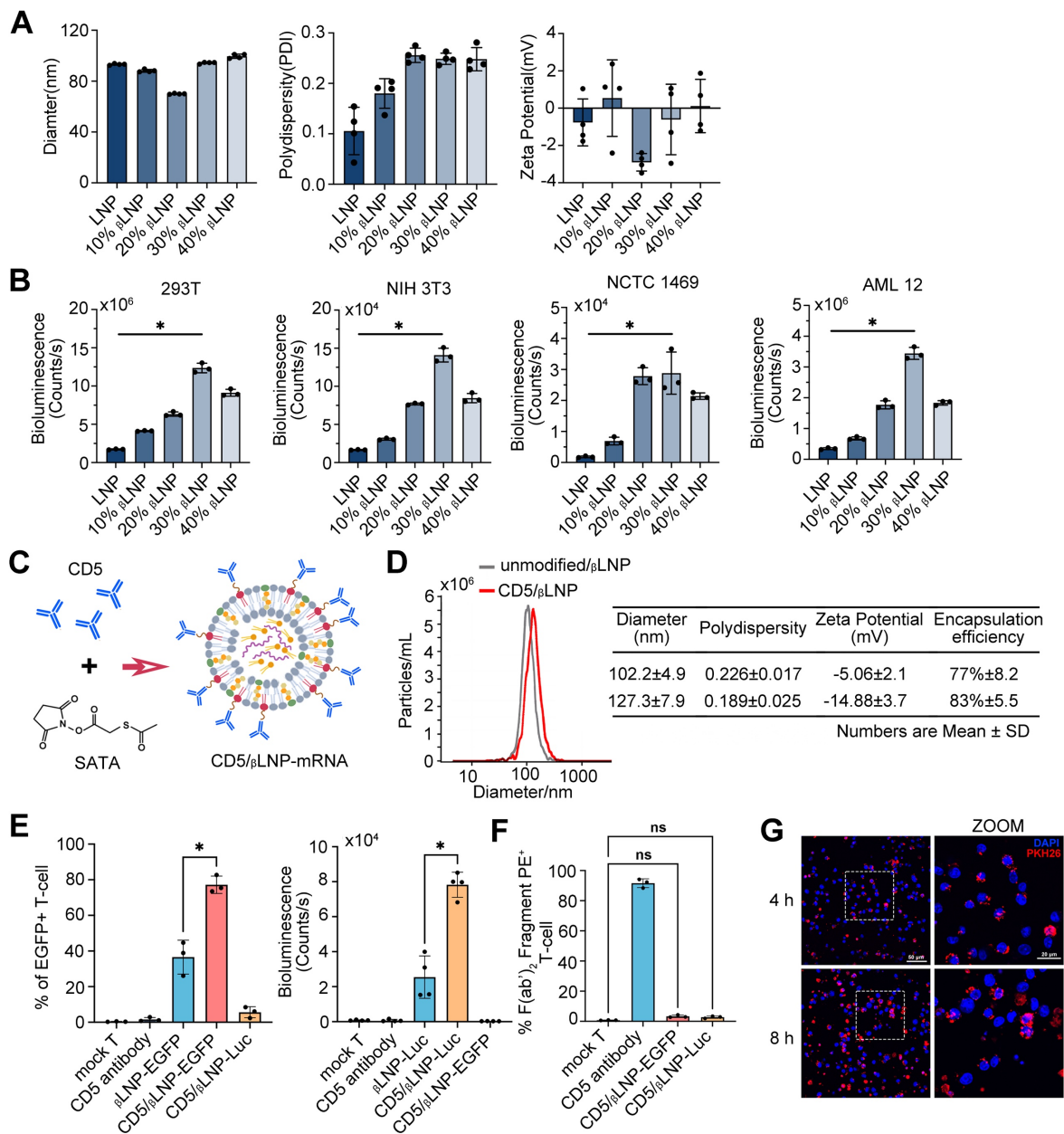


1 **Supplementary Figures**



2

3 **Figure S1. Characterization of modified LNP**

4 (A) Mean diameter, polydispersity and zeta potential of LNP with different β -sitosterol concentrations

5 (n=4). (B) Luciferase mRNA expression after incubating β LNP of different β -sitosterol concentrations

6 with 293T, fibroblast and normal liver cell lines for 24 h (n=3). (C) Schematic outlining the process

7 of β LNP modified by CD5 antibodies. (D) Distribution of β LNP (gray curve) and CD5 antibody-

8 conjugated β LNP (red curve) as a function of particular diameter as well as physicochemical properties

1 of β LNP modified with or without CD5 antibodies (n=4). (E) Percentage of EGFP positive T cells (n=3)
2 and bioluminescence intensity (n=4) after coincubated with CD5 antibodies, unmodified β LNP,
3 CD5/ β LNP-EGFP and CD5/ β LNP-Luciferase. (F) Flow cytometry assay of T cells with different
4 treatment conditions detected by F(ab')₂ Fragment antibody (PE conjugate). The presence of small
5 amount CD5 antibodies on β LNPs does not cause false positive in flow cytometry analysis (n=3). (G)
6 Coincubation of CD5/ β LNPs pre-labeled with PKH26 to T cells at 4 h and 8 h, showing significant
7 adhesion at 4 h and visible endocytosis at 8 h. Red, CD5/ β LNPs; blue, nucleus (Scale bar: 50 and 20
8 μ m). 'n' means independent biological replications. The values are the means $\pm$ SDs. * $P < 0.05$. (β LNP:
9 β -sitosterol modified lipid nanoparticle). Source data are provided as a Source Data file.

