Supplementary Information

A sensitive red/far-red photoswitch for controllable gene therapy in mouse models of metabolic diseases

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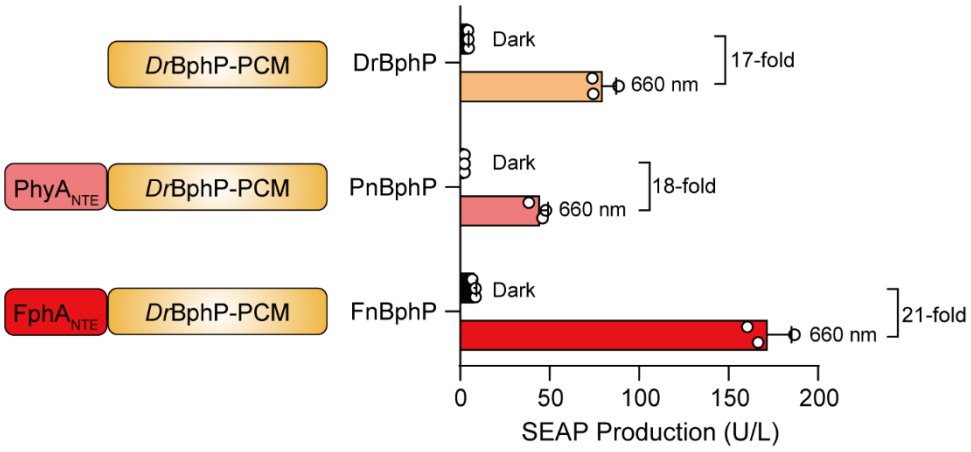
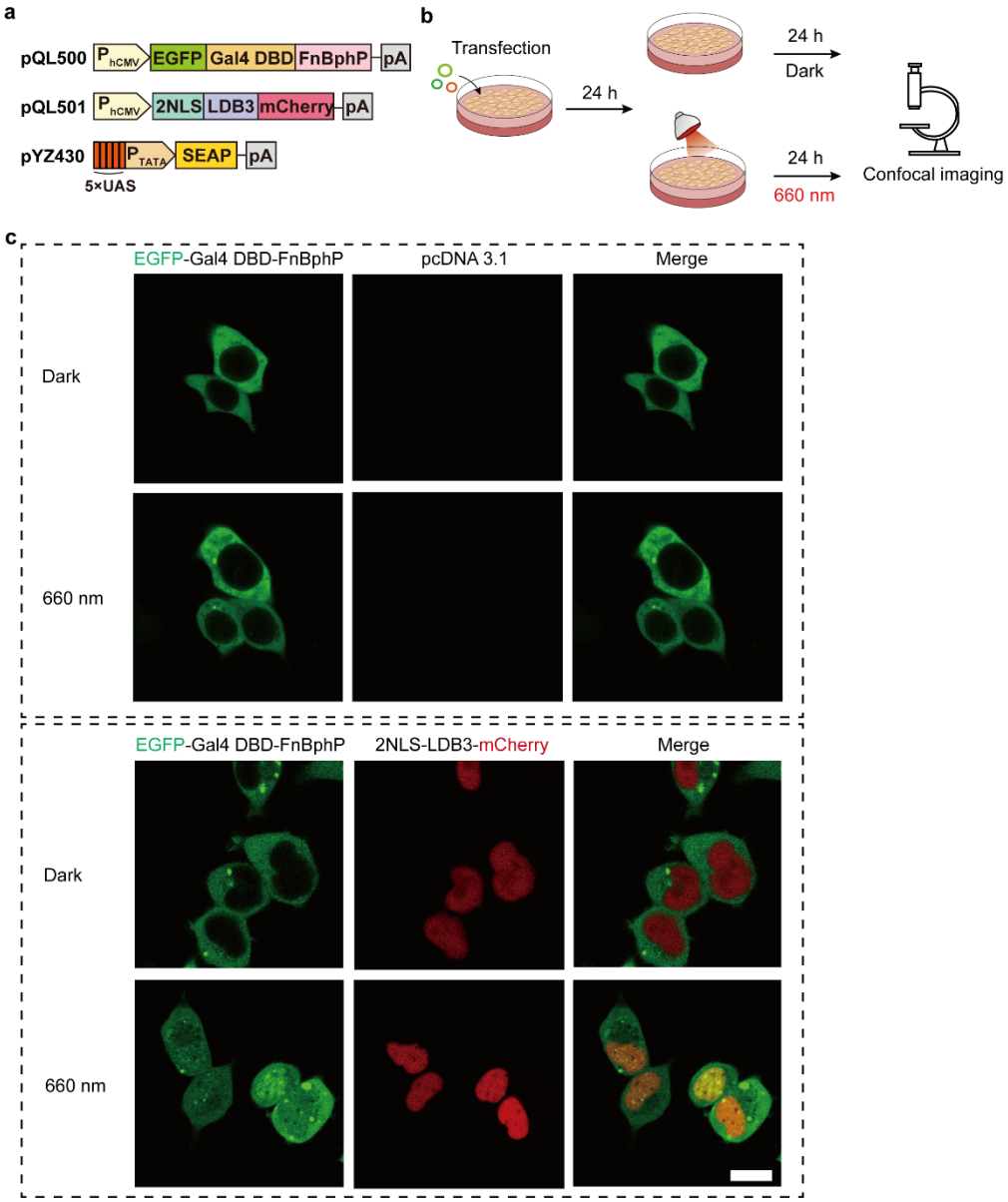
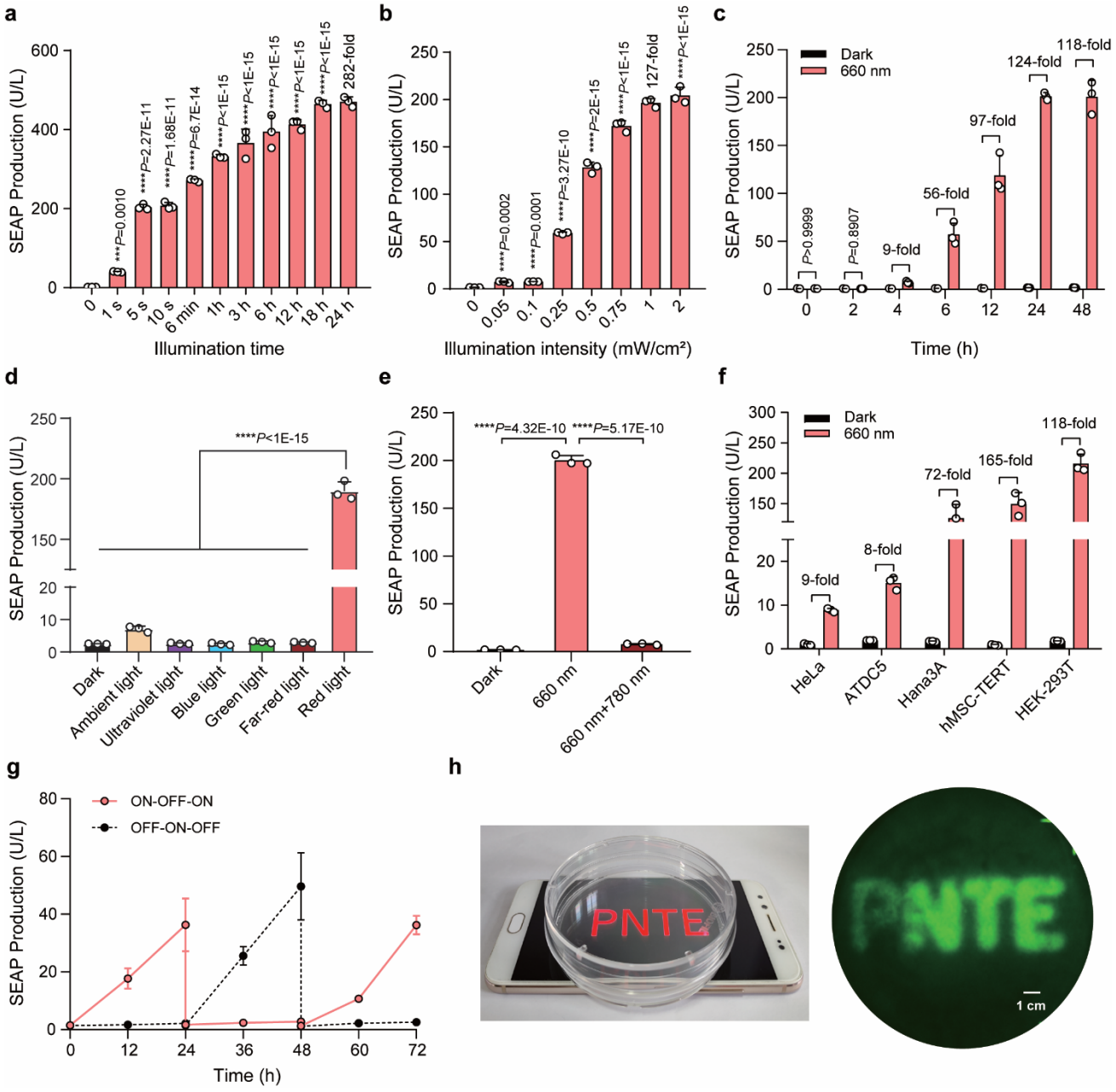


Supplementary Fig. 1 Performance comparison between the different chimeric BphP constructs fused to the Gal4 DBD domain. HEK-293T cells (6×10^4) were co-transfected with a SEAP reporter expression vector (pDL6), the LDB3-VP64 expression vector (pQL207), and the different chimeric BphP: Gal4 DBD-*Dr*BphP expression vector (pQL217), Gal4 DBD-PnBphP expression vector (pQL325), or Gal4 DBD-FnBphP expression vector (pQL326), and then illuminated with red light (RL, 660 nm, 2.0 mW/cm^2) for 24 hours; SEAP production in the culture supernatant was quantified 24 hours after illumination. Data are presented as means ± SD; n = 3 independent experiments. Detailed descriptions of the genetic constructs and transfection mixtures are provided in **Supplementary Data 1** and **Supplementary Data 4**.

