Supplemental Information

Figure S1. Characterization of dCas9-EGFP knock-in mice.

(A) Genotyping results of the dCas9-EGFP knock-in mouse strain. (B) RNA expression analysis of dCas9 in different dCas9-EGFP mouse tissues by RT-qPCR. The data are presented as relative expression level after normalization with GAPDH. (C) The Western blotting analysis of dCas9-EGFP protein expression in different mouse tissues. The α-tubulin was used as a loading control. (D) FACS gating strategies for mouse bone marrow, spleen, and thymus. (E) FACS detection of GFP fluorescence in different immune cells from dCas9-EGFP mice. The data were obtained from at least two mice for each experiment.

Figure S2. Visualizing telomere dynamics in dCas9 knock-in mouse liver.

(A) The schematic of *in vivo* CRISPR imaging of telomeres in dCas9-EGFP mouse livers. (B) Representative images for control gRNA and without gRNA in dCas9-EGFP mouse liver. (C) Representative trajectories of telomeres in one hepatocyte of dCas9-EGFP mouse liver (scale bar, 5 μm) and trajectories of three individual telomeres with different confined regions (scale bars, 200 nm). The trajectory length is 474 frames. See also Movie S1. **T**he data were obtained from at least two mice for each experiment.

Figure S3. CRISPR *in vivo* imaging of major satellites and a single genomic locus in X chromosome in dCas9-EGFP knock-in mice.

(A) Labeling of major satellite in hepatocytes of dCas9-EGFP mice. TagBFP-TRF1 was used as control. Histograms of major satellite foci number distribution in individual nucleus (lower panel). (B) Labeling of a single genomic locus in X chromosome in

dCas9-EGFP mice. Representative images for labeling in male and female mice (left panel). Histograms of foci number distribution in individual nucleus of male and female mice (ŀright panel). The data were obtained from at least two mice for each experiment.

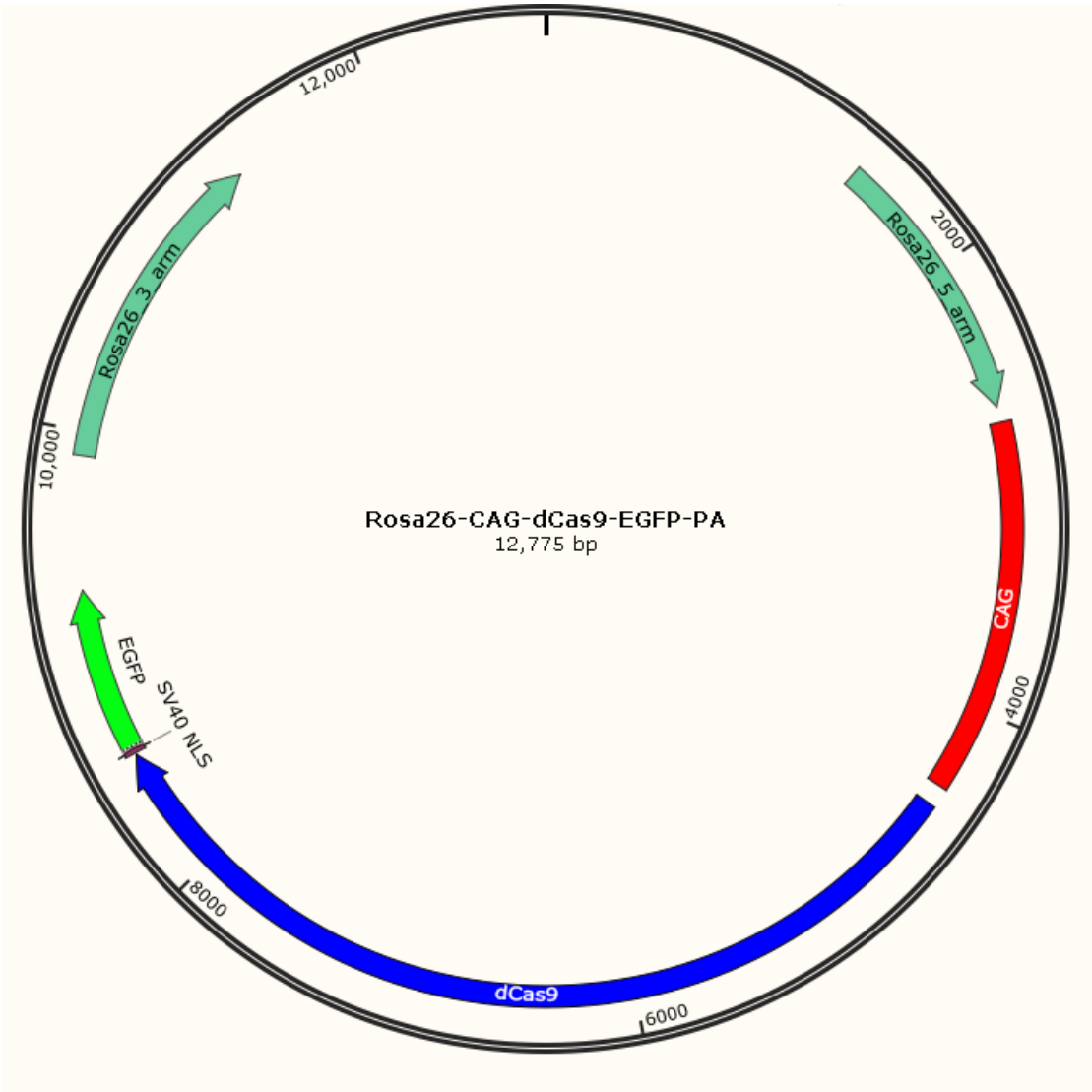
Figure S4. Compare the telomere dynamics *in vivo* and *in vitro*.