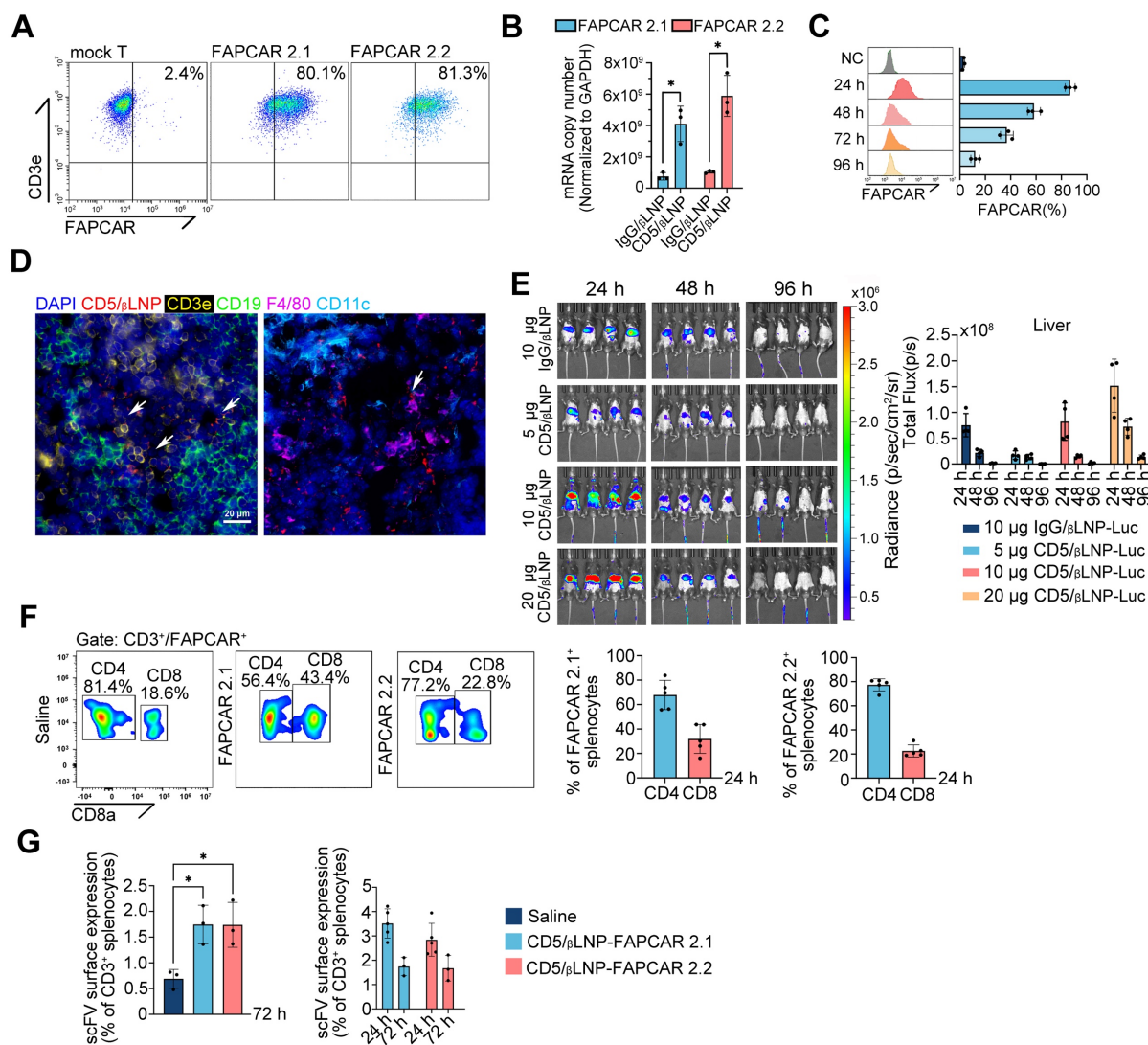


Figure S2. Transient FAPCAR-T identification *in vitro* and *in vivo*

(A) Representative flow cytometry images of FAPCAR 2.1 and FAPCAR 2.2 receptor expression in mouse T cells for 24 h after incubation with IgG/βLNP or CD5/βLNP (n=5). (B) Copy number of FAPCAR2.1/2.2 mRNA delivered by CD5/βLNP (quantified by RT-qPCR) compared with IgG group (normalized to housekeeping GAPDH gene in mouse T cells) (n=3). (C) Time-dependent changes of FAPCAR 2.1 expression (left: representative histogram image; right: percentage changes of FAPCAR positive T cells). Cell positive rate was detected by flow cytometry every 24 h within 4 days (n=3). (D) Representative co-localization immunofluorescence images of PKH-26 labeled CD5/βLNP with spleen T cells (CD3e), B cells (CD19), DCs (CD11c) and macrophages (F4/80). Blue: DAPI; Red:

1 CD5/ β LNP; Yellow: CD3e; Green: CD19; Cyan: CD11c; Magenta: F4/80. (Scale bar: 20 μ m) (E)
2 Bioluminescence images of mice after injecting IgG/ β LNP or CD5/ β LNP. Total flux intensity in liver
3 were quantified with radiance value (n=5). (F) Percentage of CD4 and CD8 cells in FAPCAR and
4 CD3e double positive populations (n=5). (G) FAPCAR surface expression rate in CD3 positive
5 splenocytes after 72 h injection and the comparison with 24 h (n=3). 'n' means independent biological
6 replications. The values are the means $\pm$ SDs. * $P < 0.05$. Source data are provided as a Source Data
7 file.
8