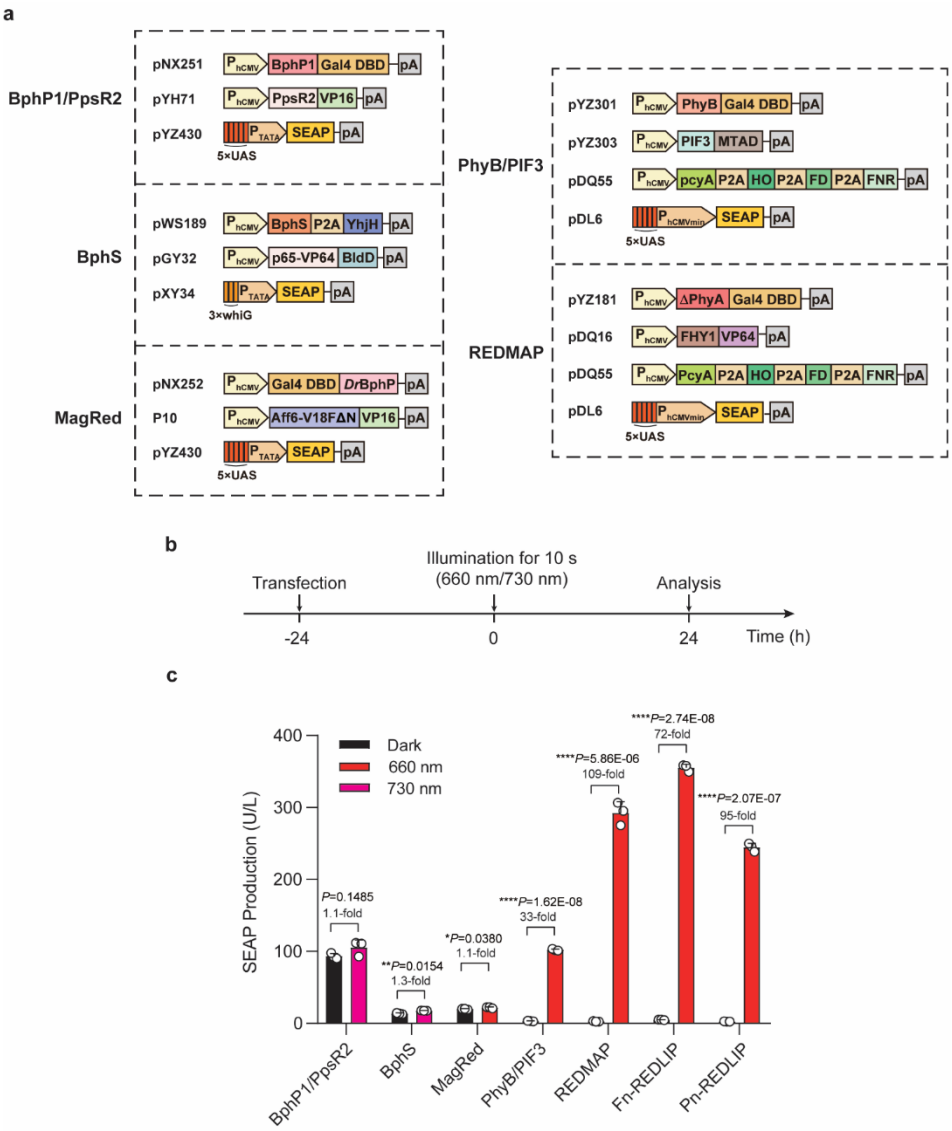


Supplementary Fig. 2 Red light induced the nuclear translocation of the REDLIP system constructs. a, Schematic representation of the genetic configuration for the red light-inducible nuclear translocation of the REDLIP system constructs. **b**, Schematic of the time schedule and experimental procedure for studying the nuclear translocation. **c**, Confocal imaging of red light-inducible nuclear localization of the REDLIP system constructs. HEK-293T cells were co-transfected with pQL500 (P_{hCMV}-EGFP-Gal4 DBD-FnBphP-pA), pYZ430, pcDNA3.1 or pQL501 (P_{hCMV}-LDB3-mCherry-pA). Twenty-four hours after transfection, one group was illuminated with red-light (660 nm, 1.5 mW/cm^2) for 24 hours, while the other group was kept in the dark. Cells were then fixed and analyzed by confocal microscopy. Scale bars: 10 μm.



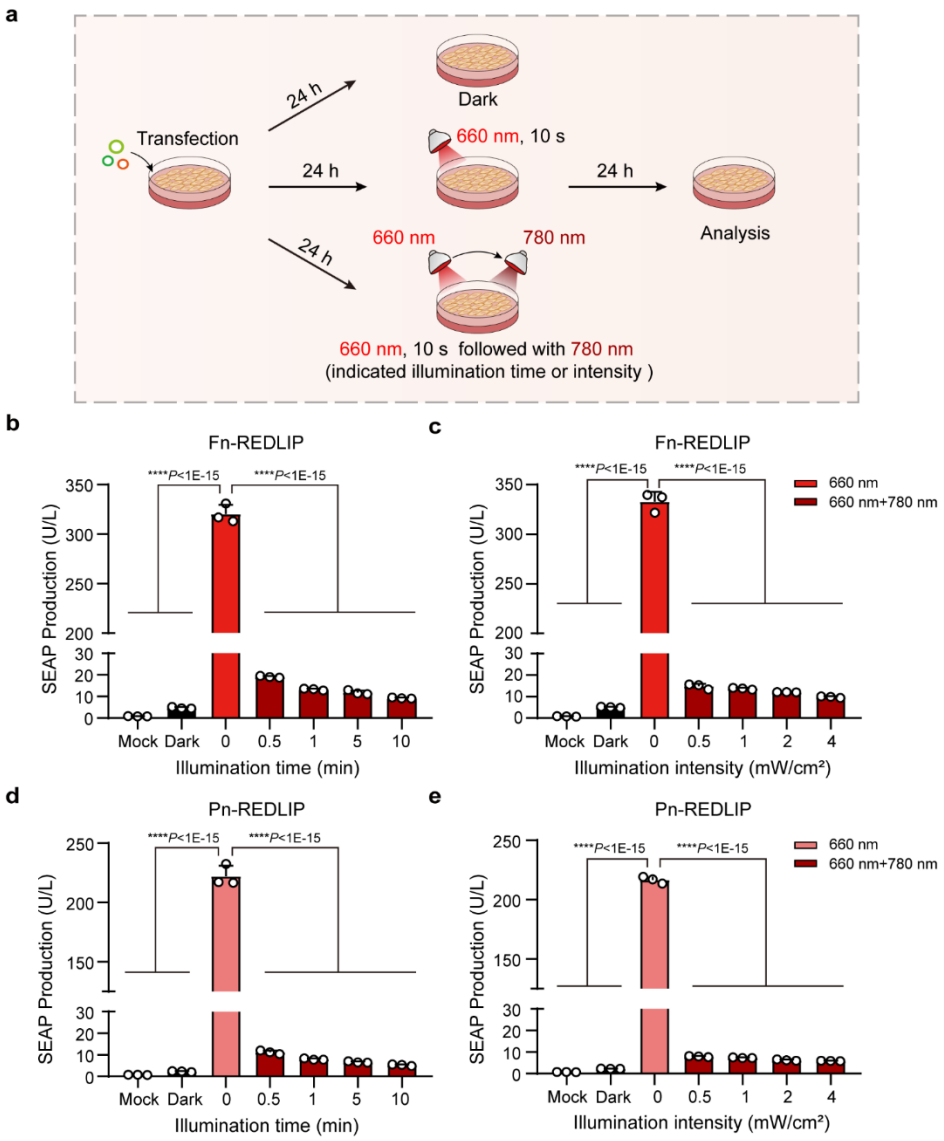
Supplementary Fig. 3 Characterization of the performance of the Pn-REDLIP system in mammalian cells. a, Assessment of illumination time-dependent Pn-REDLIP-mediated transgene expression kinetics. HEK-293T cells (6×10^4) co-transfected with Gal4 DBD-PnBphP vector (pQL325), LDB3-p65-HSF1 expression vector (pNX12), and the SEAP reporter expression vector (pYZ430, P_{RL}-SEAP-pA) at a 2:2:1 (w/w/w) ratio were illuminated with RL (660 nm, 2.0 mW/cm^2) for the indicated time (0-24 hours). SEAP production was quantified 24 hours after initial illumination. **b,** Illumination intensity-dependent Pn-REDLIP-mediated transgene expression kinetics. **c,** Quantification of Pn-REDLIP-mediated transgene expression kinetics. **d,** Chromatic specificity of the Pn-REDLIP system. **e,** The switch ON/OFF performance of the Pn-REDLIP system. **f,** Pn-REDLIP-mediated SEAP

expression in the indicated mammalian cell lines. **g,** Reversibility of Pn-REDLIP-mediated transgene expression. **h,** Spatial control of Pn-REDLIP-mediated transgene expression. Scale bar, 1 cm. Three times the experiment was repeated with similar results. Data in a-g are presented as means ± SD; n = 3 independent experiments. P values in (**a**, **b**, **d**, and **e**) were calculated by one-way ANOVA with multiple comparisons. P values in **c** were calculated using a two-tailed unpaired t-test. Detailed descriptions of the genetic constructs and transfection mixtures are provided in **Supplementary Data 1** and **Supplementary Data 4**.