(A) The schematic of CRISPR imaging and interference (CRISPRii) strategy in dCas9-EGFP mouse. (B) RT-qPCR analysis of TRF1 repression by CRISPRi. The data are presented as relative expression fold change comparing TRF1 gRNA and control gRNA injected dCas9-EGFP mice. (C) MSD curves of individual telomeres (colored curves) and the average MSD curves (bold black curve with shaded area indicating ± SE) as a function of time interval between observations. The upper red dashed line: slope=0.5. The bottom red dashed line: slope=0. (D) The left panel is MSD curves of individual telomeres (colored curves) and the average MSD curves (bold black curve with shaded area indicating ± SE) as a function of time interval between observations for HepG2 cells in matrix gel cultured for 72 hours. The upper red dashed line: slope=0.5. The bottom red dashed line: slope=0. The right panel is distribution of α values calculated for individual telomeres of HepG2 cultured on plate (blue) and in Matrix gel for 72h (green). (E) Summary of MSD analysis (Data are shown as mean ± SD)

Table S1: Primer sequences

Name	Sequence	Note
Rosa-SG	GGCATTCTACACGTTATTGCTGG	Knock-in site
TRF1-re-SG1	CACGGCGCCAGCTGAGGCA	Repression site
TRF1-re-SG2	GAAGGCTCGGCACAGAGAC	Repression site
TRF1-re-SG3	GGGACGCGCCGAGCCGTGA	Repression site
Telo-sg	GTTAGGGTTAGGGTTAGGGTTA	Labeling site, telomeres
Majset-sg	CCATATTCCACGTCCTACAG	Labeling site, major satellites
X386-sg	CACACACAGCAGAGGATGTG	Labeling site, X chromosome
P1	GTACACATCTGTAAAAGGTGGTTCC	Genotyping primer
P2	TAGAGCACAAGCACACACAACAC	Genotyping primer
P3	CCATAGAAAAGCCTTGACTTGAGGTTAG	Genotyping primer
P4	ATGGGCTATGAACTAATGACCCCG	Genotyping primer
P5	TTACGAGAAGCTGAAGGGG	Genotyping primer/dCas9 qPCR primer
P6	GAACTTGTGGCCGTTTACGT	Genotyping primer/dCas9 qPCR primer
P7	AAGAGAATAGCAGGCATGCTGG	Genotyping primer
P8	GACTTTGGCTGTGAAGAATTTGGAT	Genotyping primer
TRF1-F	TTTCGTCGTACTCGTGACAGCG	qPCR primer
TRF1-R	GGGAGTGGAACACATCCTTCTGA	qPCR primer
GAPDH-F	TGAAGCAGGCATCTGAGGG	qPCR primer
GAPDH-R	CGAAGGTGGAAGAGTGGGAG	qPCR primer