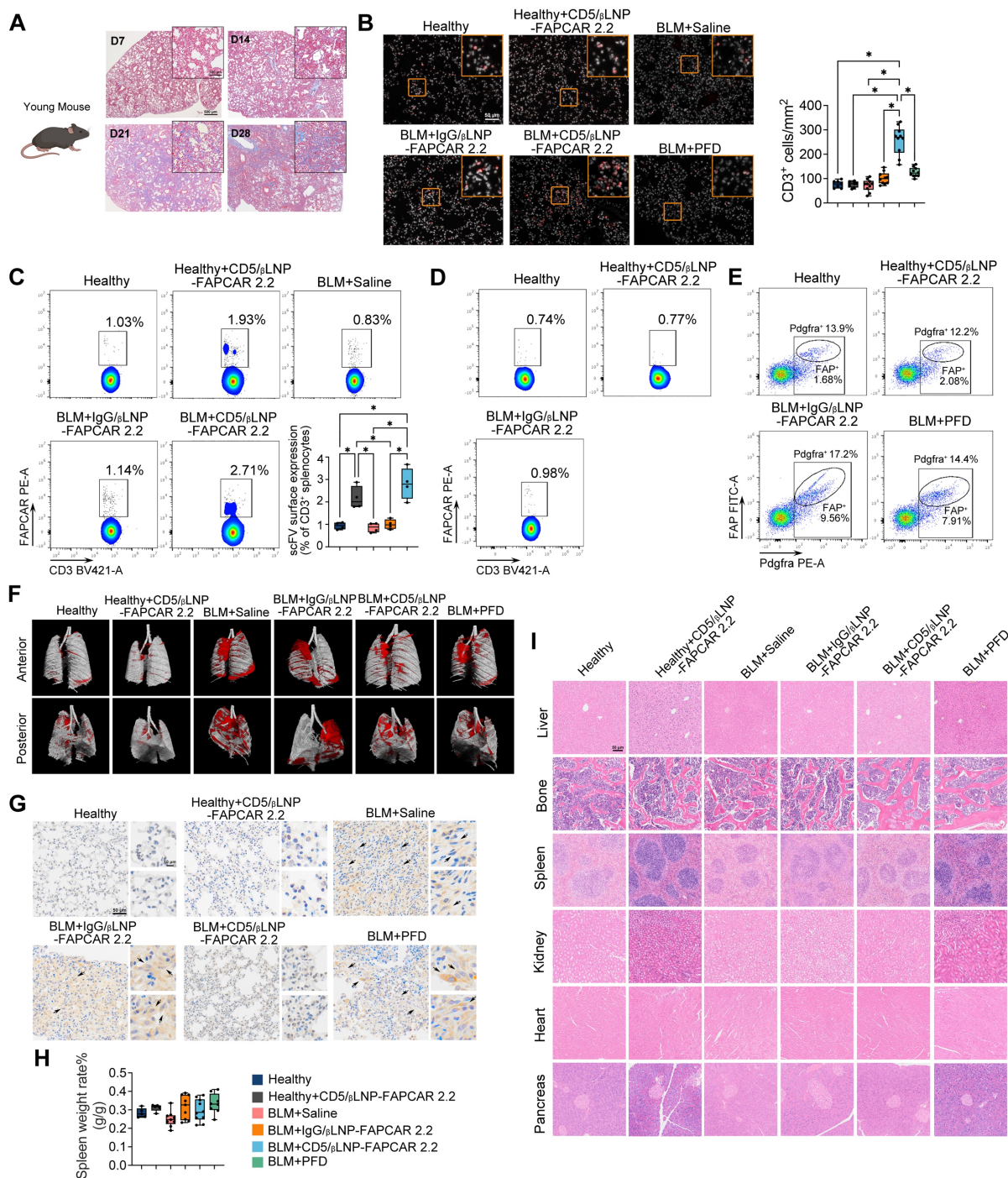


Figure S3. Pulmonary fibrotic changes and systemic by-effect assay after CD5 β LNP-FAPCAR 2.2 treatment in young mouse

(A) Masson staining for fibrotic lung tissue at postoperative 7, 14, 21 and 28 days. There was a gradual extension of fibrosis and parenchymatous lung tissue during the fibrotic progression (Scale bar: 100 and 500 μ m). (B) Immunofluorescence images and quantification of T cells accumulation in the lung.

1 Cell numbers from five fields were averaged (Scar bar: 50 μ m, n=7,7,10,10,10,10). (C) Dot plots from
2 the flow cytometry analysis and the ratio of FAPCAR T cells to CD3⁺ splenocytes (n=4). (D) Flow
3 cytometry plots for FAPCAR T cell in pulmonary T cells. (E) Flow cytometry plots for ratio of
4 FAP⁺/Pdgfra⁺ fibroblasts in all lung cells. (F) 3D model of lung from micro-CT. Red: fibrosis area;
5 Grey: normal area. (G) Immunohistochemistry staining for FAP positive cells after treatment with
6 saline, IgG/ β LNPs, CD5/ β LNPs-FAPCAR 2.2 or PFD (Scale bar: 10 μ m and 50 μ m). (H) The ratio of
7 spleen weight to body weight for different groups. (n=5,5,9,9,10,8) (I) H&E staining for multiple
8 organs in control, saline, IgG/ β LNP-FAPCAR 2.2, CD5/ β LNP-FAPCAR 2.2 and PFD groups after
9 termination (Scale bar: 50 μ m). ‘n’ means independent biological replications. The values are the
10 means $\pm$ SDs. **P* < 0.05. (PFD: Pirfenidone). Source data are provided as a Source Data file. Created
11 in BioRender. yan, j. (2025) <https://BioRender.com/c53i130>.