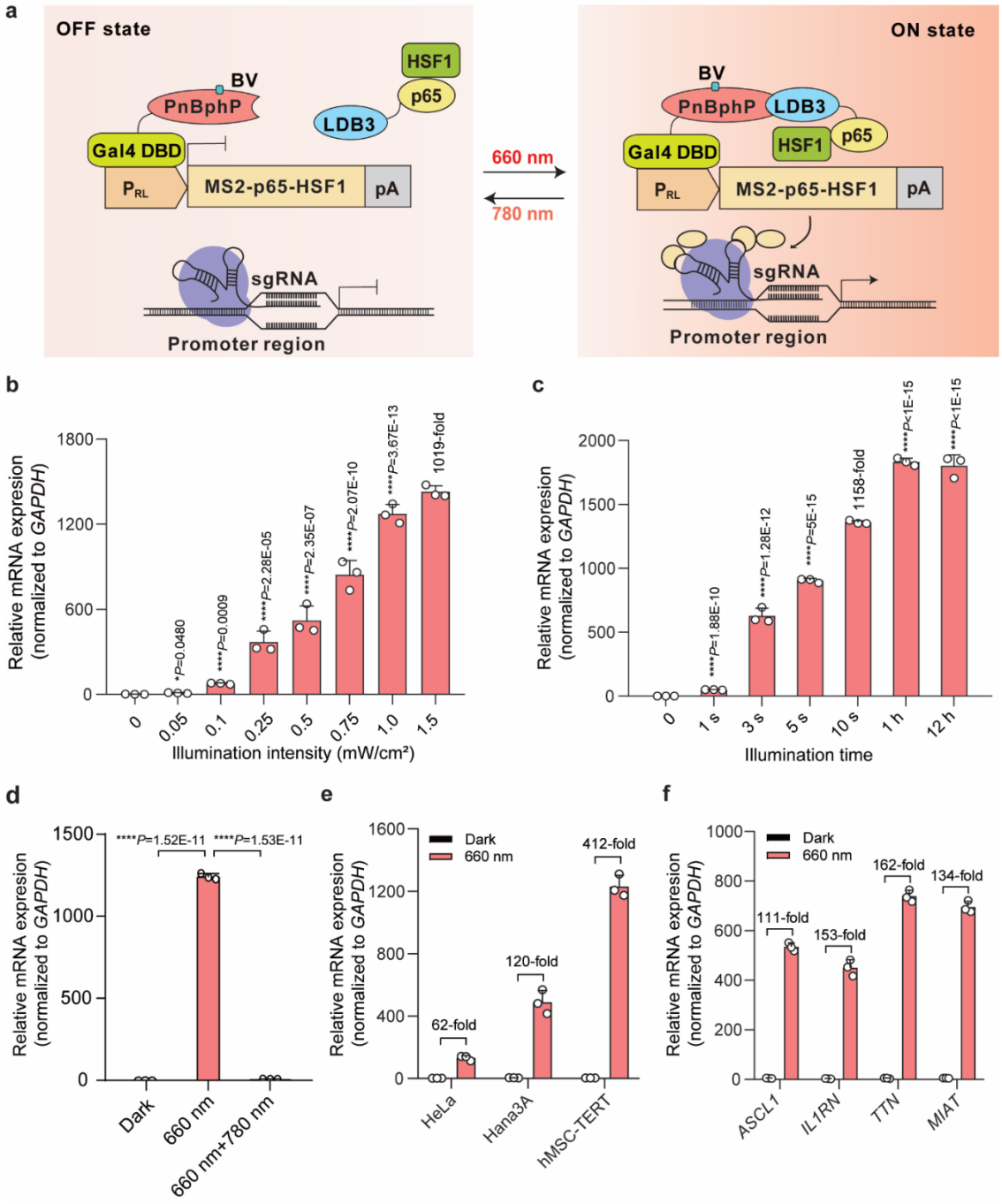


Supplementary Fig. 4 Comparison of the Fn-REDLIP and Pn-REDLIP systems with other red/far-red light-inducible transgene expression systems. a, Schematic representation of the genetic configurations for BphP1/PpsR2, BphS, MagRed, PhyB/PIF3, and REDMAP systems. **b,** Schematic representation of the experimental procedure and time schedule for all red/far-red light-mediated transgene expression systems in HEK-293T cells. HEK-293T cells (6×10^4) were co-transfected with the plasmids encoding BphP1/PpsR2, BphS, MagRed, PhyB/PIF3, REDMAP, Fn-REDLIP or Pn-REDLIP systems, and a SEAP reporter expression vector. Twenty-four hours after transfection, cells were then exposed to light (730 nm or 660 nm, 2.0 mW/cm^2) for 10 seconds. **c,** SEAP expression in the culture supernatant was scored 24 hours after illumination. Data are presented as means ± SD; n = 3 independent experiments. P values in **c** were calculated using a two-tailed unpaired t-test. Detailed

descriptions of genetic components and transfection mixtures are provided in **Supplementary Data 1** and **Supplementary Data 4**.

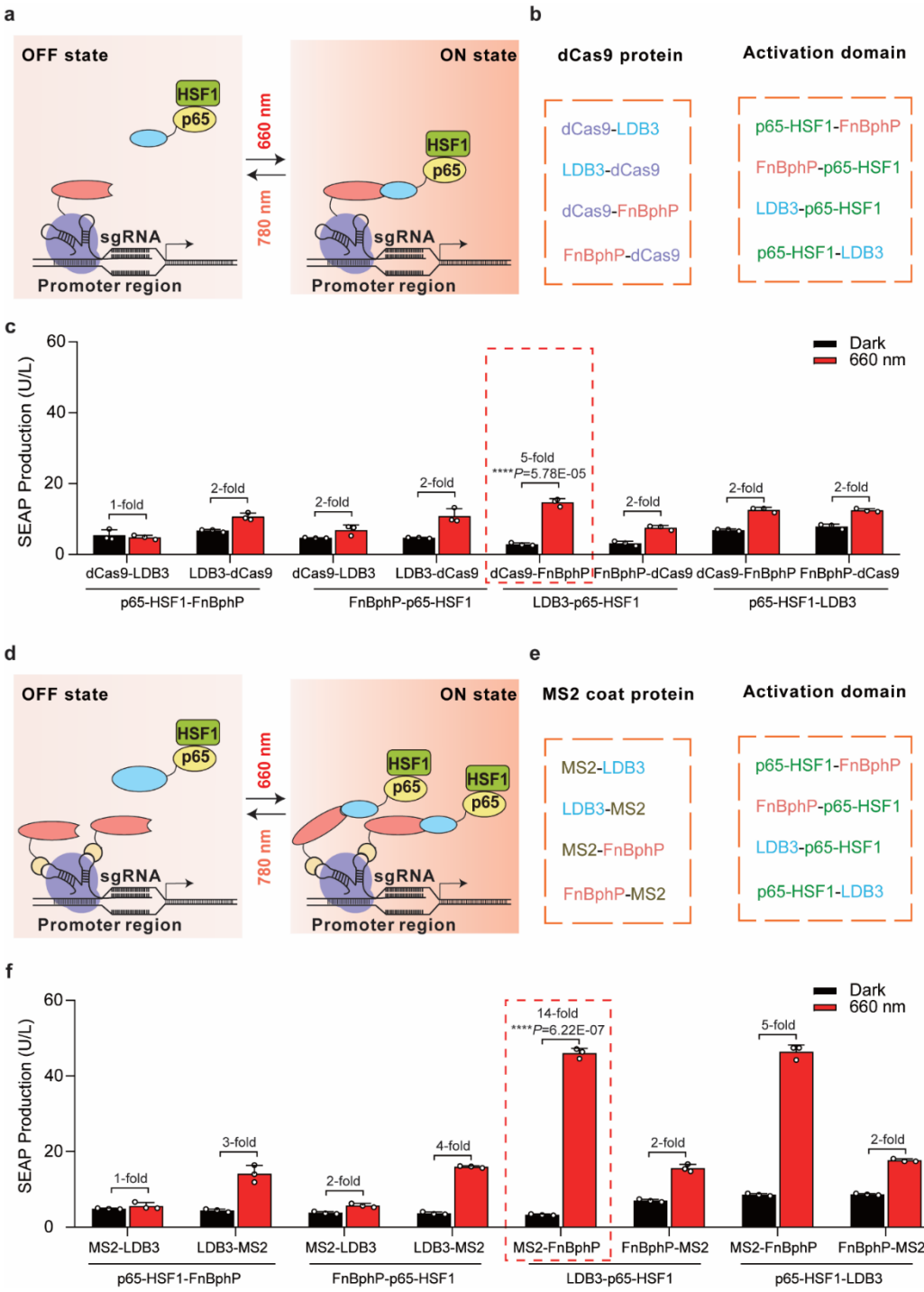


Supplementary Fig. 5 Characterization of far-red light-dependent OFF kinetics of the Fn-REDLIP and Pn-REDLIP systems. a, Schematic for the time schedule and experimental procedure of the activation/deactivation performance of the Fn-REDLIP and Pn-REDLIP systems. **b,** Illumination time-dependent Fn-REDLIP-mediated OFF kinetics of transgene expression. **c,** Illumination intensity-dependent Fn-REDLIP-mediated OFF kinetics of transgene expression. **d,** Illumination time-dependent Pn-REDLIP-mediated OFF kinetics of transgene expression. **e,** Illumination intensity-dependent Pn-REDLIP-mediated OFF kinetics of transgene expression. Data are presented as means ± SD; n = 3 independent experiments. P values were calculated by one-way ANOVA with multiple comparisons. Detailed descriptions of genetic components and transfection mixtures are provided in **Supplementary Data 1** and **Supplementary Data 4**.