Table S2: Sequences of plasmids



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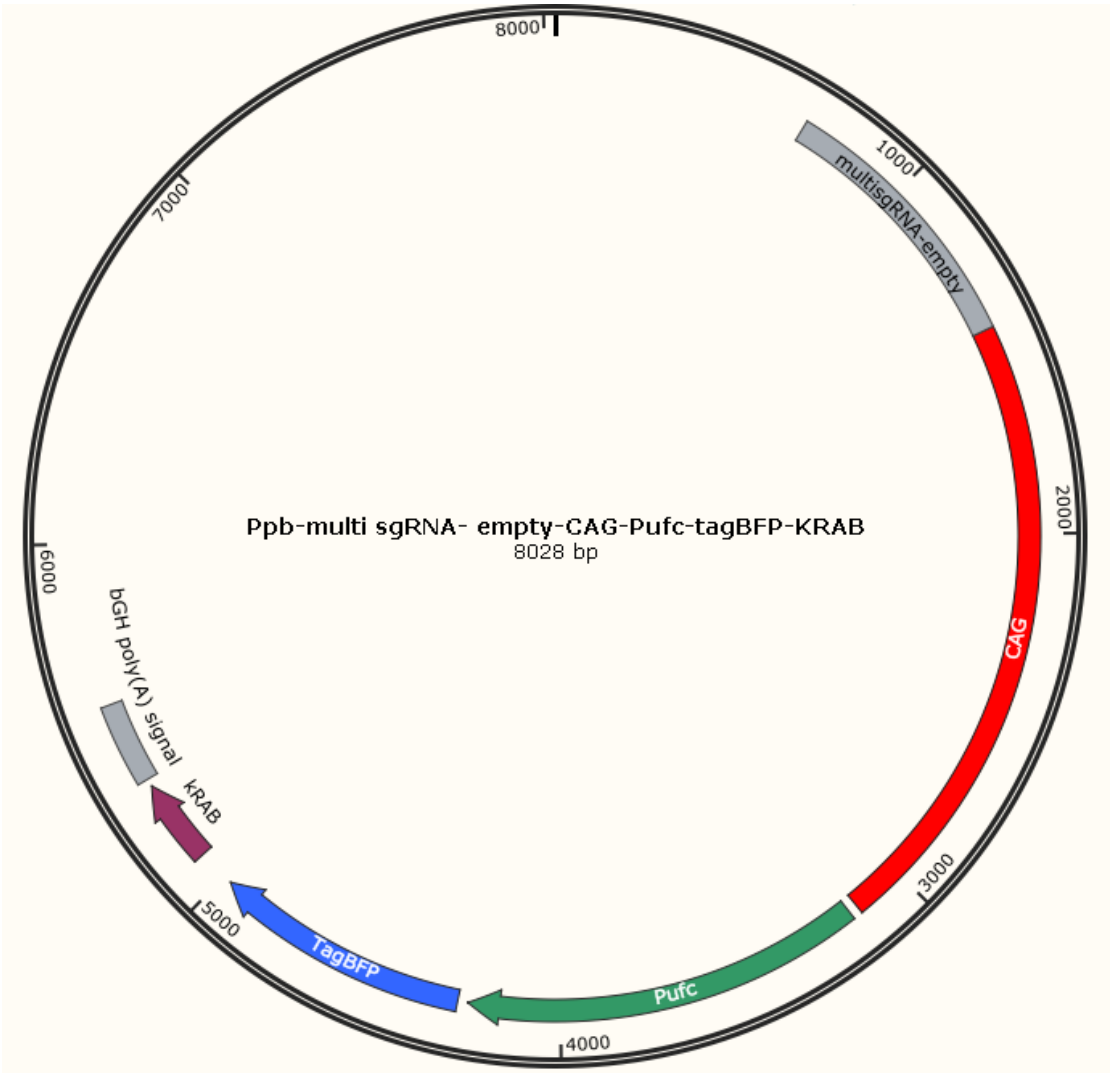

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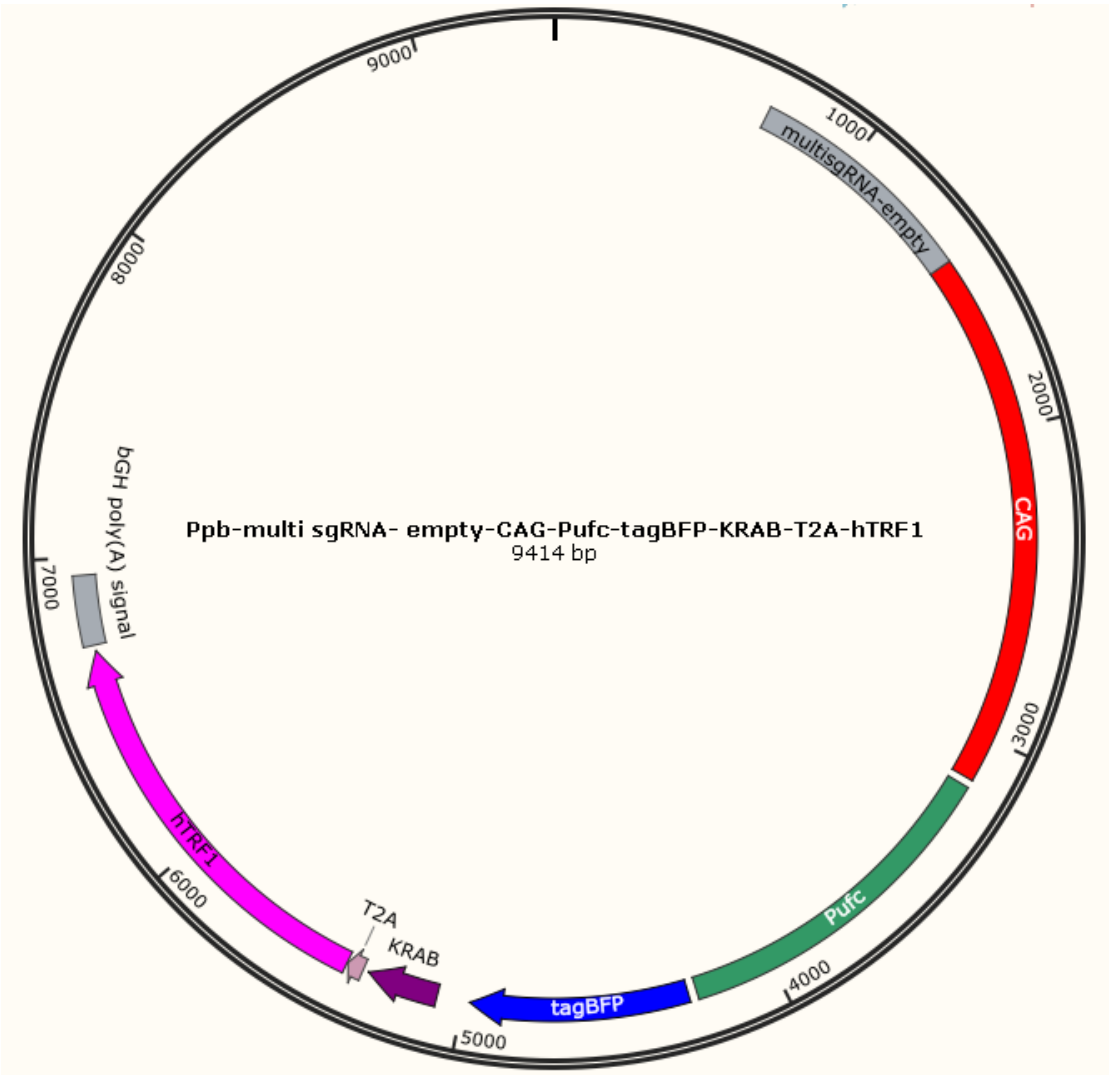