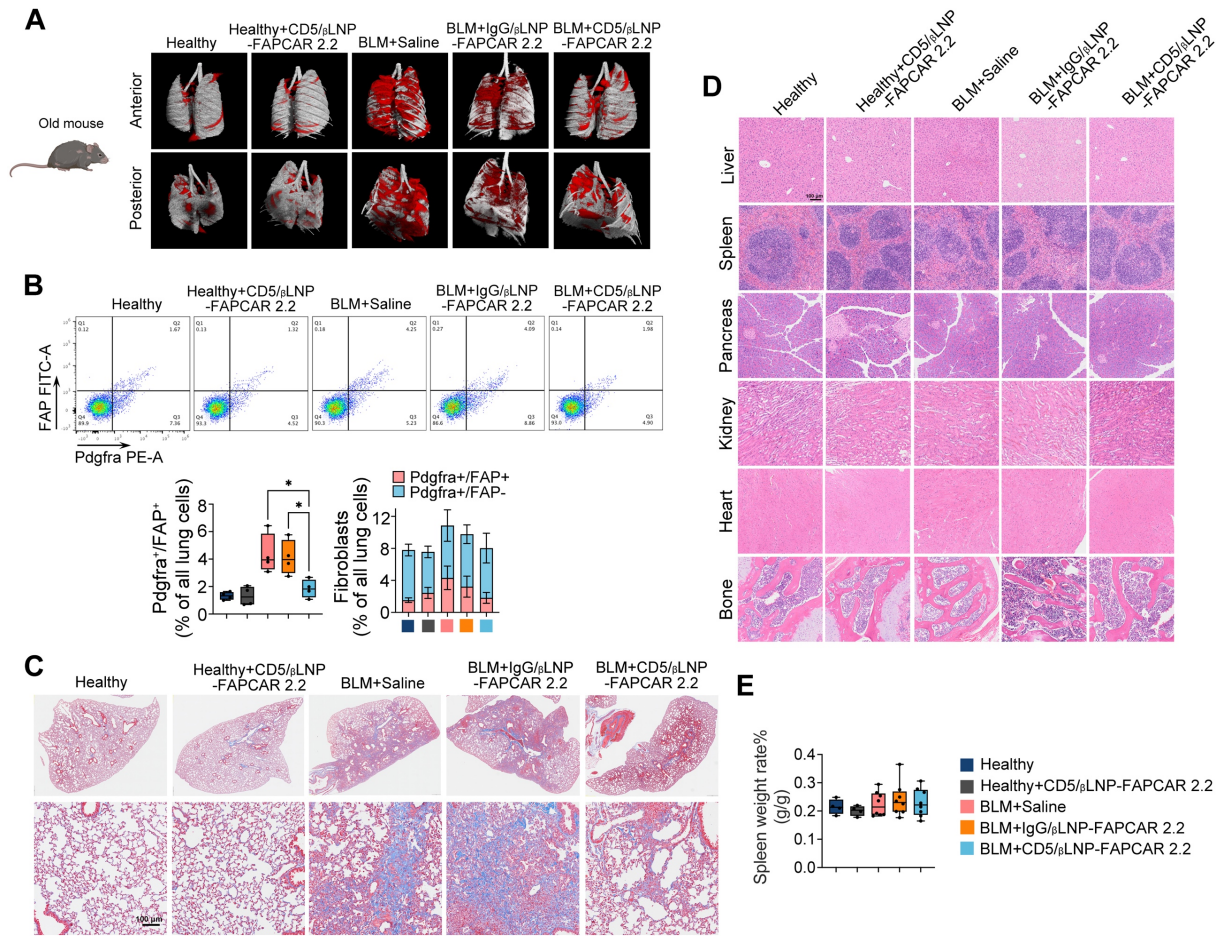


Figure S4. Pulmonary fibrosis was rescued in aged mice by CD5/βLNP-FAPCAR 2.2 therapy

(A) 3D model from micro-CT for aged mice. Red: fibrosis area; Grey: normal area. (B) Flow cytometry plots of FAP⁺/Pdgfra⁺ fibroblasts in all lung cells (n=4). (C) Masson staining showing fibrotic area for each group (Scar bar: 100 μm). (D) H&E staining for multiple organs of aged mice (Scar bar: 50 μm). (E) The ratio of spleen to body weights (n=4,4,8,8,8). 'n' means independent biological replications. The values are the means ± SDs. *P < 0.05. Source data are provided as a Source Data file. Created in BioRender. yan, j. (2025) <https://BioRender.com/c53i130>.