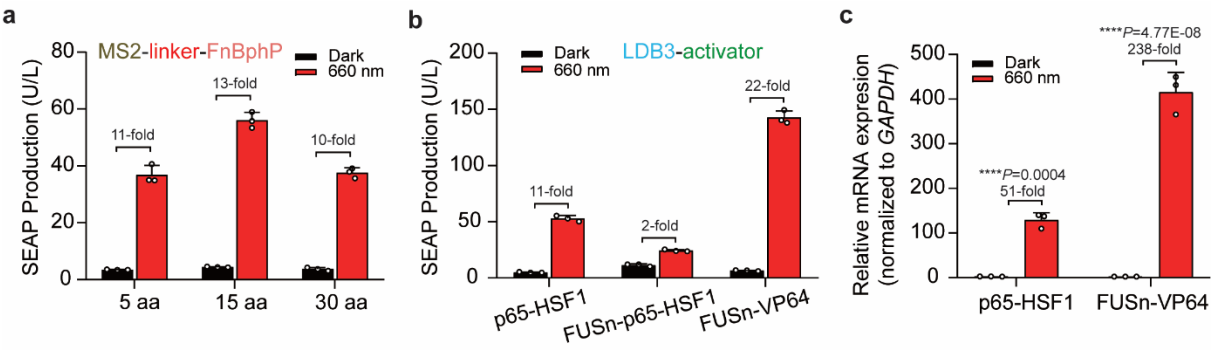
Supplementary Fig. 6 Pn-REDLIP-controlled CRISPR-dCas9 system (Pn-REDLIP$_{cas}$) for endogenous gene activation *in vitro*. a, Schematic design of the Pn-REDLIP$_{cas}$ system for transcriptional activation. The RL chimeric promoter (P_{RL}) drove the expression of the *trans*-activator MS2-p65-HSF1, which can be recruited by the MS2 box of the sgRNA-dCas9 complex to activate target gene transcription under RL (660 nm) illumination. FRL (780 nm) illumination can switch the Pn-REDLIP$_{cas}$ system back to an inactive state. **b,** Illumination intensity-dependent Pn-REDLIP$_{cas}$ system-mediated activation of endogenous gene transcription. HEK-293T (6×10^4) cells were co-

transfected with pQL325, pNX12, a P_{RL}-driven MS2-p65-HSF1 expression vector (pDQ100), dCas9 expression vector (pSZ69), and two sgRNAs targeting the RHOXF2 locus (pSZ105, P_{U6}-sgRNA1$_{RHOXF2}$-pA; pSZ106, P_{U6}-sgRNA2$_{RHOXF2}$-pA) at a 15:15:1:10:5:5 (w/w/w/w/w/w) ratio, followed by illumination with RL (660 nm) at the indicated intensities (0 to 1.5 mW/cm^2) for 10 seconds. **c,** Illumination time-dependent Pn-REDLIP$_{cas}$ system-mediated activation of endogenous gene transcription. **d,** The switch ON/OFF performance of the Pn-REDLIP$_{cas}$ system. **e,** The Pn-REDLIP$_{cas}$-mediated endogenous gene activation in the indicated mammalian cell lines. **f,** The Pn-REDLIP$_{cas}$-mediated activation of different endogenous genes. Data in **b-f** are presented as relative mRNA expression levels quantified by qPCR 24 hours after illumination. All data are represented as means ± SD; n = 3 independent experiments. P values were calculated by one-way ANOVA with multiple comparisons. Detailed descriptions of genetic components and transfection mixtures are provided in **Supplementary Data 1** and **Supplementary Data 4**.

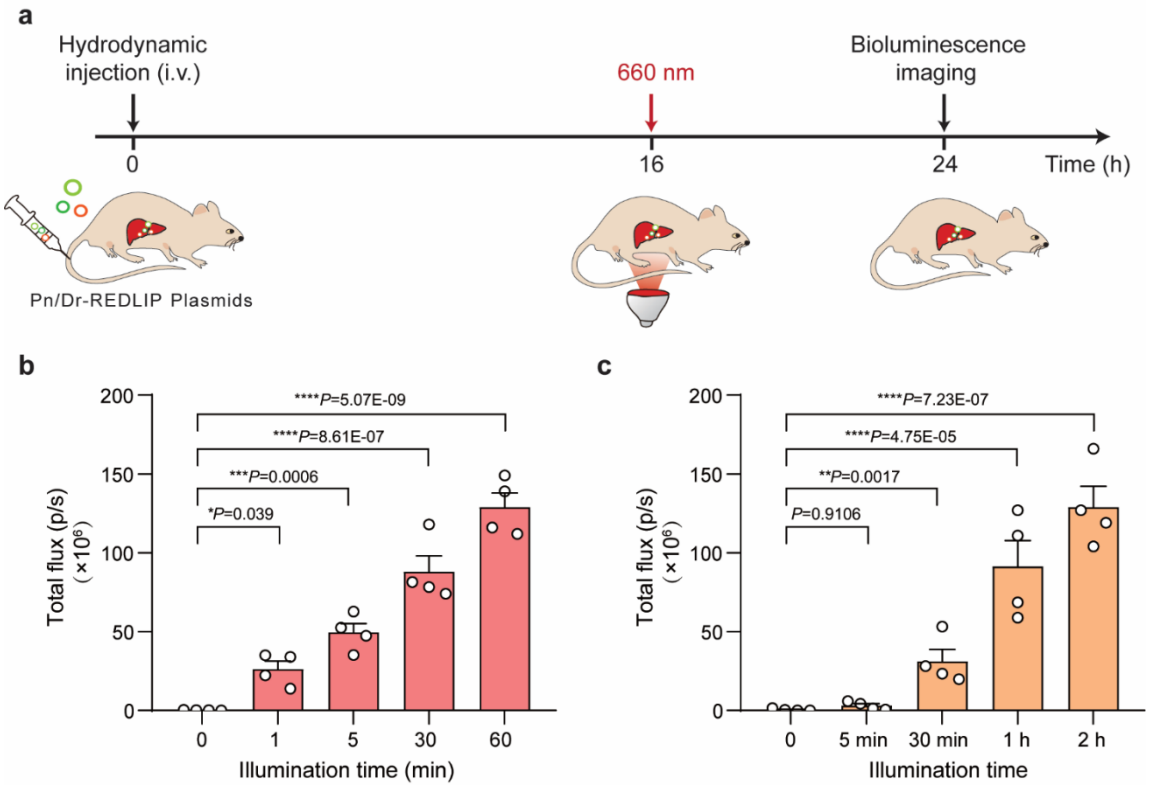


Supplementary Fig. 7 Fn-REDLIP-controlled CRISPR-dCas9 system (Fn-REDLIP$_{cas}$) for target gene activation in mammalian cells. a, Schematic design of the Fn-REDLIP$_{cas}$ system for transcriptional activation by directly fusing FnBphP or its interacting partner LDB3 to dCas9 protein. **b**, Comprehensive architectures with FnBphP or LDB3 fused to either the N- or C-terminus of the p65-HSF1 transactivation domain and the dCas9 protein. **c,** Activation of SEAP reporter gene expression in eight different combinations. HEK-293T (6×10^4) cells were co-transfected with the fusion light