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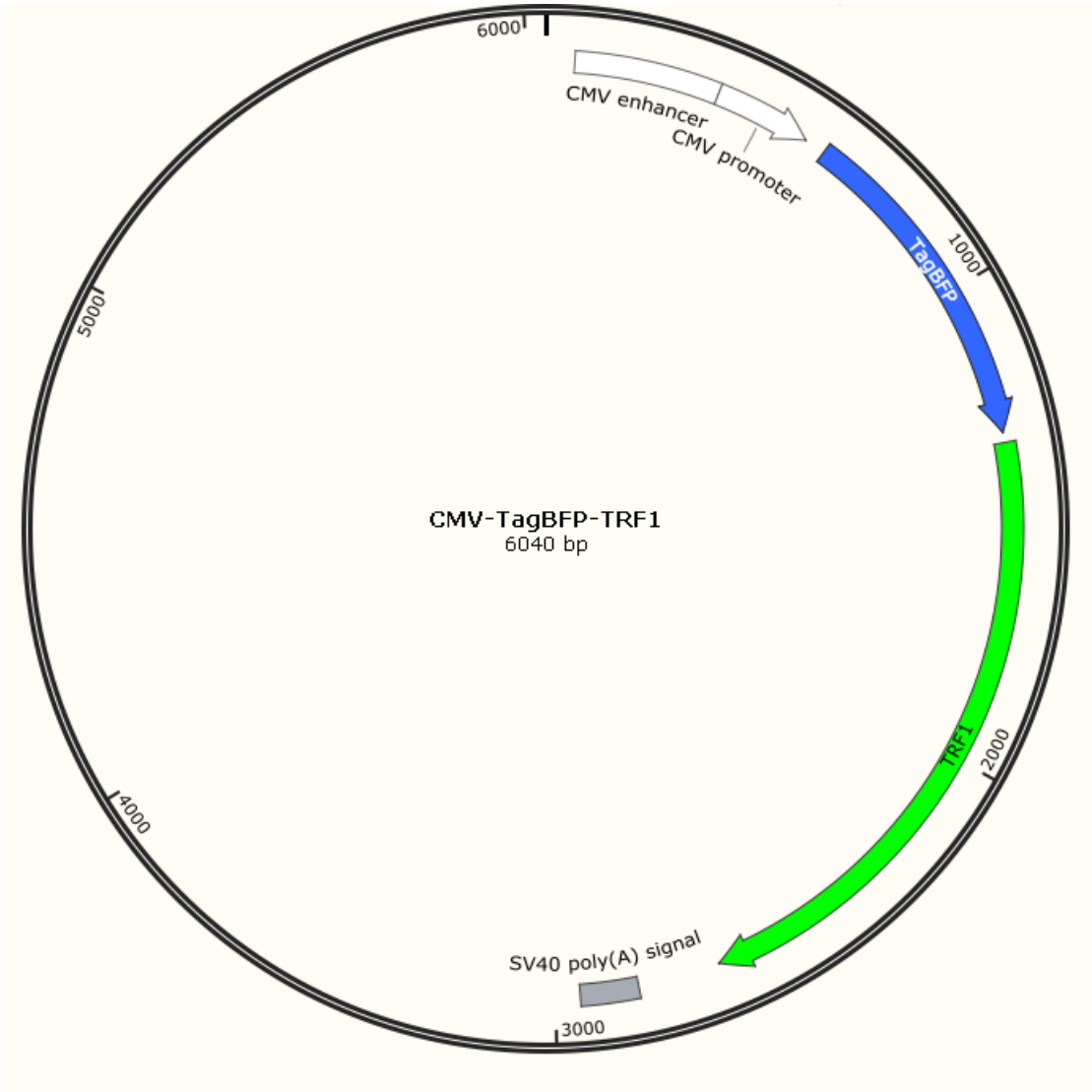

