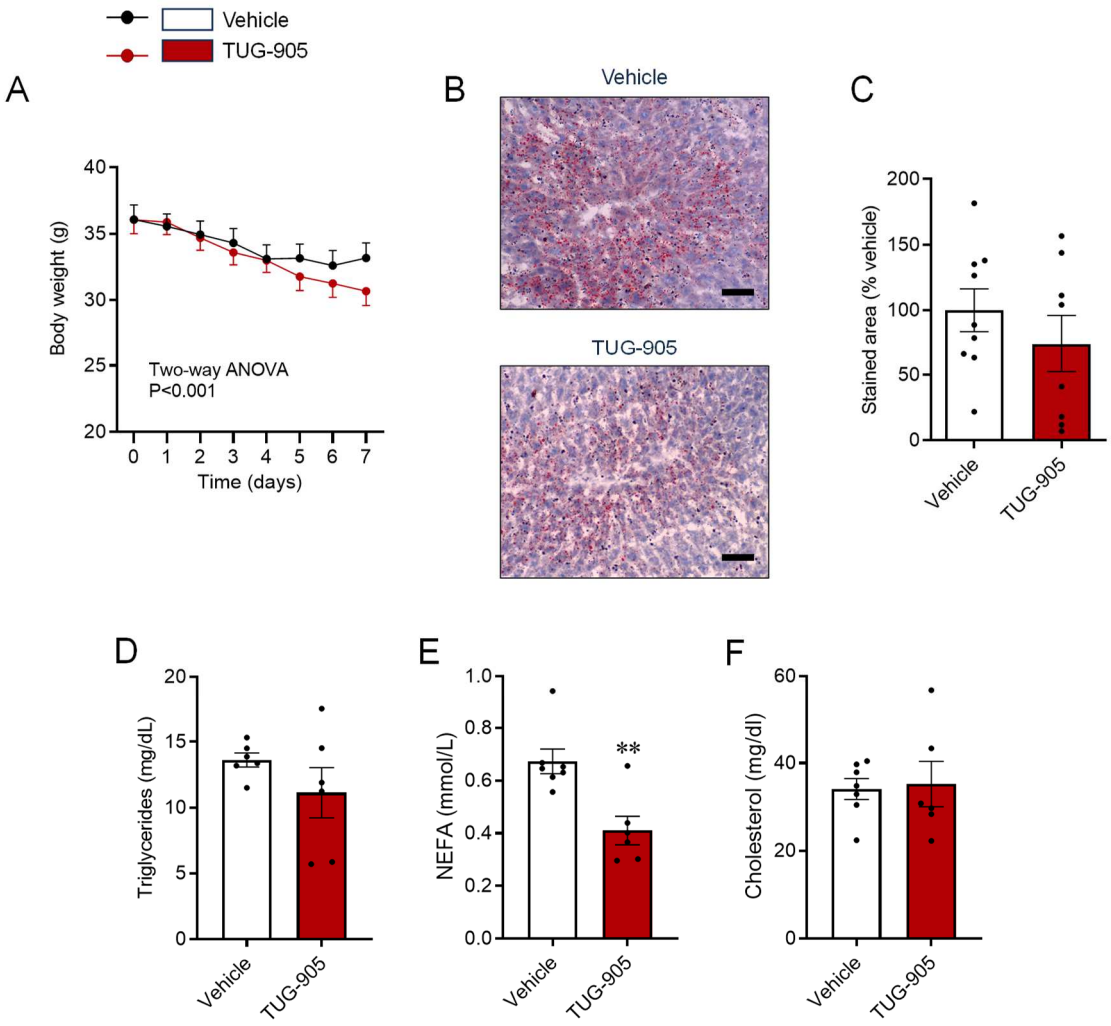
Supplementary Table 1. Antibodies used for western blot

Protein target	Company (catalog number)	Specie	Dilution
FFAR1	Sigma-Aldrich (SAB2108661)	rabbit	1:5000
β-Actin	Sigma-Aldrich (A5316)	mouse	1:5000
UCP1	Abcam (ab10983)	rabbit	1:5000
UCP3	Santa Cruz (sc-33182)	rabbit	1:1000
PGC1α	Santa Cruz (sc-17380)	mouse	1:1000
PPARγ	Santa Cruz (sc-7273)	mouse	1:1000
DIO2	Abcam (ab ab77779)	rabbit	1:1000
α-Tubulin	Sigma-Aldrich (T5168)	mouse	1:5000
p-IKK α/β (Ser- 180)	Santa Cruz (sc-23470)	rabbit	1:1000
p- SAPK/JNK (Thr183/Tyr185)	Cell Signaling (#4671)	rabbit	1:1000
GPR78	Cell Signaling (#3183)	rabbit	1:1000
p-IRE1 (Ser724)	Abcam (ab48187)	rabbit	1:1000
p-PERK (Thr980)	Cell Signaling (#3179)	rabbit	1:1000
p-eiF2a (Ser 52)	Santa Cruz (sc-101670)	rabbit	1:1000
ATF-6α (F-7)	Santa Cruz (sc-166659)	mouse	1:1000
CHOP	Cell Signaling (#5554)	rabbit	1:1000
p-STAT3 (Y705)	Abcam (ab76315)	rabbit	1:1000
SOCS3	Cell Signaling (#23064)	rabbit	1:1000
p-AKT (Ser 473)	Cell Signaling (#9271)	rabbit	1:1000
AKT	Cell Signaling (#9272)	rabbit	1:1000