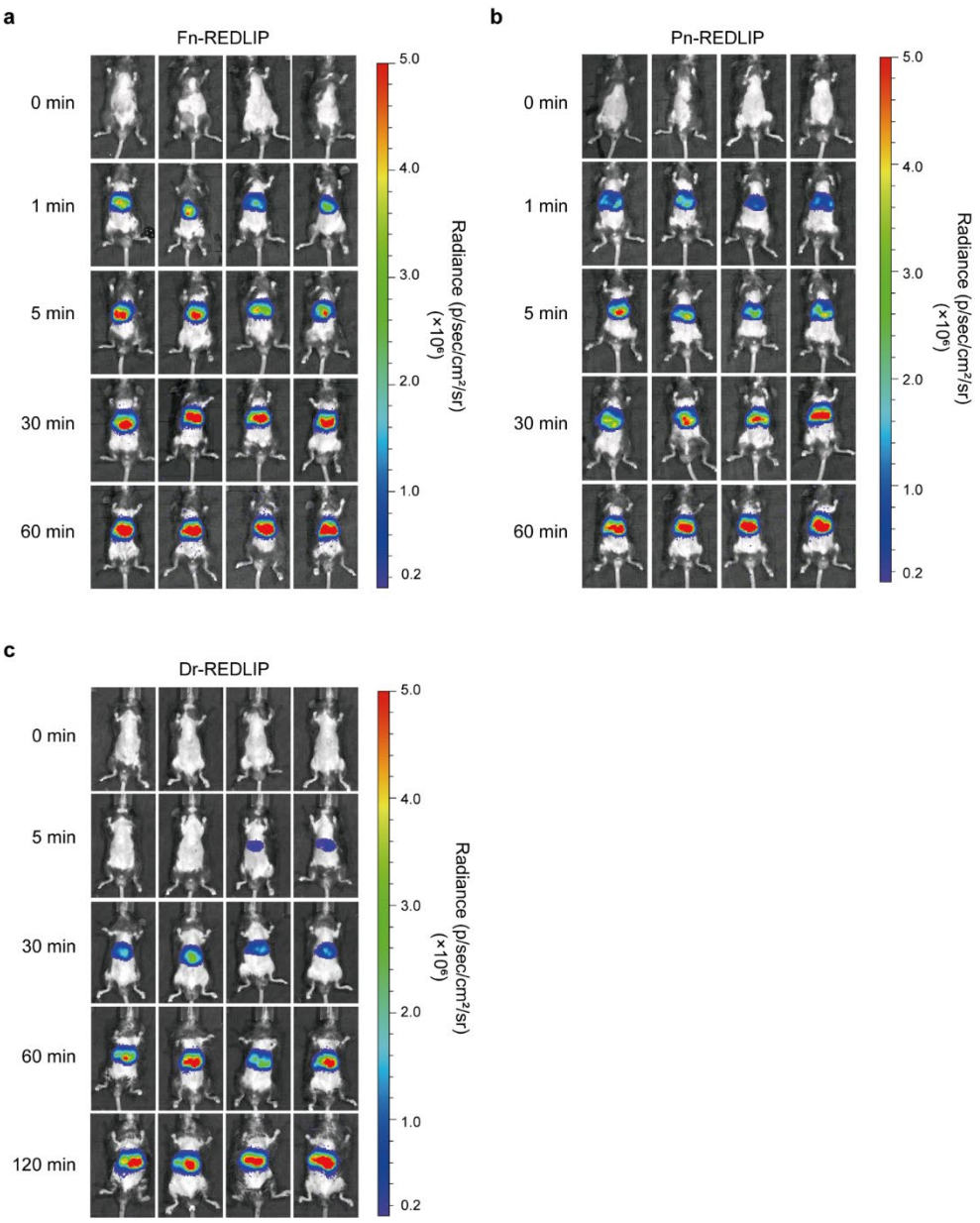
sensor domain (left box in b), RL-dependent *trans*-activator (right box in b), a P_{RL}-driven SEAP expression vector (pWH91) and a sgRNA targeting the exogenous *SEAP* gene (pWH189, P_{U6}-sgRNA1$_{SEAP}$-pA) at a 3:3:1:1 (w/w/w/w) ratio, followed by illumination with RL (660 nm) at 1.5 mW/cm^2 for 24 hours. SEAP production was quantified 24 hours after illumination. **d**, Schematic design of the Fn-REDLIP$_{cas}$ system for transcriptional activation by directly fusing FnBphP or its interacting partner LDB3 to the MS2 coat protein. **e**, Comprehensive architectures with FnBphP or LDB3 fused to either the N- or C-terminus of the p65-HSF1 transactivation domain and the MS2 coat protein. **f,** Activation of SEAP reporter gene expression in eight different combinations. HEK-293T (6×10^4) cells were co-transfected with the fusion light sensor domain (left box in e), RL-dependent *trans*-activator (right box in e), dCas9 expression vector (pSZ69), a P_{RL}-driven SEAP expression vector (pWH91), and a sgRNA targeting the exogenous *SEAP* gene (pWH189, P_{U6}-sgRNA1$_{SEAP}$-pA) at a 3:3:2:1:1 (w/w/w/w/w) ratio, followed by illumination with RL (660 nm) at 1.5 mW/cm^2 for 24 hours. SEAP production was quantified 24 hours after illumination. All data are represented as means ± SD; $n = 3$ independent experiments. *P* values in **c**, **d** were calculated using a two-tailed unpaired *t*-test. Detailed descriptions of genetic components and transfection mixtures are provided in **Supplementary Data 1** and **Supplementary Data 4**.



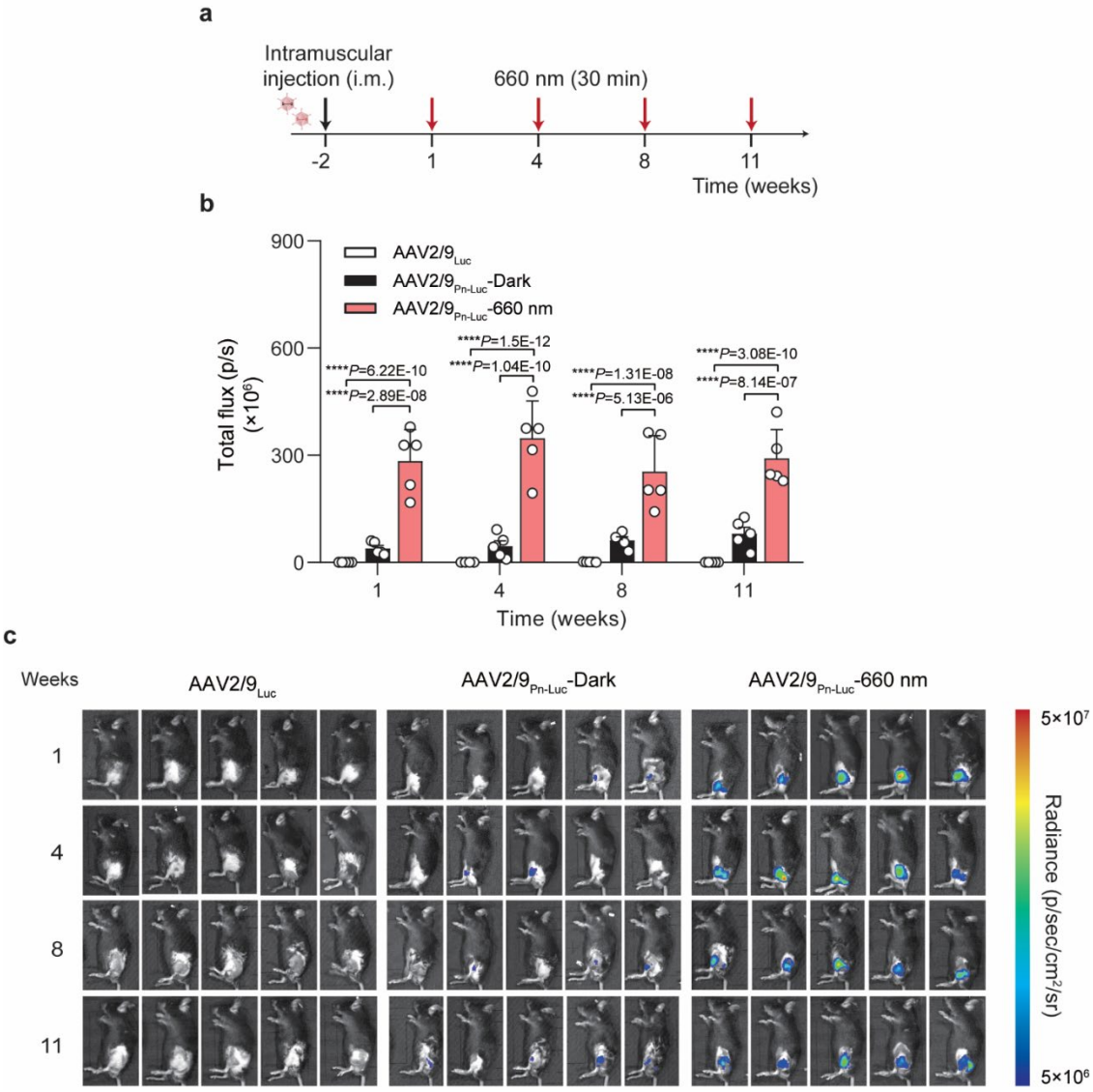
Supplementary Fig. 8 Optimization of the Fn-REDLIP$_{cas}$ system for target gene activation in mammalian cells. a, Optimization of the linker length between MS2 and FnBphP. HEK-293T cells (6×10^4) were co-transfected with pQL236, pWH91, pWH189, pSZ69, and MS2-linker-FnBphP expression vectors: pQL518 (5 aa), pQL508(15 aa), or pQL517(30 aa), followed by illumination with RL (660 nm, 1.5 mW/cm^2) for 24 hours; SEAP production in the culture supernatant was quantified 24 hours after illumination. **b,** Optimization of different transcriptional activators fused to LDB3. HEK-293T cells (6×10^4) were co-transfected with pWH91, pWH189, pSZ69, pQL508, and LDB3-p65-HSF1 (pQL236), LDB3-FUSn-p65-HSF1 (pQL526), or LDB3-FUSn-VP64 (pQL527), followed by illumination with RL at 1.5 mW/cm^2 for 24 hours. SEAP production was quantified 24 hours after illumination. **c,** Activation of the endogenous gene expression. HEK-293T (6×10^4) cells were co-transfected with pSZ69, pQL508, two sgRNAs targeting the *RHOXF2* locus (pSZ105, P_{U6}-sgRNA1$_{RHOXF2}$-pA; pSZ106, P_{U6}-sgRNA2$_{RHOXF2}$-pA), and either pQL236 or pQL527, followed by illumination with RL (660 nm) at 1.5 mW/cm^2 for 24 hours. Endogenous *RHOXF2* levels were quantified by qPCR at 24 hours after illumination. *P* values in **c** were calculated using a two-tailed unpaired *t*-test. Detailed descriptions of genetic components and transfection mixtures are provided in **Supplementary Data 1** and **Supplementary Data 4**.



Supplementary Fig. 9 Pn-REDLIP and Dr-REDLIP mediated transgene expression in mice. a, Schematic representation of the experimental procedure and time schedule for Pn-REDLIP and Dr-REDLIP mediated transgene expression in mice. **b,** Exposure time-dependent Pn-REDLIP-mediated transgene expression kinetics in mice. Mice hydrodynamically injected with Pn-REDLIP-encoding plasmids were illuminated with RL (660 nm, 20 mW/cm^2) for different time periods. The bioluminescence signal was quantified 8 hours after illumination using an *in vivo* imaging system. **c,** Exposure time-dependent Dr-REDLIP-mediated transgene expression kinetics in mice. Mice hydrodynamically injected with Dr-REDLIP-encoding plasmids were illuminated with RL (660 nm, 20 mW/cm^2) for different time periods. The bioluminescence signal was quantified 8 hours after illumination using an *in vivo* imaging system. Data are presented as means ± SEM (n = 4 mice). P values were calculated by one-way ANOVA with multiple comparisons. Detailed bioluminescence images of the mice are provided in **Supplementary Fig. 10b, c**.