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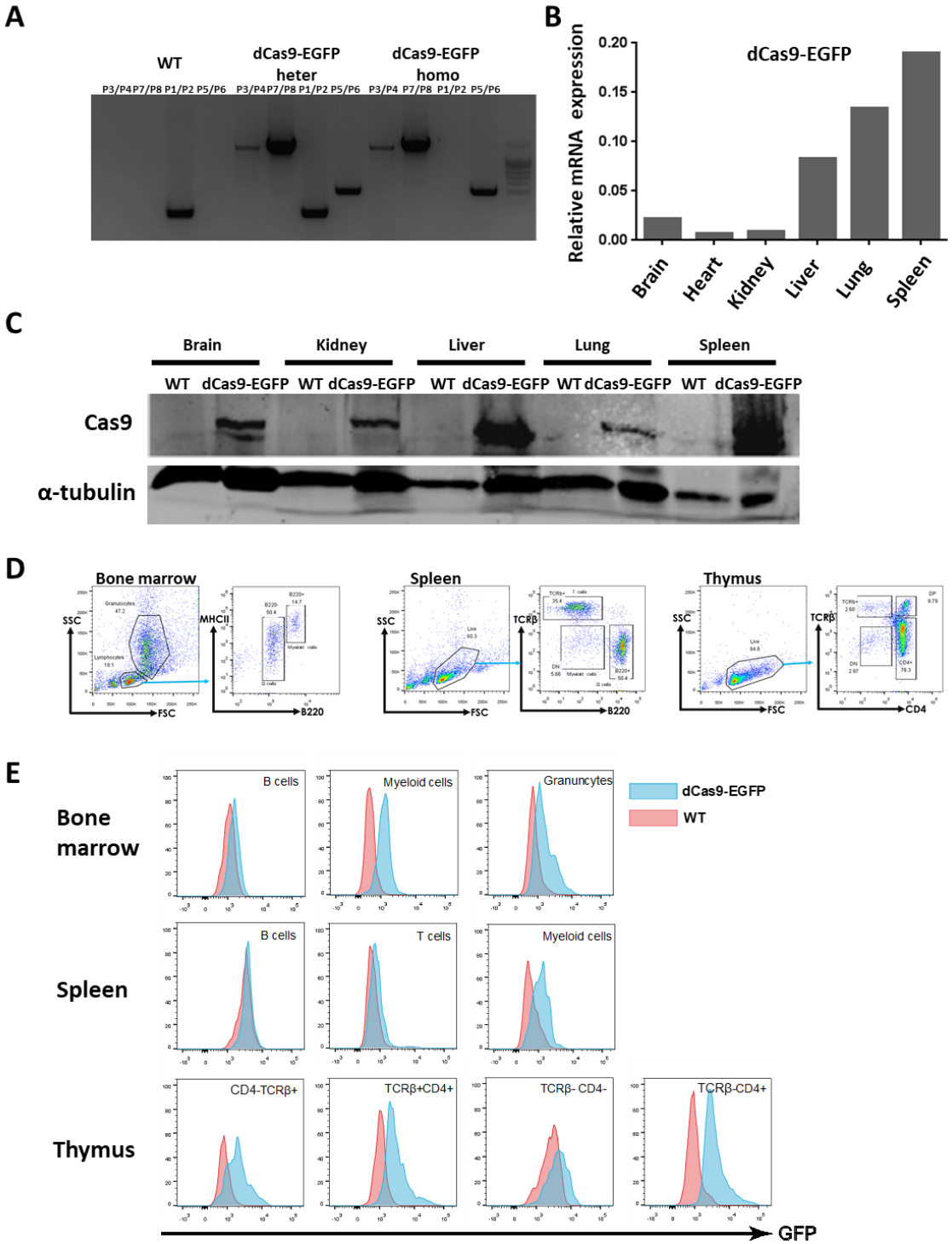
A
WT
dCas9-EGFP heter
dCas9-EGFP homo
P3/P4 P7/P8 P1/P2 P5/P6
B
dCas9-EGFP
Relative mRNA expression
0.20
0.15
0.10
0.05
0.00
Brain
Heart
Kidney
Liver
Lung
Spleen
C
Brain
Kidney
Liver
Lung
Spleen
WT dCas9-EGFP
Cas9
α-tubulin
D
Bone marrow
Spleen
Thymus
SSC
FSC
MHCII
B220
TCRβ
CD4
E
Bone marrow
Spleen
Thymus
B cells
Myeloid cells
Granuncytes
T cells
CD4-TCRβ+
TCRβ+CD4+
TCRβ- CD4-
TCRβ-CD4+
dCas9-EGFP
WT
GFP

