66	0.30±0.14
PLT-O (10^3/μL)	1029.70±39.57	1098.00±336.95	1481.33±214.85	1075.83±408.32
PLT-I (10^3/μL)	1516.00±64.39	1635.33±554.86	2355.50±375.39	1549.66±515.92
PLT-F (10^3/μL)	1702.67±629.05	1141.66±257.52	1630.83±207.16	1202.33±400.34
RBC-O (10^6/μL)	9.69±0.13	11.91±1.42	13.01±0.73	13.20±0.93

The wild-type mice group data were obtained from 8-week-old male C57BL/6J mice.

Supplementary Table 11. Serum biochemistry analysis in db/db mice after oral gavage of $GIFT_{GLP-1}$ cells (10^9 CFU/mouse/day) or injection of semaglutide (0.12 mg/kg/week) for two months.

Index	Wild-type mice	db/db mice		
		Untreated	Semaglutide	$GIFT_{GLP-1}$
ALT (U/L)	36.11±3.80	314.75±99.05	136.75±48.34	194.78±35.90
AST (U/L)	126.11±10.23	441.04±92.75	256.67±62.41	345.82±55.64
UREA (mM)	10.62±1.35	14.25±2.69	13.24±2.43	12.60±1.10
CK (U/L)	1388.33±124.63	2214.36±519.76	1719.33±596.59	1785.70±840.36
LDH (U/L)	410.00±34.93	2838.61±414.29	2380.23±293.66	2345.31±116.03

The wild-type mice group data were obtained from 8-week-old male C57BL/6J mice.
Abbreviations: **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **CK**, creatine Kinase; **LDH**, lactate dehydrogenase.

Supplementary Table 12. Serum biochemistry analysis in type 2 diabetic monkeys following a single oral dose of GIFT$_{GLP-1}$.

		No. 1		No. 2		No. 3		No. 4	
Index	Normal range	Day -2	Day 3	Day -2	Day 3	Day -2	Day 3	Day -2	Day 3
ALT (U/L)	(0.0-40.0)	126.2	85.0	138.3	58.1	222.5	195.7	43.4	33.9
AST (U/L)	(0.0-40.0)	29.6	31.6	40.7	22.2	40.2	33.4	23.4	15.6
BUN (mM)	(2.90-8.20)	8.51	7.42	10.50	10.40	8.87	8.15	6.77	8.07
CRE (μM)	(40.0-120.0)	61.6	59.6	52.4	51.6	56.9	55.1	60.7	68.1
TG (mM)	(0.40-1.80)	6.05	2.83	7.37	4.32	5.19	3.80	12.91	9.04
T-CHO (mM)	(2.80-5.70)	4.76	3.80	5.07	3.52	3.40	3.10	8.13	6.67
HDL (mM)	(0.80-1.96)	1.14	1.02	1.22	1.07	1.02	1.00	1.84	1.66
LDL (mM)	(2.10-3.60)	2.07	1.96	1.98	1.49	1.44	1.40	2.91	2.63
A/G	(1.1-2.7)	1.5	1.6	1.0	1.1	0.8	0.9	1.1	1.1

Serum biochemistry analysis of the four type 2 diabetic monkeys (No.1, No.2, No.3, and No.4) was performed on Day -2 and Day 3 during treatment with a single administration.

Abbreviations: **ALT**, alanine aminotransferase; **AST**, aspartate aminotransferase; **BUN**, blood urea nitrogen; **CRE**, creatinine; **A/G**, albumin/globulin ratio.

Supplementary Table 13. Serum biochemistry analysis in type 2 diabetic monkeys treated with GIFT$_{GLP-1}$ for five weeks.

		No. 1		No. 2		No. 3		No. 4		No. 5	
Index	Normal range	Day -5	Day 35	Day -5	Day 35	Day -5	Day 35	Day -5	Day 35	Day -5	Day 35
ALT (U/L)	(0.0-40.0)	94.5	118.7	255.0	263.9	52.3	33.2	209.3	112.7	171.4	82.0
AST (U/L)	(0.0-40.0)	35.8	42.3	48.3	47.7	18.9	37.4	42.6	42.8	42.1	81.7
BUN (mM)	(2.90-8.20)	9.29	6.95	5.81	5.88	9.06	4.99	9.20	9.16	4.18	4.50
CRE (μM)	(40.0-120.0)	89.3	82.1	81.8	94.0	77.0	75.3	79.2	82.8	68.1	76.4
TG (mM)	(0.40-1.80)	3.38	3.17	7.10	7.64	9.52	3.48	1.20	1.76	6.20	1.38
T-CHO (mM)	(2.80-5.70)	3.18	2.84	6.15	5.44	6.72	3.35	4.04	3.96	5.67	2.95
HDL (mM)	(0.80-1.96)	1.24	1.13	1.60	1.45	1.99	1.36	1.70	1.59	1.69	1.17
LDL (mM)	(2.10-3.60)	1.37	1.04	3.25	2.77	3.03	1.35	2.04	2.00	3.00	1.45
A/G	(1.1-2.7)	0.9	0.9	1.1	1.2	1.1	1.1	1.2	1.2	1.1	1.3

Serum biochemistry analysis of the five type 2 diabetic monkeys (No.1, No.2, No.3, No.4, and No.5) was performed on Day -5 and Day 35 during the long-term study.