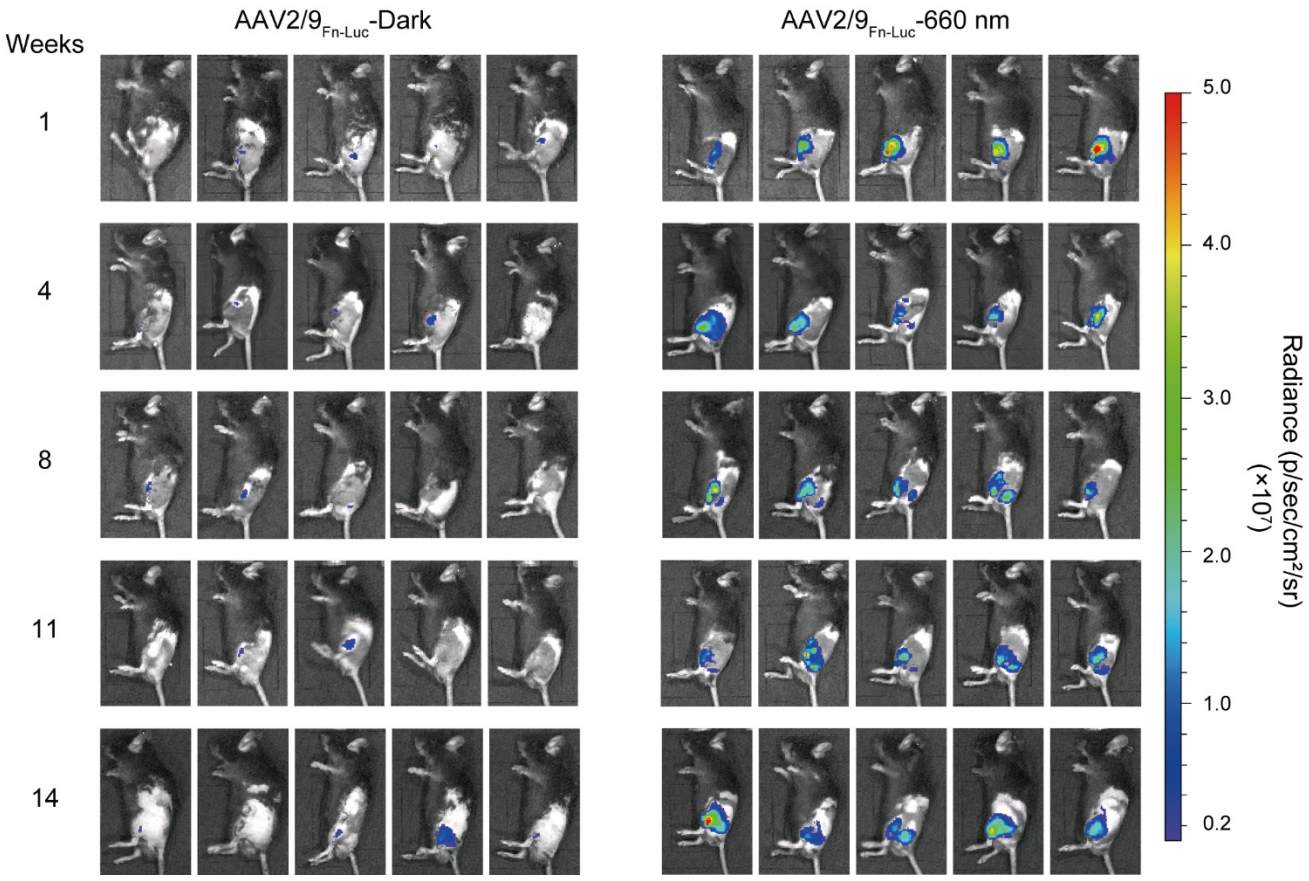


Supplementary Fig. 10 Illumination of three types of time-dependent REDLIP systems-mediated transgene expression kinetics in mice (related to Fig. 4c and Supplementary Fig. 9b, c). *In vivo* bioluminescence images of mice illuminated with RL for different time periods. Mice hydrodynamically injected with three types of REDLIP system-encoded plasmids were illuminated with RL (660 nm, 20 mW/cm^2) for different time periods, and bioluminescence was quantified at 8 hours after illumination. (**a**) Fn-REDLIP; (**b**) Pn-REDLIP; (**c**) Dr-REDLIP). n = 4 mice.

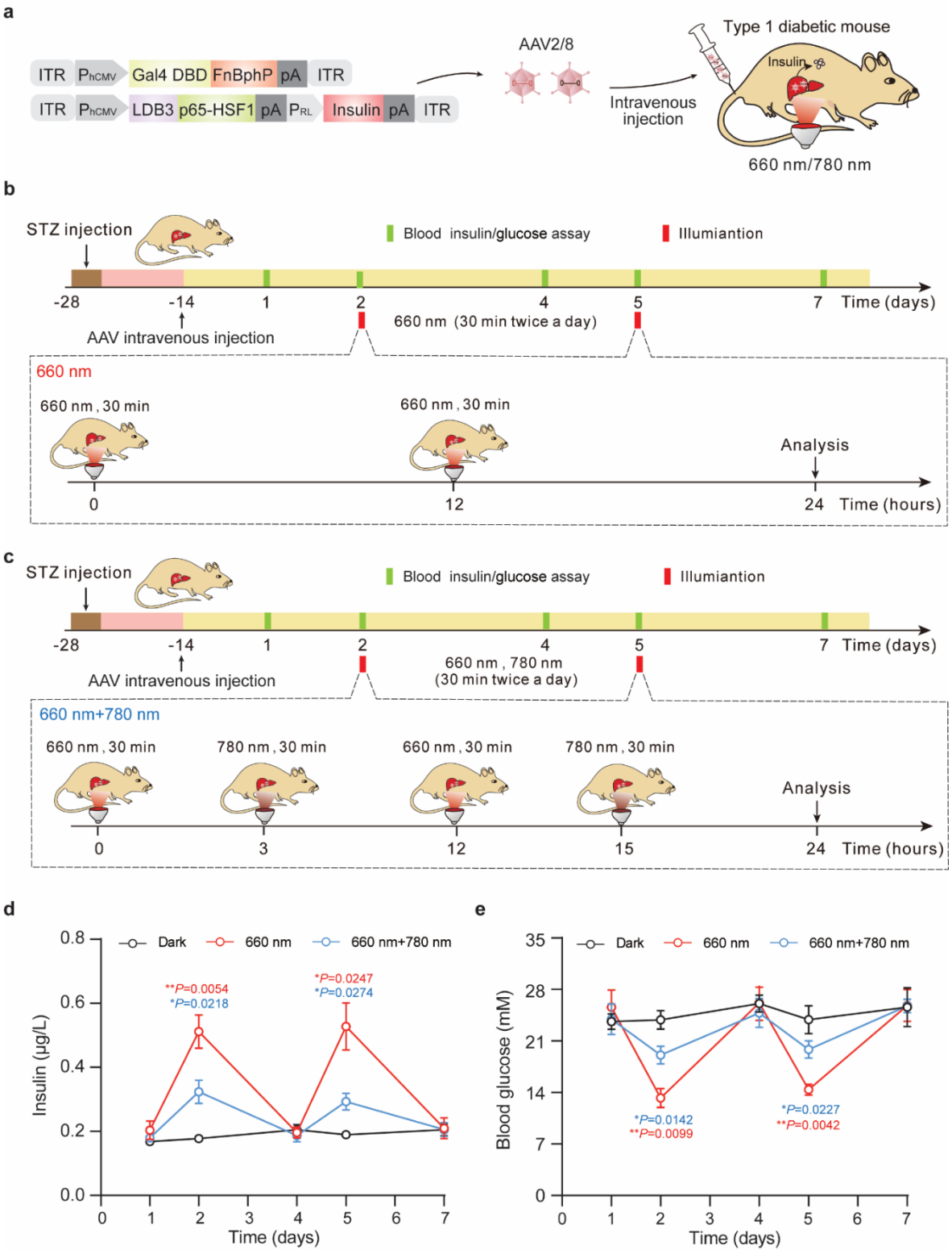


Supplementary Fig. 11 Pn-REDLIP-mediated transgene expression in mice. a, Schematic representation of the experimental procedure and time schedule for the AAV-2/9 delivery of Pn-REDLIP-mediated transgene expression in the mouse left gastrocnemius muscle. Mice were intramuscularly injected with a mixture of AAV2/9 vectors encoding the Pn-REDLIP system [(pNX257 (ITR-P_{EMS}-Gal4 DBD-PnBphP-pA-ITR)，pNX137 (ITR-P_{EMS}-LDB3-p65-HSF1-pA-ITR)] and the luciferase reporter pQL271 (ITR-P_{RL}-Luciferase-pA-ITR) or only the luciferase reporter pQL271 at an AAV titer of 2×10^{11} vg. The control group received an intramuscular injection (left gastrocnemius muscle) of the RL-responsive luciferase reporter (AAV2/9_{Luc}, 2×10^{11} vg). After 2 weeks, the injected mice were illuminated at an intensity of 20 mW/cm^2 for 30 minutes once every three or four weeks. **b,** Bioluminescence was quantified 8 hours after illumination. **c,** Bioluminescence measurements of Pn-REDLIP-mediated luciferase expression in AAV-transduced mice under RL

illumination. Data in **b** are presented as means ± SEM (n = 5 mice). P values in **b** were calculated by one-way ANOVA with multiple comparisons.