Figure S1

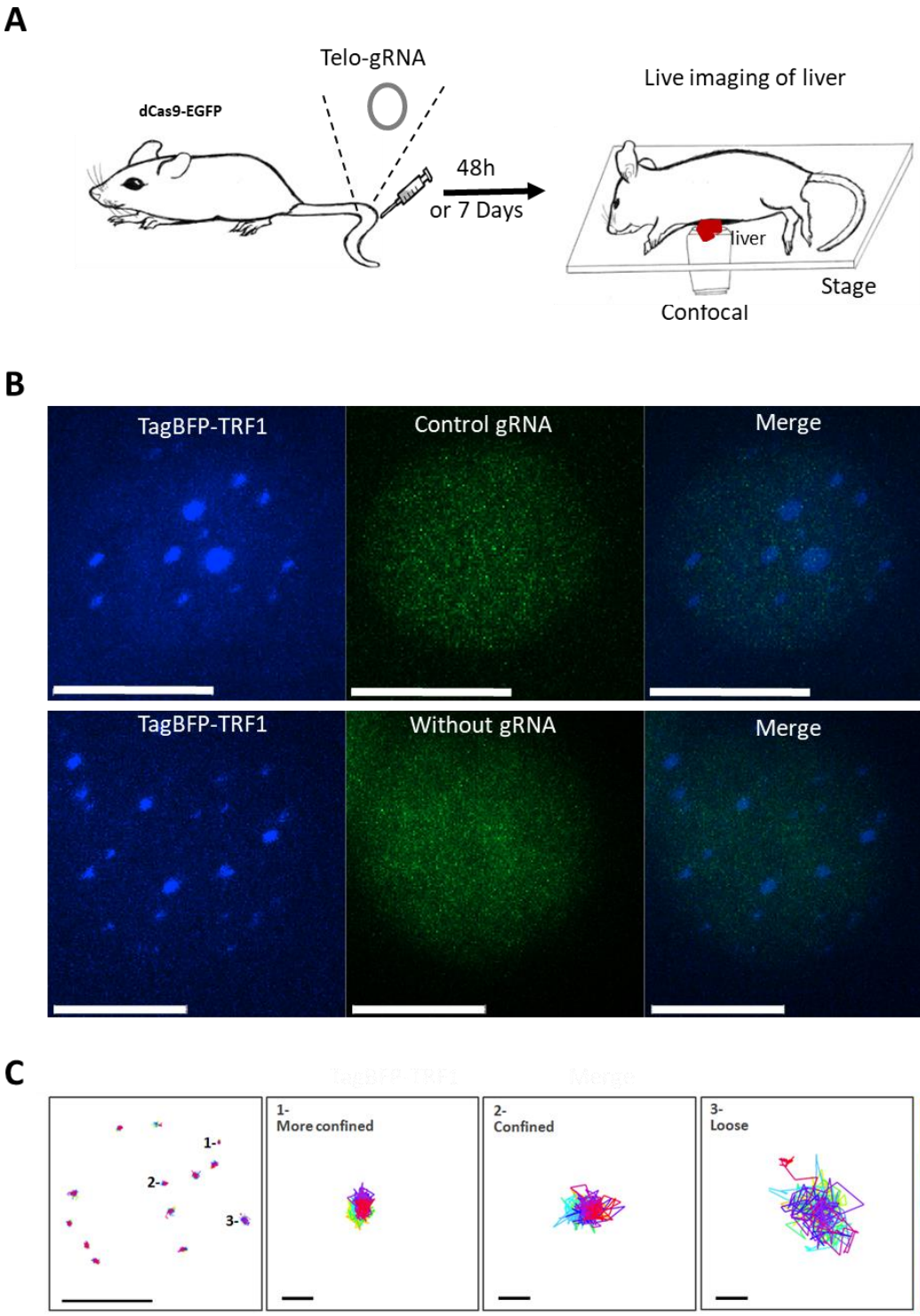
A
Telo-gRNA
dCas9-EGFP
48h
or 7 Days
Live imaging of liver
liver
Stage
Confocal
B
TagBFP-TRF1
Control gRNA
Merge
TagBFP-TRF1
Without gRNA
Merge
C
1-
More confined
2-
Confined
3-
Loose
Time