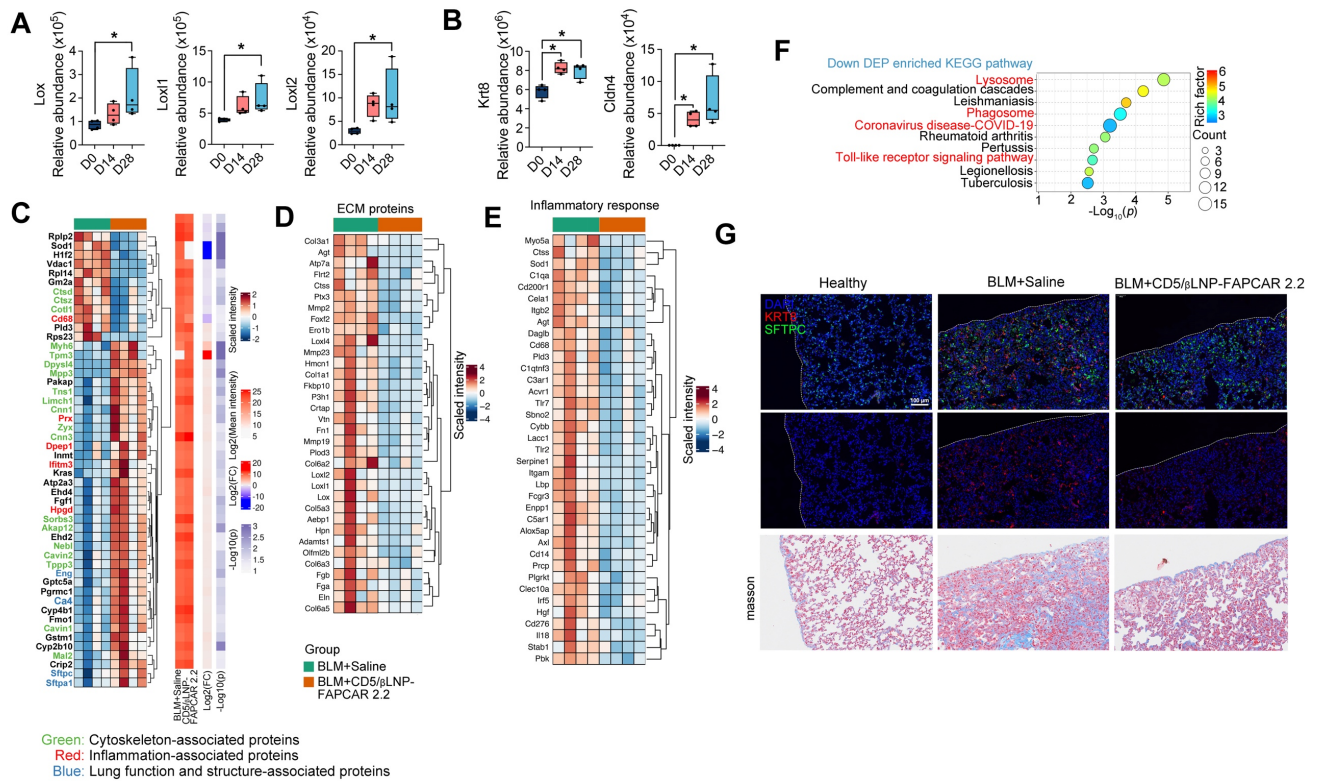


Figure S5. Proteomics analysis of DEPs for 0, 14 and 28 days after BLM administration

(A) Relative abundance of ECM stiffness regulation genes. (n=4) (B) An increase of PATS makers in the development of pulmonary fibrosis. (n=4) (C) Heatmap for top-50 proteins of all DEPs. (D) Heatmap for DEPs enriched in ECM regulation. (n=4) (E) Gene expression heatmap enriched in cluster 2 relevant to immune regulation. (n=4) (F) Enriched KEGG pathways of downregulated DEPs. (G) Immunofluorescence images for PATS showing accumulation in fibrotic area of the BLM+Saline group. (Red: Krt8; Green: Sftpc; Blue: DAPI) (Scar bar: 100 μ m) 'n' means independent biological replications. The values are the means $\pm$ SDs. * $P < 0.05$. (DEP: differentially expressed protein; ECM: extra cellular matrix; PATS: pre-alveolar type I transitional cell state; KEGG: Kyoto Encyclopedia of Genes and Genome). Source data are provided as a Source Data file.