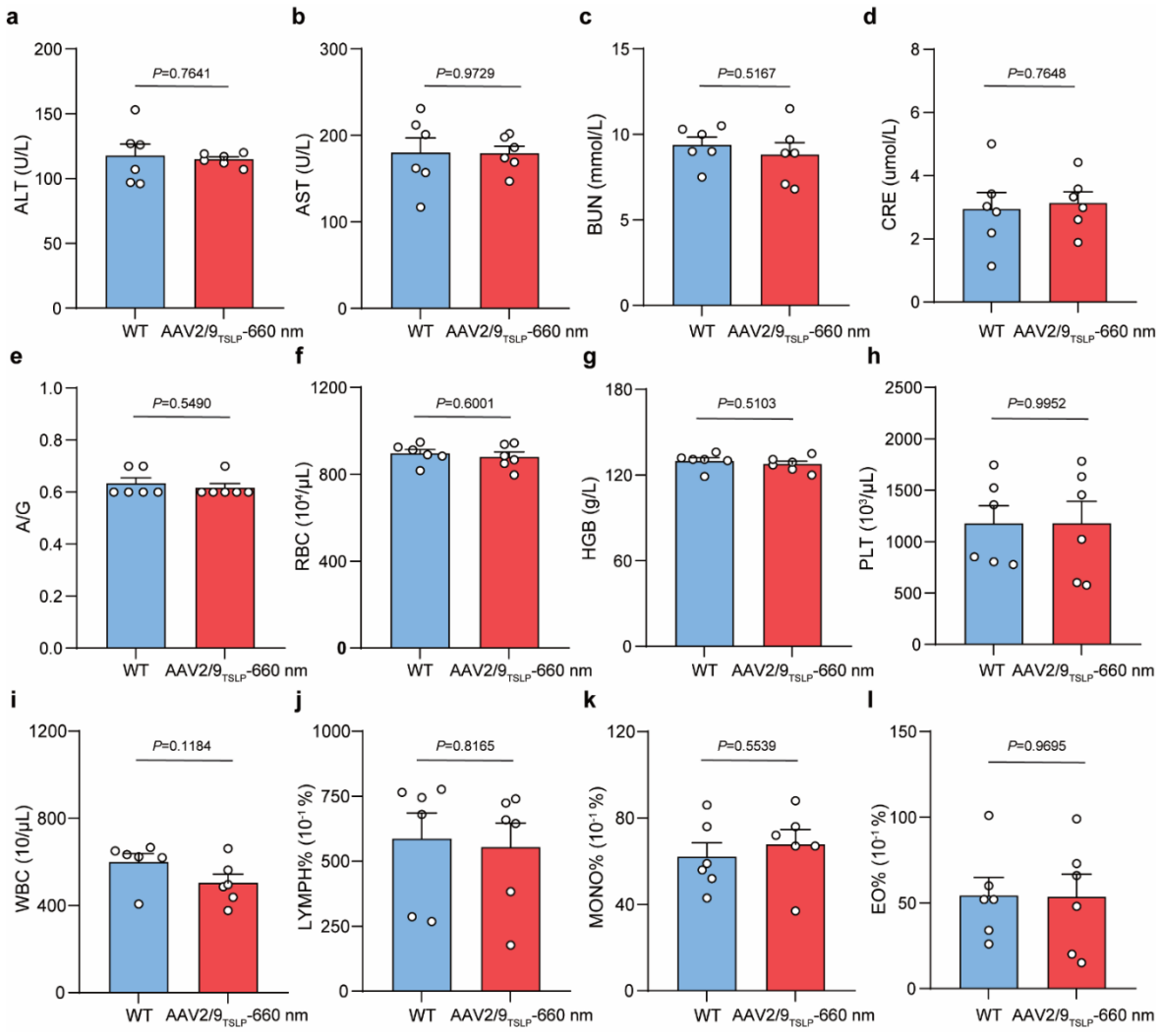


Supplementary Fig. 12 Long-term study of AAV-delivered Fn-REDLIP-mediated transgene expression in mice (related to Fig. 4e). A mixture of AAV-2/9 vectors encoding Fn-REDLIP systems were intramuscularly injected into the left gastrocnemius muscle of mice. Two weeks after the AAV transduction, mice were illuminated with RL (20 mW/cm^2) at an intensity of 20 mW/cm^2 for 30 minutes once every three or four weeks. Bioluminescence was quantified 8 hours after illumination. *n* = 5 mice.

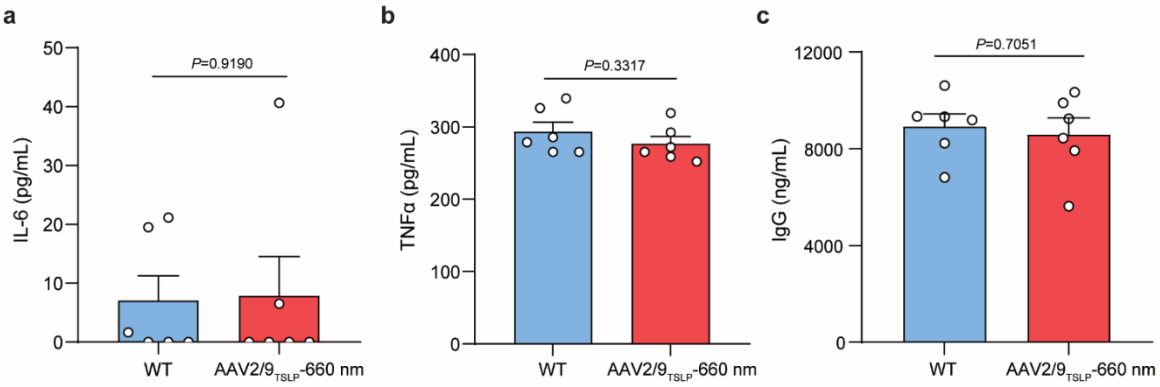


Supplementary Fig. 13 AAV-delivered Fn-REDLIP system controlling hepatic insulin expression in T1D mice with on/off capability. a, Schematic for the AAV-2/8 vectors for the Fn-REDLIP system iteration containing pNX177 (ITR-P_{hCMV}-Gal4 DBD-FnBphP-pA-ITR) and the concatenated vector pQL318 (ITR-P_{hCMV}-LDB3-p65-HSF1-pA::P_{RL}-insulin-pA-ITR). **b, c,** Schematic illustration for the

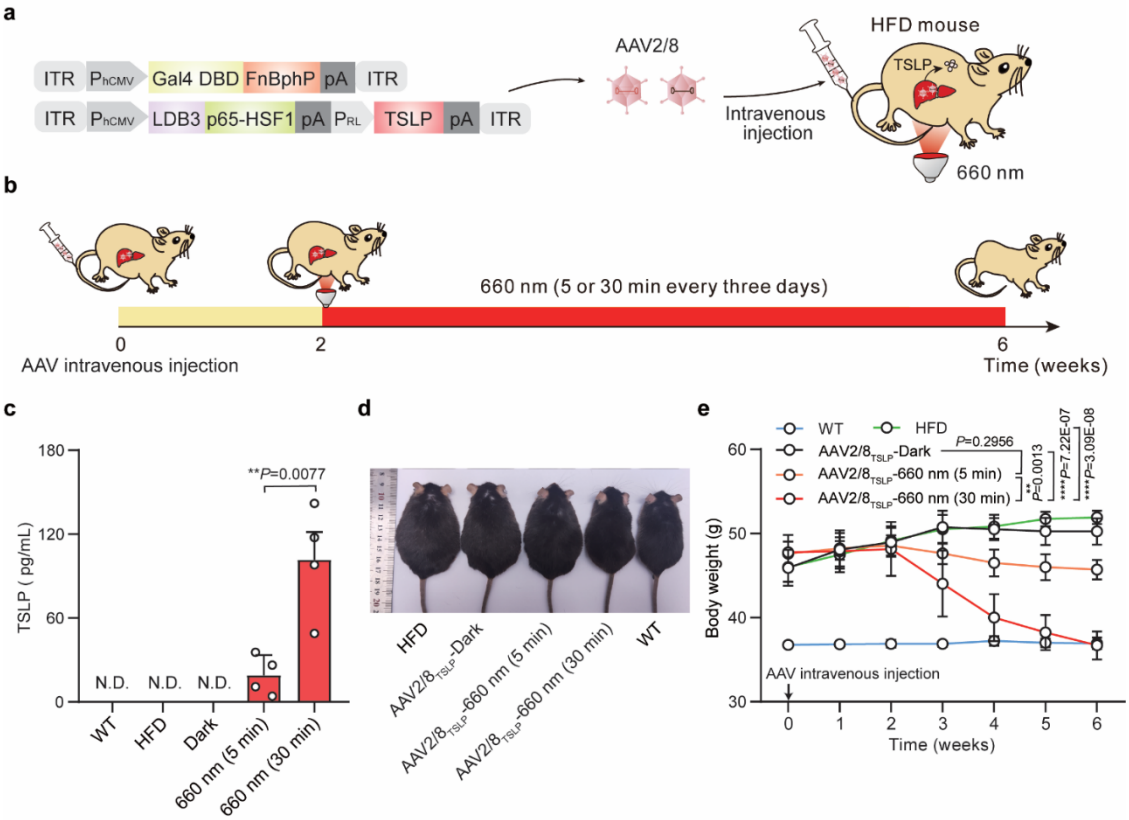
experimental procedure and time schedule for AAV-delivered Fn-REDLIP-mediated insulin expression in T1D model mouse livers. T1D mice were intravenously injected with a mixture of AAV-2/8 vectors (targeting the livers) encoding the Fn-REDLIP system. After 2 weeks, the injected T1D mice were randomly divided into three groups: i) Dark group: T1D mice kept in the dark; ii) 660 nm group: T1D mice exposed to RL (660 nm, 20 mW/cm^2) for 30 minutes twice a day; iii) 660 nm+780 nm group: T1D mice exposed to RL (660 nm, 20 mW/cm^2) for 30 minutes twice a day (ON), followed by exposure to FRL (780 nm, 20 mW/cm^2) for 30 minutes twice a day (OFF) after a 3-hour interval. **d,** Blood insulin was profiled at the indicated time points using a mouse insulin ELISA kit. **e,** Blood glucose was profiled at the indicated time points using a blood glucose meter. Data in **d, e** are presented as means ± SEM (n = 5 mice). P values in **d**, **e** were calculated by one-way ANOVA with multiple comparisons. P values in **d**, **e** were calculated by comparing the 660 nm group or the 660 nm+780 nm group with the Dark group.