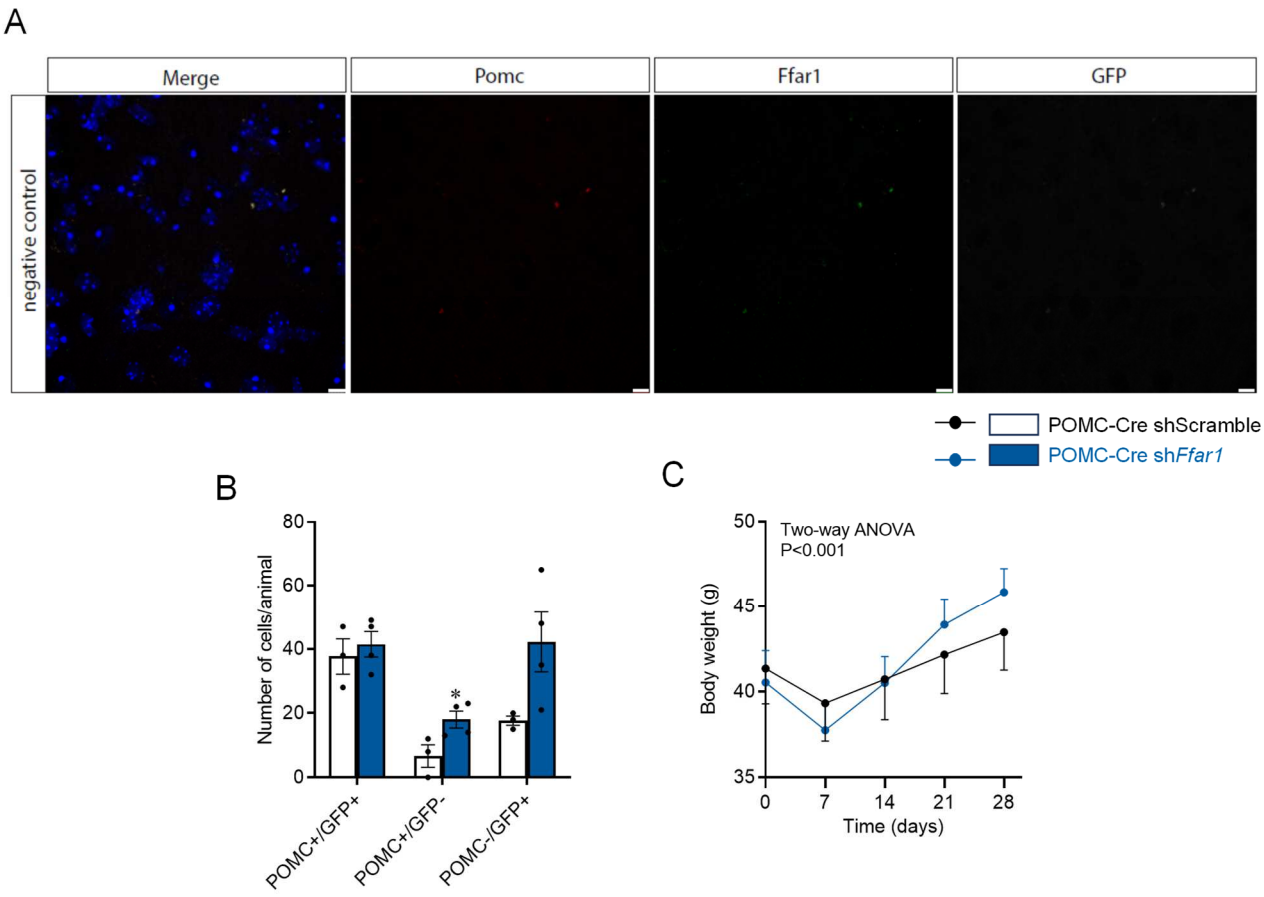
Supplementary Table 2. Primers used for RT-PCR

Primers	ThermoFisher TaqManGene Expression Assays ID
Ucp1	Mm01244861_m1
Pparg	Mm01184322_m1
Ppargc1a	Mm01208835_m1
Prdm16	Mm01266512_m1
Hprt	Mm01545399_m1



Supplementary Figure 1. Effect of central TUG-905 administration on energy balance and lipid metabolism

(A) Absolute body weight change during the 7 days experimental period (n=20-24 mice/group), **(B)** representative microphotographs of Oil-Red staining (10X, scale bar: 200 μm), **(C)** hepatic lipid content in Oil Red O-stained sections (n=8-9 mice/group), circulating **(D)** triglycerides, **(E)** NEFA and **(F)** cholesterol (n=6-7 mice/group) of vehicle and TUG-905 ICV-treated DIO mice. Data are expressed as MEAN±SEM. Statistical significance was determined by two-way ANOVA (A) or Student's t-test (C, D, E, and F); **P<0.01 vs. vehicle.



Supplementary Figure 2. Effect of POMC-specific Ffar1 knockdown on energy balance
(A) Negative control probes for GFP and FFAR1, **(B)** number of $POMC^{+}/GFP^{+}$, $POMC^{+}/GFP^{-}$, $POMC^{-}/GFP^{-}$ cells (n= 3-4 mice/group) and **(C)** absolute body weight change (n= 11 mice/group) of POMC-Cre mice treated with AAV encoding shScramble or shFfar1. Data are expressed as MEAN±SEM. Statistical significance was determined by two-way ANOVA (C) or Student's t-test (B). $*P < 0.05$ vs. shScramble.