Figure S2

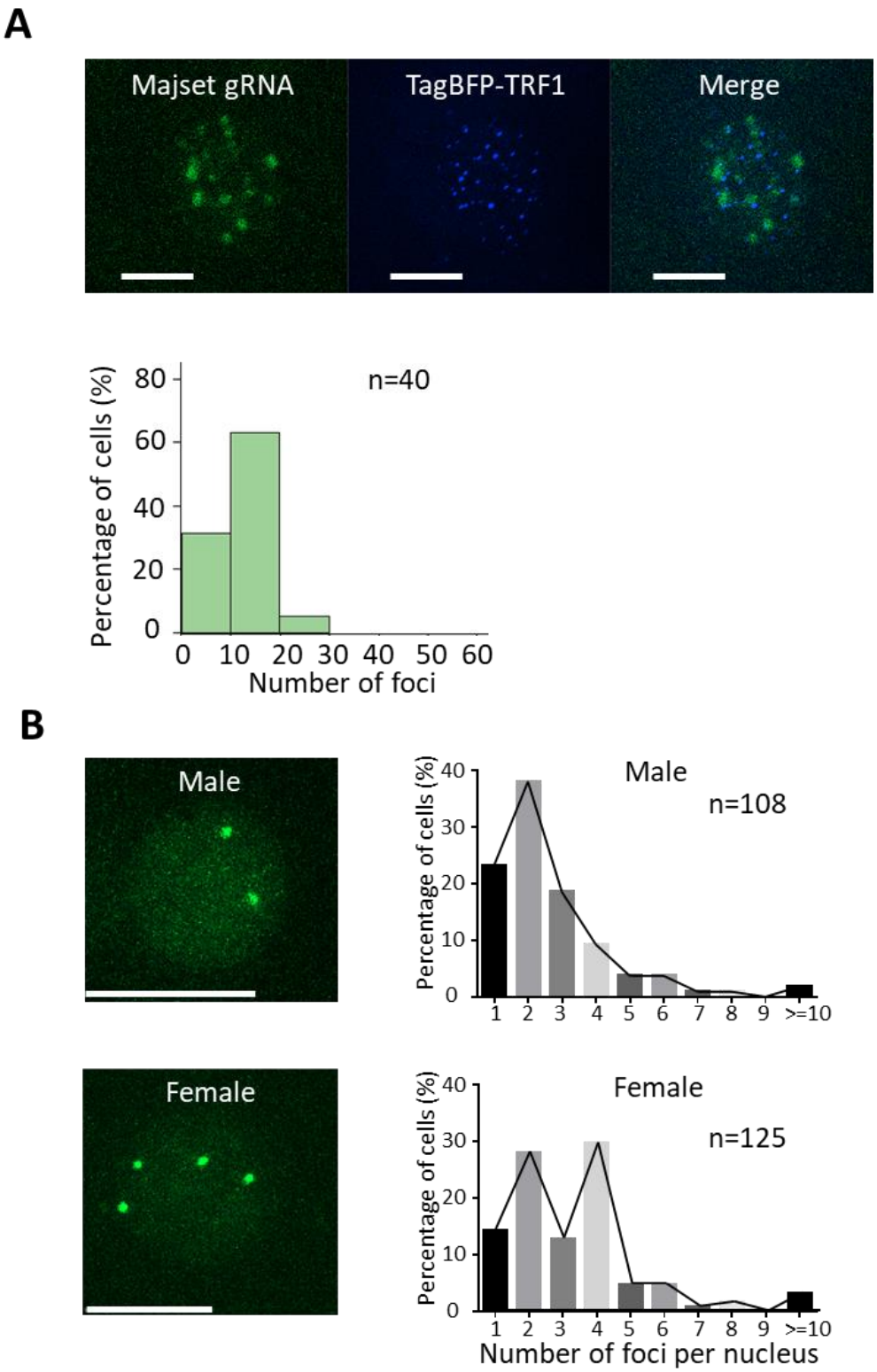
A
Majset gRNA
TagBFP-TRF1
Merge
Percentage of cells (%)
n=40
Number of foci
B
Male
Male
n=108
Female
Female
n=125
Number of foci per nucleus