Supplementary Table 14. Complete blood count (CBC) in type 2 diabetic monkeys following a single oral dose of $GIFT_{GLP-1}$.

		No. 1		No. 2		No. 3		No. 4	
Index	Normal range	Day -2	Day 3	Day -2	Day 3	Day -2	Day 3	Day -2	Day 3
WBC (10^9/L)	(3.5-9.5)	9.4	11.8	11.3	13.1	14.7	17.0	14.3	15.0
NEU (%)	(40.0-75.0)	37.1	46.9	32.2	39.7	22.3	23.9	38.8	45.4
LYM (%)	(20.0-50.0)	53.6	41.2	58.5	50.6	63.9	67.0	52.5	48.6
MON (%)	(3.0-10.0)	7.0	10.3	8.1	8.6	11.7	7.2	7.1	4.8
EOS (%)	(0.4-8.0)	2.2	1.5	1.0	1.0	2.0	1.8	1.5	1.1
BAS (%)	(0.0-1.0)	0.1	0.1	0.2	0.1	0.1	0.1	0.1	0.1
NEU (10^9/L)	(1.8-6.3)	3.5	5.5	3.6	5.2	3.3	4.1	5.5	6.8
LYM (10^9/L)	(1.1-3.2)	5.0	4.9	6.6	6.6	9.4	11.4	7.5	7.3
MON (10^9/L)	(0.10-0.60)	0.66	1.22	0.92	1.13	1.72	1.22	1.02	0.72
EOS (10^9/L)	(0.02-0.52)	0.21	0.18	0.11	0.13	0.29	0.31	0.21	0.17
BAS (10^9/L)	(0.00-0.06)	0.01	0.01	0.02	0.01	0.01	0.02	0.01	0.02
RBC (10^{12}/L)	(4.30-5.80)	5.96	4.91	7.32	6.58	5.58	5.14	5.91	5.53
HGB (g/L)	(130-175)	139	114	169	152	122	111	137	127
HCT	(40.0-50.0)	44.6	37.0	54.7	49.4	39.8	36.6	44.8	41.4
MCV (fL)	(82.0-100.0)	74.8	75.4	74.7	75.1	71.3	71.2	75.8	74.9

MCH (pg)	(27.0-34.0)	23.3	23.2	23.1	23.1	21.9	21.6	23.2	23.0
MCHC (g/L)	(316-354)	312	308	309	308	307	303	306	307
RDW-SD (fL)	(37.0-54.0)	30.0	30.4	34.8	34.8	30.1	30.4	31.7	31.4
RDW-CV (%)	(11.6-14.6)	11.3	11.4	15.2	13.9	12.1	12.2	11.8	11.6
PLT (10^9/L)	(125-350)	276	248	503	505	512	470	403	439
MPV (fL)	(7.6-13.2)	12.7	12.3	12.0	11.7	9.8	9.6	11.7	11.3
PCT	(0.11-0.28)	0.35	0.31	0.61	0.59	0.50	0.45	0.47	0.50
PDW (%)	(15.0-17.0)	15.2	14.1	15.9	14.6	10.8	10.9	14.4	13.5
P-LCR (%)	(13.0-43.0)	43.0	40.8	43.0	38.7	22.8	21.1	38.6	35.2

CBC assays of the four type 2 diabetic monkeys (No.1, No.2, No.3, and No.4) were performed on Day -2 and Day 3 during treatment with a single administration.

Abbreviations: **WBC**, white cell count; **NEU**, neutrophils; **LYM,** lymphocytes; **MON**, monocytes; **EOS**, eosinophils; **BAS**, basophils; **RBC**, red cell count; **HGB**, hemoglobin; **HCT**, hemoglobin; **MCV**, mean corpusular volume; **MCH**, mean corpusular volume; **MCHC**, mean corpusular volume; **RDW**, mean corpusular volume; **PLT**, platelet count; **MPV**, mean platelet volume; **PCT**, mean platelet volume; **PDW**, mean platelet volume; **P-LCR**, platelet -larger cell ratio.