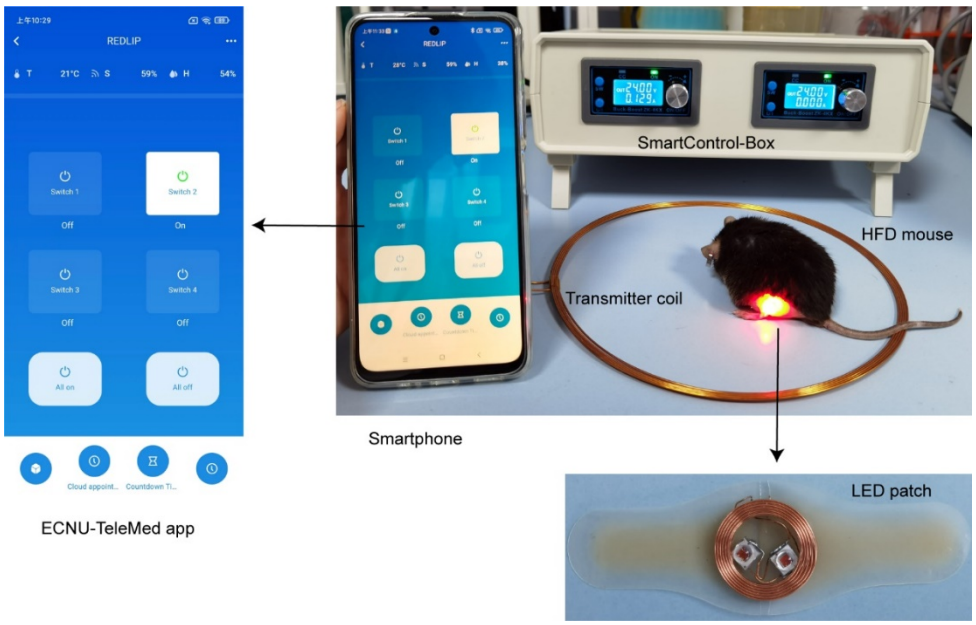
Supplementary Fig. 14 Blood biochemistry and hematology assay of HFD mice treated with AAV-delivered Fn-REDLIP and healthy wild type (WT) C57BL/6 mice for two months. HFD mice were intramuscularly injected in the left gastrocnemius muscle with a mixture of AAV-2/9 vectors encoding Fn-REDLIP. After 2 weeks, the injected HFD mice were illuminated with RL at an intensity of 20 mW/cm^2 for 30 minutes every three days for 6 weeks (AAV2/9$_{TSLP}$-660 nm). The examined control was non-model wild-type mice. Eight weeks after AAV transduction, mouse blood was collected to quantify the (**a**) glutamic-pyruvic transaminase (ALT), (**b**) aspartate aminotransferase (AST), (**c**) blood urea nitrogen (BUN), (**d**) creatinine (CRE), (**e**) albumin/globulin ratio (A/G), (**f**) counts for red blood cells (RBC), (**g**) hemoglobin (HGB), (**h**) platelet (PLT), (**i**) total white blood cells (WBC), (**j**) percentage of blood lymphocytes (LYMPH), (**k**) blood monocytes (MONO), and (**l**) blood eosinophil (EO). All data are expressed as means ± SEM (n = 6 mice). P values were calculated using a two-tailed unpaired t-test.



Supplementary Fig. 15 Serum inflammatory cytokines and immunoglobulin in HFD mice treated with AAV-delivered Fn-REDLIP and wild-type C57BL/6 mice for two months. HFD mice were intramuscularly injected in the left gastrocnemius muscle with a mixture of AAV-2/9 vectors encoding Fn-REDLIP. Two weeks after AAV transduction, the injected HFD mice were illuminated with RL at an intensity of 20 mW/cm^2 for 30 minutes every three days for 6 weeks (AAV2/9$_{TSLP}$-660 nm). The examined control was non-model wild-type mice. Eight weeks after the AAV transduction, mouse blood was collected to quantify (**a**) serum IL-6, (**b**) serum TNF-α, and (**c**) serum IgG production by ELISA. All data are expressed as means ± SEM (n = 6 mice). P values were calculated using a two-tailed unpaired t-test.



Supplementary Fig. 16 AAV-delivered Fn-REDLIP system for hepatic TSLP expression to regulate body weight in HFD mice. a, Schematic for the genetic configuration of the AAV-2/8 vectors for the Fn-REDLIP system used for the HFD obesity model mice experiment. **b,** Schematic for the experimental procedure and time schedule for AAV-delivered Fn-REDLIP-mediated TSLP transgene expression in HFD obesity model mouse livers. HFD mice were intravenously injected with a mixture of AAV-2/8 vectors (targeting the livers) encoding the Fn-REDLIP system iteration containing pNX177 (ITR-P_{hCMV}-Gal4 DBD-FnBphP-pA-ITR) and the concatenated vector pNX166 (ITR-P_{hCMV}-LDB3-p65-HSF1-pA::P_{RL}-TSLP-pA-ITR) at an AAV titer of 2×10^{11} vg. After 2 weeks, the injected HFD mice were illuminated with RL (20 mW/cm^2) for 5 or 30 minutes every three days for 4 weeks (AAV2/8_{TSLP}-660 nm). The examined controls included non-model wild-type control mice (WT group), untreated HFD control mice (HFD group), and AAV-injected HFD mice kept in the dark (AAV2/8_{TSLP}-Dark). **c,** The levels of TSLP in serum were quantified using a mouse TSLP ELISA kit. N.D., Not detected. **d,** Representative images of the AAV2/8_{TSLP}-660 nm group at 6 weeks after AAV injection. **e,** Analysis of body weight of HFD mice injected with the AAV2/8-delivered Fn-REDLIP system. Data in **c**, **e** are presented as means ± SEM (n = 4 mice). P values in **c** were calculated using a two-tailed unpaired t-test. P values in **e** were calculated by one-way ANOVA with multiple comparisons.



Supplementary Fig. 17 Experimental setup for the regulating electronic devices through a smartphone-controlled SmartController. The ECNU-TeleMed smartphone app remotely controls the SmartControl-Box via the GSM (Global System for Mobile Communications) network[1], automatically triggering the LED patch illumination.

Supplementary Table 1. Oligonucleotide sequences used for qPCR analysis

Gene name	Primer name	Primer sequence (5'-3')
GAPDH (human)	Forward	CGAGATCCCTCCAAAATCAA
	Reverse	ATCCACAGTCTTCTGGGTGG
RHOXF2 (human)	Forward	AGTGTAGCCAGTATATGACCAGC
	Reverse	TGACCTCTTCAGTAAGCGACAG
ASCL1 (human)	Forward	CGCGGCCAACAAGAAGATG
	Reverse	CGACGAGTAGGATGAGACCG
IL1RN (human)	Forward	CATTGAGCCTCATGCTCTGTT
	Reverse	CGCTGTCTGAGCGGATGAA
TTN (human)	Forward	CCCCATCGCCCATAAGACAC
	Reverse	CCACGTAGCCCTCTTGCTTC
MIAT (human)	Forward	TGGCTGGGGTTTGAACCTTT
	Reverse	AGGAAGCTGTTCCAGACTGC
Gapdh (mouse)	Forward	ATGACATCAAGAAGGTGGTG
	Reverse	CATACCAGGAAATGAGCTTG
Ascl1 (mouse)	Forward	GGAACAAGAGCTGCTGGACT
	Reverse	GTTTTTCTGCCTCCCCATTT

Supplementary Table 2. Target sequences of sgRNAs used in this study

Gene name	sgRNA name	Guide sequence of sgRNA (5'-3')
RHOXF2 (human)	sgRNA1$_{RHOXF2}$	ACGCGTGCTCTCCCTCATC
	sgRNA2$_{RHOXF2}$	CTGTGGGTTGGGCCTGCTG
ASCL1 (human)	sgRNA1$_{ASCL1}$	GGCTGGGTGTCCCATTGAAA
	sgRNA2$_{ASCL1}$	ATGGAGAGTTTGCAAGGAGC
IL1RN (human)	sgRNA1$_{IL1RN}$	TGTACTCTCTGAGGTGCTC
	sgRNA2$_{IL1RN}$	GAGTCACCCTCCTGGAAAC
TTN (human)	sgRNA1$_{TTN}$	CCTTGGTGAAGTCTCCTTTG
	sgRNA2$_{TTN}$	ATGTTAAAATCCGAAAATGC
MIAT (human)	sgRNA1$_{MIAT}$	GCGCCCATGAAATTTTAATG
	sgRNA2$_{MIAT}$	GCTTCTGCGCCCCTGGTCCG
Ascl1	sgRNA1$_{Ascl1}$	GCAGCCGCTCGCTGCAGCAG

(mouse)	sgRNA2$_{Ascl1}$	AGCTGAGGAGGTGGGGGAAG

References

1. Shao, J. et al. Smartphone-controlled optogenetically engineered cells enable semiautomatic glucose homeostasis in diabetic mice. *Sci. Transl. Med.* **9**, eaal2298 (2017).