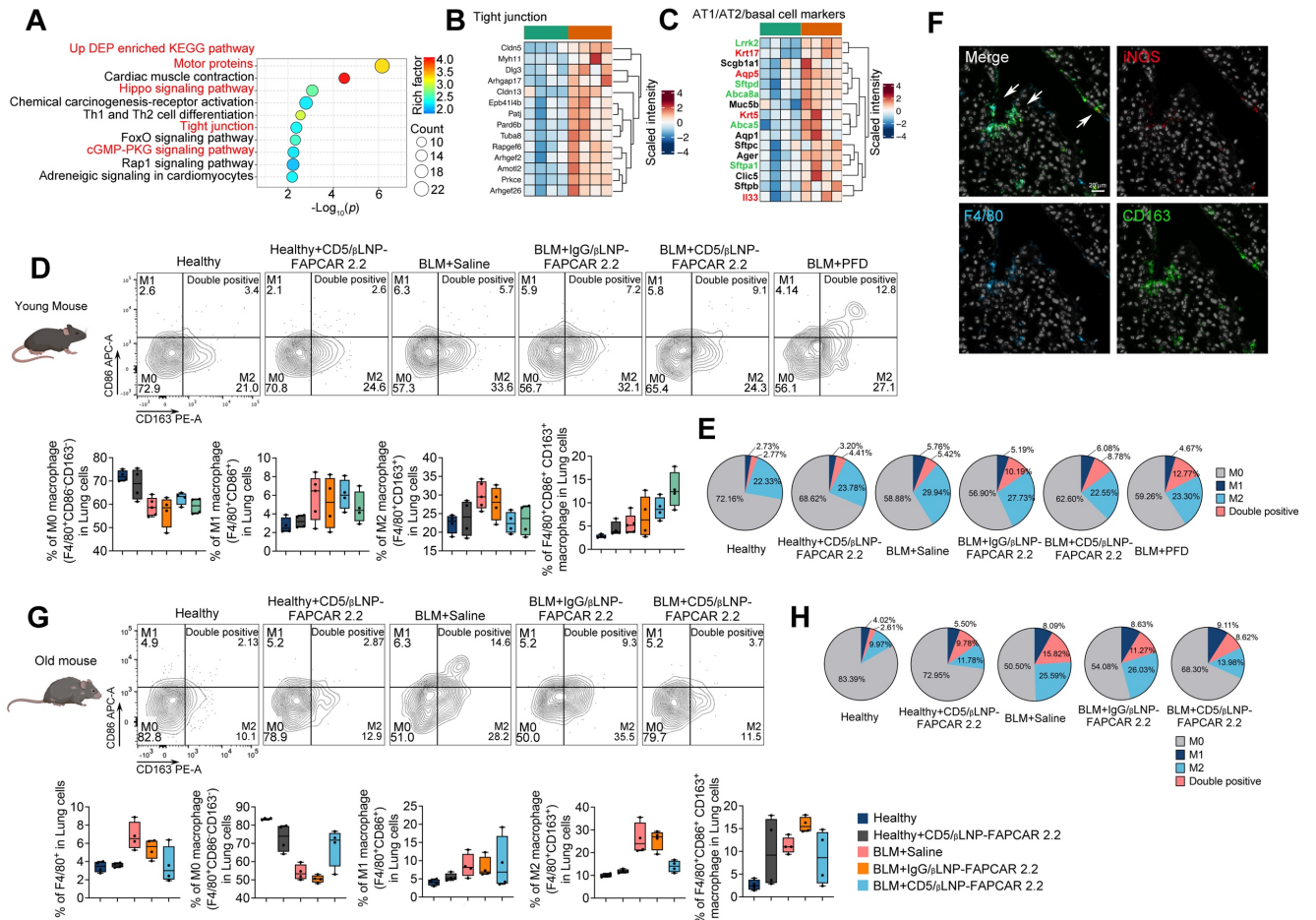


Figure S6. Upregulated DEPs and exclusion of macrophage polarization after CD5/βLNP-FAPCAR 2.2 therapy

(A) Enriched KEGG pathways of upregulated DEPs (n=4). (B) Heatmap for tight junction genes (n=4). (C) Heatmap for alveolar cell markers (n=4). (D) Flow cytometry plots of macrophage phenotypes in young mice (n=4). (E) Pie chart of phenotypic macrophages (ratio of phenotypes averaged in 4 mice). (F) Immunofluorescence images of macrophages expressing both M1 and M2 markers. (Red: iNOS; Green: CD163; Cyan: F4/80; Grey: DAPI) (Scar bar: 20 μm). (G, H) Flow cytometry plots and pie chart in aged mice corresponding to Fig. D and E (n=4). ‘n’ means independent biological replications. The values are the means ± SDs. *P < 0.05. Source data are provided as a Source Data file. Created in BioRender. yan, j. (2025) <https://BioRender.com/c53i130>.

- 1 clusters in alveolar cell cluster. (G) Sample distribution within clusters in alveolus cells. (H)
- 2 Highlighted cluster 12, which was increased after CD5/ β LNP-FAPCAR 2.2 treatment.
- 3

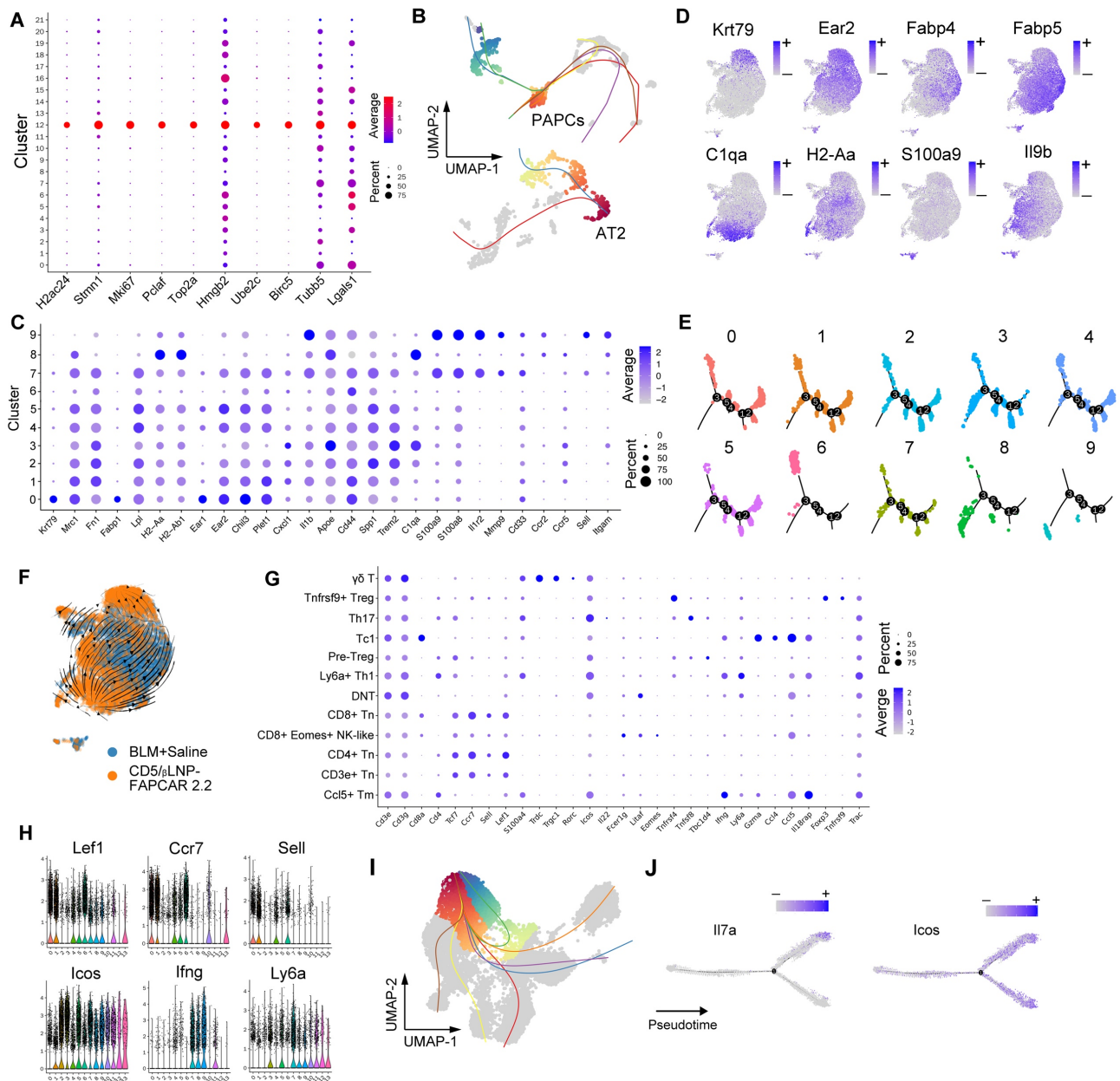
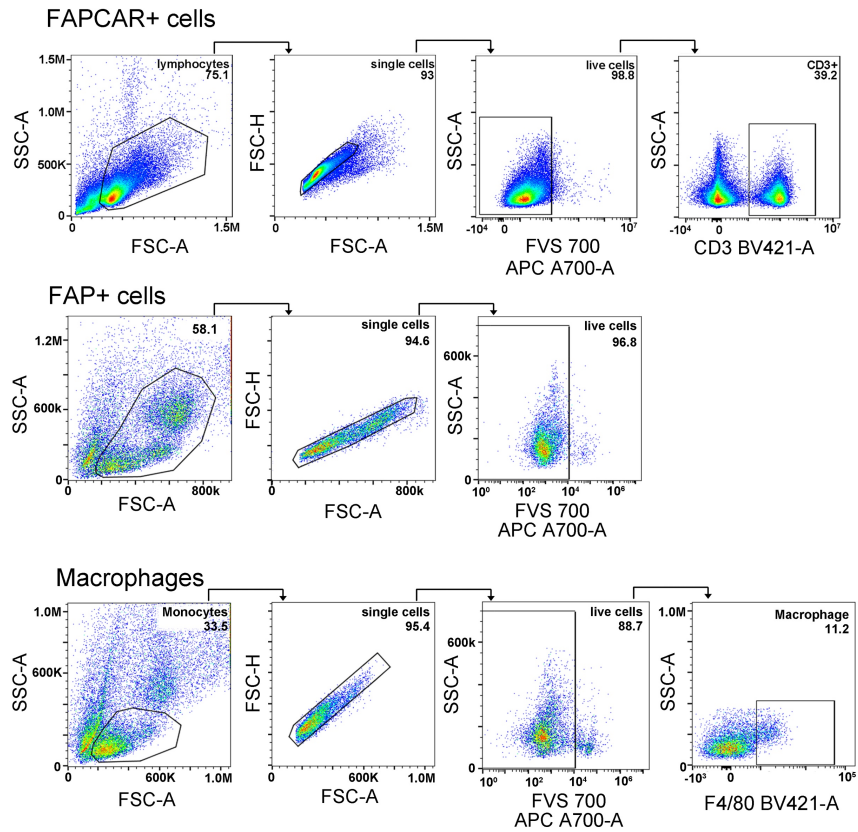