Supplementary Table 15. Complete blood count (CBC) in type 2 diabetic monkeys treated with $GIFT_{GLP-1}$ for five weeks.

		No. 1		No. 2		No. 3		No. 4		No. 5	
Index	Normal range	Day -5	Day 35	Day -5	Day 35	Day -5	Day 35	Day -5	Day 35	Day -5	Day 35
WBC (10^9/L)	(3.5-9.5)	10.7	10.6	14.7	14.0	13.9	14.1	13.2	13.2	15.1	15.5
NEU (%)	(40.0-75.0)	34.2	36.9	25.1	30.7	45.9	42.9	37.6	42.4	48.4	64.3
LYM (%)	(20.0-50.0)	49.6	44.0	64.9	60.1	47.2	50.3	51.3	49.0	44.0	29.2
MON (%)	(3.0-10.0)	13.8	17.1	6.8	7.1	5.5	4.8	8.8	6.9	4.9	5.3
EOS (%)	(0.4-8.0)	2.3	1.9	2.9	1.9	1.2	1.9	2.1	1.5	2.5	0.9
BAS (%)	(0.0-1.0)	0.1	0.1	0.3	0.1	0.2	0.1	0.2	0.2	0.2	0.3
NEU (10^9/L)	(1.8-6.3)	3.7	3.9	3.7	4.3	6.4	6.1	5.0	5.6	7.3	10.0
LYM (10^9/L)	(1.1-3.2)	5.3	4.7	9.5	8.4	6.6	7.1	6.8	6.5	6.6	4.5
MON (10^9/L)	(0.10-0.60)	1.48	1.81	1.00	1.00	0.76	0.68	1.16	0.91	0.74	0.82
EOS (10^9/L)	(0.02-0.52)	0.25	0.20	0.43	0.27	0.17	0.27	0.28	0.20	0.38	0.14
BAS (10^9/L)	(0.00-0.06)	0.01	0.01	0.04	0.02	0.03	0.02	0.03	0.03	0.03	0.05
RBC (10^{12}/L)	(4.30-5.80)	6.83	6.31	5.76	5.79	6.12	6.15	6.59	5.94	6.69	6.55
HGB (g/L)	(130-175)	146	133	146	144	139	135	147	130	162	153
HCT	(40.0-50.0)	49.4	44.8	47.0	46.5	45.0	45.6	48.6	43.2	49.7	48.3
MCV (fL)	(82.0-100.0)	72.3	71.0	81.6	80.3	73.5	74.1	73.7	72.7	74.3	73.7

MCH (pg)	(27.0-34.0)	21.4	21.1	25.3	24.9	22.7	22.0	22.3	21.9	24.2	23.4
MCHC (g/L)	(316-354)	296	297	311	310	309	296	302	301	326	317
RDW-SD (fL)	(37.0-54.0)	31.3	29.9	37.8	35.1	30.5	31.1	33.8	33.8	33.1	32.6
RDW-CV (%)	(11.6-14.6)	13.2	12.2	13.1	12.0	12.0	11.7	13.4	12.9	13.6	12.8
PLT (10^9/L)	(125-350)	335	383	440	630	482	492	373	449	528	570
MPV (fL)	(7.6-13.2)	12.7	12.6	13.7	11.9	11.3	11.6	13.0	11.7	12.2	12.1
PCT	(0.11-0.28)	0.43	0.48	0.60	0.75	0.55	0.57	0.48	0.52	0.64	0.69
PDW (%)	(15.0-17.0)	18.0	16.5	19.0	15.3	14.4	14.0	17.1	14.2	14.7	15.2
P-LCR (%)	(13.0-43.0)	49.5	47.1	55.0	41.7	36.2	37.7	50.9	39.8	43.2	42.5

CBC assays of the five type 2 diabetic monkeys (No.1, No.2, No.3, No.4, and No.5) were performed on Day 5 and Day 35 during the long-term study.

Supplementary Table 17. Plasmids used in this study.