Figure S3

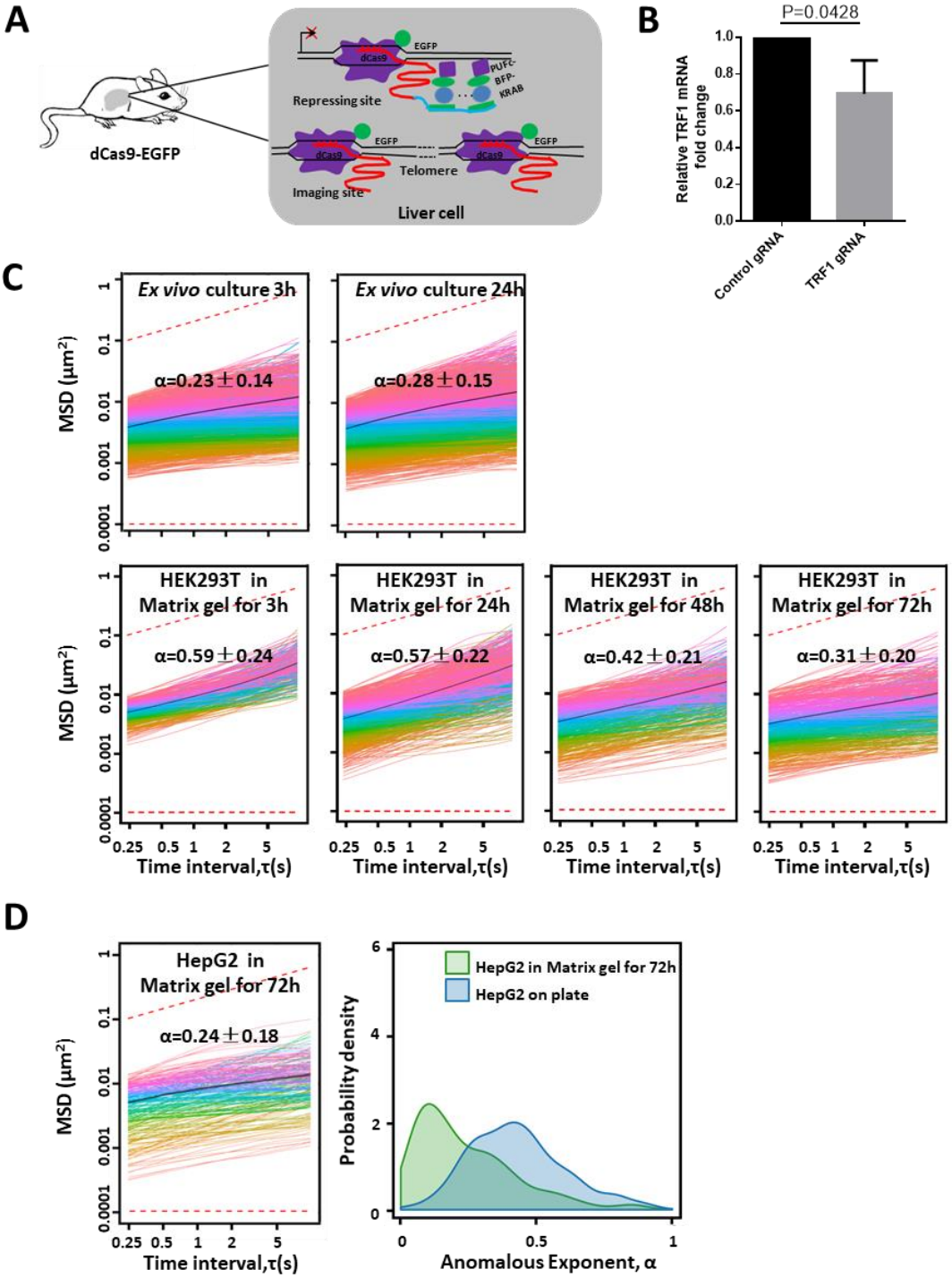
A
dCas9-EGFP
dCas9
EGFP
PUF-
BFP-
KRAB
Repressing site
Telomere
Imaging site
Liver cell
B
P=0.0428
Relative TRF1 mRNA fold change
Control gRNA
TRF1 gRNA
C
Ex vivo culture 3h
α=0.23±0.14
Ex vivo culture 24h
α=0.28±0.15
HEK293T in Matrix gel for 3h
α=0.59±0.24
HEK293T in Matrix gel for 24h
α=0.57±0.22
HEK293T in Matrix gel for 48h
α=0.42±0.21
HEK293T in Matrix gel for 72h
α=0.31±0.20
MSD (μm²)
Time interval,τ(s)
D
HepG2 in Matrix gel for 72h
α=0.24±0.18
HepG2 in Matrix gel for 72h
HepG2 on plate
Probability density
Anomalous Exponent, α

Figure S4

E

	Number of mice	Experimental repeats	Cell number	Foci number	$MSD(t) = 4D_\alpha t^\alpha$		$MSD(t) = A(1 - e^{-t/\delta}) + 4D_{macro}$		
					α	D_α ($\mu m^2 s^{-\alpha} x10^{-4}$)	D_{micro} ($10^{-3}\mu m^2/s$)	D_{macro} ($10^{-5}\mu m^2/s$)	$L_{confinement}$ (nm)
dCas9-EGFP mouse liver	5		129	1055	0.18 ± 0.15	29.49 ± 15.55	9.66 ± 4.53	9.07 ± 37.51	83.17 ± 36.01
Ex vivo culture 3h	4		84	1127	0.23 ± 0.14	16.01 ± 12.70	5.12 ± 3.75	10.09 ± 20.49	57.18 ± 28.44
Ex vivo culture 24h	4		87	1502	0.28 ± 0.15	17.22 ± 14.80	4.16 ± 3.42	11.35 ± 33.01	61.17 ± 38.22
HEK293T		3	67	590	0.46 ± 0.20	24.70 ± 15.59	5.50 ± 4.18	36.76 ± 54.38	76.72 ± 41.37
Hep1-6		3	64	867	0.52 ± 0.25	22.71 ± 14.42	4.95 ± 3.30	42.37 ± 56.31	74.77 ± 43.65
HepG2		3	58	691	0.45 ± 0.22	26.98 ± 15.21	4.98 ± 2.94	37.11 ± 73.95	86.10 ± 51.30
HEK293T in Matrix gel for 3h		2	30	295	0.59 ± 0.24	20.70 ± 9.33	5.48 ± 3.68	52.46 ± 39.68	69.33 ± 24.50
HEK293T in Matrix gel for 24h		4	74	827	0.57 ± 0.22	18.85 ± 12.24	3.64 ± 3.14	43.40 ± 55.07	68.48 ± 39.53
HEK293T in Matrix gel for 48h		4	42	485	0.42 ± 0.21	14.20 ± 9.59	3.62 ± 3.38	19.10 ± 25.81	57.10 ± 26.66
HEK293T in Matrix gel for 72h		4	53	597	0.31 ± 0.20	12.24 ± 10.98	4.68 ± 4.42	10.45 ± 23.93	49.72 ± 29.09
HepG2 in Matrix gel for 72h		3	26	243	0.24 ± 0.18	19.70 ± 14.90	7.30 ± 5.38	10.32 ± 17.02	62.52 ± 27.79

Figure S4 (continued)