Figure S8. Apoe⁺ macrophage and effector T cells reestablished pulmonary immunity

(A) Dot plot of specific genes expression in cluster 12. (B) Slingshot analysis for alveolar cells and PAPCs (above) and the only alveolar cells (bottom), root clusters of which were PAPCs and AT2, respectively. (C, D) Dot plot (C) and UMAP embedding (D) for top marker genes of the macrophage cluster. (E) The distribution of each cluster in pseudotime trajectory analysis. (F) RNA velocity analysis for macrophages in the BLM+Saline and BLM+CD5/ β LNP-FAPCAR 2.2 groups. (G, H) Dot

- 1 plot (G) and violin plots (H) for representative marker genes of T cells. (I) Slingshot analysis for T
- 2 cell clusters. (J) Pseudotime trajectory analysis for T cells and marker genes along the trajectory.



1

2 **Figure S9. Flow cytometry gating strategy**

3 Lymphocytes, monocytes and single cells were isolated according to the cell size and dot plot
 4 distribution of FSC/SSC gates. FVS 700 staining was used to exclude dead cells. CD3e and f4/80 gates
 5 were for T cells and macrophages, respectively.

6

1
2 **Supplementary Table 1. Blood routine parameter in young mice**

Index	Healthy	Healthy+ CD5/ β LNP- FAPCAR 2.2	BLM	BLM +IgG/ β LNP- FAPCAR 2.2	BLM +CD5/ β LNP- FAPCAR 2.2	BLM +PFD
RBC (10 ¹² /L)	9.13±0.55	9.47±0.48	9.05±0.45	8.95±0.43	9.15±0.4	10.03±0.64*
HGB (g/L)	132.14±6.91	133.6±6.15	136.3±8.79	131.11±6.62	129.9±5.26	141.4±7.25
HCT (%)	44.06±3.15	44.7±2.4	43.77±2.13	43.53±2.09	43±2.02	46±2.5
MCV (fL)	48.44±0.61	49.4±0.9	48.36±0.87	48.68±0.48	47.86±0.67	48.9±0.7
MCH (pg)	14.24±0.16	14.1±0.2	14.43±0.19	14.31±0.18	14.22±0.14	14.1±0.2
MCHC (g/L)	298±3.96	280±1.26	301.6±7.63	296.78±4.74	300.6±4.74	288.6±3.44
PLT (10 ⁹ /L)	1044.4±157.4	1268±304.91	969.7±165.82	1155.67±96.4	1249.3±149.8	1569.6±222*
RDWSD (fL)	24.81±1.38	24.8±0.6	24.42±1.17	26.63±1.1	24.28±1.3	26.4±1.9
RDWCV(%)	15.89±0.29	17.3±0.5	15.24±0.76	16.6±0.36	15.99±0.98	17.1±1.1
PDW (fL)	6.04±0.31	6.4±0.6	5.94±0.15	6.24±0.17	6.27±0.16	6.7±0.2
MPV (fL)	6.37±0.19	6.51±0.4	6.28±0.09	6.46±0.11	6.48±0.09	6.6±0.2
P-LCR (%)	2.29±0.74	2.34±1.9	2.03±0.37	2.29±0.85	2.29±0.43	3.2±0.6*
PCT (%)	0.65±0.13	0.61±0.28	0.61±0.1	0.74±0.07	0.67±0.1	0.87±0.17
WBC (10 ⁹ /L)	1.75±0.59	1.53±0.72	1.65±1.6	4.12±2.12* [#]	3.4±1.88* [#]	2.08±1.04*
NEUT# (10 ⁹ /L)	0.48±0.16	0.44±0.05	0.5±0.21	0.58±0.3	0.46±0.24	0.25±0.11*
LYMPH# (10 ⁹ /L)	1.2±0.84	1.33±0.67	0.84±0.6*	1.14±1.08	2.08±1.71* [#]	1.72±1.01*
MONO# (10 ⁹ /L)	0.05±0.01	0.04±0.01	0.08±0.03*	0.1±0.04*	0.05±0.05 [#]	0.08±0.03*
EO# (10 ⁹ /L)	0.08±0.05	0.06±0.01	0.09±0.05	0.1±0.05	0.11±0.04	0.02±0.02*