Plasmid	Description and cloning strategy	Reference
pGN70	Constitutive sfGFP report vector (P_{tac}-RBS-sfGFP)	This work
pGN11	HexR–based glucose sensor report vector (P_{hexR1} (P_{tac}-HexO)-RBS-sfGFP)	This work
pGN227	HexR–based glucose sensor report vector (P_{hexR2} (P_{tac}-2×HexO)-RBS-sfGFP)	This work
pGN12	HexR–based glucose sensor report vector (P_{hexR3} (P_{tac}-3×HexO)-RBS-sfGFP)	This work
pGN228	HexR–based glucose sensor report vector (P_{hexR4} (P_{tac}-4×HexO)-RBS-sfGFP)	This work
pGN229	HexR–based glucose sensor report vector (P_{hexR5} (P_{tac}-5×HexO)-RBS-sfGFP)	This work
pGN69	Constitutive HexR expression vector ($P_{BBA23100}$-RBS1-HexR)	This work
pGN89	Constitutive HexR expression vector (P_{Tac}-RBS1-HexR)	This work
pGN90	Constitutive HexR expression vector (P_{Lac}-RBS1-HexR)	This work
pGN231	Constitutive HexR expression vector (P_{Tac}-RBS2-HexR)	This work
pGN232	Constitutive HexR expression vector (P_{Tac}-RBS3-HexR)	This work
pGN233	Constitutive HexR expression vector (P_{Tac}-RBS4-HexR)	This work
pGN66	HexR–based glucose sensor report vector (P_{hexR4}-RBS-Luciferase)	This work
pGN201	HexR–based glucose sensor report vector (P_{hexR4}-RBS-lacZ)	This work
pGN65	HexR–based glucose sensor report vector (P_{hexR4}-RBS-LuxCDABE)	This work
pXG42	HexR–based glucose sensor GLP1 (7-37)-hFC fusion protein expression vector (P_{hexR4}-RBS-OmpT-GLP1 (7-37)-hFc)	This work
pGN339	HexR–based glucose sensor GLP1 (7-37) expression vector (P_{hexR4}-RBS-OmpT-GLP1 (7-37))	This work
pGN335	HexR–based glucose sensor 4×GLP1 (7-37) expression vector (P_{hexR4}-RBS-LamB-4×GLP1 (7-37))	This work
pGN335	Constitutive GLP-1 secretion expression vector (P_{Tac}-RBS-LamB-GLP1 (7-37))	This work
pMY425	Constitutive GLP-1 secretion expression vector (P_{LacUV5}-RBS-LamB-GLP1 (7-37))	This work
pM8	Constitutive GLP-1 secretion expression vector (P_{Lac}-RBS-LamB-GLP1 (7-37))	This work
pGN426	Constitutive GLP-1 non-secretion expression vector (P_{Tac}-RBS-GLP1 (7-37))	This work

Abbreviations: **sfGFP**, superfolder green fluorescent protein; **HexO**, HexR-specific operator DNA sequence; **HexR**, transcriptional regulator that controls metabolic genes of *N. meningitidis* in response to glucose; **GLP-1 (7-37)**, a shortened variant of human glucagon-like peptide-1; **hFC**, human fragment crystallizable domain of immunoglobulin G; **OmpT**, outer membrane protease T secretion signal peptide; **LamB**, maltoporin secretion signal peptide.

Supplementary Table 18. Oligonucleotide sequences utilized for qPCR analysis.

Gene name	Sense primer (5'-3')	Anti-sense primer (5'-3')
glk	cgccctttatcttcaaatgc	gtcgctgttttgcgtcatta
pgi	aagagacgctggcgaaatta	ccagaatcggggtattgcta
pfkA	ggttcctacatgggtgcaat	acttccaccacggaaatacg
pfkB	agcggtgagcagtatcgttt	agcggaaatcagttgggtta
zwf	ctgccacggtaatctcaaca	gcgaatacttcgaggagtgc
gcd	ggtcaggataccaccgctaa	actatgatttggggcgtctg
pgl	gttgatcacagcggcaagta	tagtgcgcgttgaccactac
fbaA	acgagcgatcatcgaagtct	cggcgtagtgaaaatgaaca
fbaB	gttagcggcaaatgaagctc	ctacgtagaccgcgtgatga
fbaB	gttagcggcaaatgaagctc	ctacgtagaccgcgtgatga
gntK	gtcaccagcatttgggtttt	tatgcagcgcaccaataaag
edd	catgcggtccactttacctt	tgatggtgctctgtttctcg
eda	ccgtagtccatacccagcat	gtacggtgctgaatccacag
gapA	aggtctgatgaccaccgttc	ggaacgccataccagtcagt
pgk	tcaccttcagcaacgtcaac	aaacaaggcgcaaaagtgat
aceF	gccgtaaaggtcgtatcctg	ggttcgcaccagagattttc
aceE	cgtcagaaactgcacggtta	atgatcggtaccagcctgtc
pykA	ccaacctgggtaaaggtgaa	ttcggtgaacactttcatgc
pykF	gaaatccgcaccatgaaact	ataccgatcagaccgtcgtc
eno	cagcgatggtagcatcttca	atcgaaaaaggcatcgctaa
gpmA	ggtttccgctttgttcagac	agcaaaagcagcaggtaagc
gpmM	tcgtgatgctgaccgaatac	ttcgcctttgaacgactctt
16s rRNA	ctcagaccagctagggatcg	cggacgggtgagtaatgtct