BLM, Bleomycin; PFD, Pirfenidone
n=7,7,10,10,10,10
Numbers are mean $\pm$ SDs
*compared to Healthy group; #compared to BLM group, $P < 0.05$
 P -value determined by two tailed unpaired Student's t -test

1 **Supplementary Table 2. Blood routine parameter in aged mice**

Index	Healthy	Healthy+ CD5/ β LNP- FAPCAR 2.2	BLM	BLM+ IgG/ β LNP- FAPCAR 2.2	BLM+ CD5/ β LNP- FAPCAR 2.2
RBC ($10^{12}/L$)	8.64 $\pm$ 0.27	8.93 $\pm$ 0.38	8.65 $\pm$ 0.39	8.72 $\pm$ 0.43	9.19 $\pm$ 0.41
HGB (g/L)	127.33 $\pm$ 3.77	125 $\pm$ 2.16	127.75 $\pm$ 6.17	126.67 $\pm$ 7.98	131.75 $\pm$ 20.90
HCT (%)	40.9 $\pm$ 0.80	42.1 $\pm$ 1.04	44.5 $\pm$ 1.30	45.31 $\pm$ 1.02	47.9 $\pm$ 5.50
MCV (fL)	47.3 $\pm$ 1.10	47.2 $\pm$ 1.10	51.6 $\pm$ 3.02	50.6 $\pm$ 2.17	48.4 $\pm$ 2.40
MCH (pg)	14 $\pm$ 0.46	14 $\pm$ 0.43	14.8 $\pm$ 0.91	14.1 $\pm$ 0.76	13.9 $\pm$ 0.82
MCHC (g/L)	296.67 $\pm$ 4.03	297 $\pm$ 2.16	287.25 $\pm$ 7.08	294.31 $\pm$ 3.88	285.75 $\pm$ 1.92
PLT ($10^9/L$)	1859.3 $\pm$ 67.65	1774 $\pm$ 168.29	2572.75 $\pm$ 184.39*	2718.32 $\pm$ 172.3*	2749.25 $\pm$ 62.10*
RDWSD (fL)	27.3 $\pm$ 2.13	26.8 $\pm$ 1.88	32.5 $\pm$ 2.31*	33.4 $\pm$ 2.17*	27.4 $\pm$ 2.76 [#]
RDWCV (%)	17.1 $\pm$ 0.53	17.1 $\pm$ 0.31	17.9 $\pm$ 1.26	17.1 $\pm$ 0.47	17.4 $\pm$ 1.8
PDW (fL)	6.8 $\pm$ 0.22	6.7 $\pm$ 0.16	7.1 $\pm$ 0.2	7.2 $\pm$ 0.33	7.3 $\pm$ 0.46
MPV (fL)	6.9 $\pm$ 0.26	6.9 $\pm$ 0.1	7.1 $\pm$ 0.1	7 $\pm$ 0.1	6.9 $\pm$ 0.11
P-LCR (%)	4.2 $\pm$ 0.92	4.0 $\pm$ 0.77	5.7 $\pm$ 0.61*	5.3 $\pm$ 0.74*	4.5 $\pm$ 0.73 [#]
PCT (%)	1.28 $\pm$ 0.03	1.22 $\pm$ 0.10	1.82 $\pm$ 0.14*	1.61 $\pm$ 0.78	1.91 $\pm$ 0.03*
WBC ($10^9/L$)	2.27 $\pm$ 0.33	2.25 $\pm$ 0.22	3.16 $\pm$ 0.7	2.73 $\pm$ 0.53	2.55 $\pm$ 1.04
NEUT# ($10^9/L$)	0.3 $\pm$ 0.09	0.26 $\pm$ 0.09	1.22 $\pm$ 0.57*	1.32 $\pm$ 0.47*	1.11 $\pm$ 0.51*
LYMPH# ($10^9/L$)	1.78 $\pm$ 0.38	1.83 $\pm$ 0.29	1.49 $\pm$ 0.41*	1.51 $\pm$ 0.73	1.17 $\pm$ 0.39*
MONO# ($10^9/L$)	0.11 $\pm$ 0.01	0.11 $\pm$ 0.02	0.47 $\pm$ 0.16*	0.32 $\pm$ 0.02*	0.21 $\pm$ 0.28* [#]
EO# ($10^9/L$)	0.08 $\pm$ 0.02	0.06 $\pm$ 0.02	0.02 $\pm$ 0.02*	0.02 $\pm$ 0.02*	0.02 $\pm$ 0.01*

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n=4,4,8,8,8
Numbers are mean $\pm$ SDs
*compared to Healthy group; #compared to BLM group, $P < 0.05$
 P -value determined by two tailed unpaired Student's t -test

1 **Supplementary Table 3. Blood biochemical analysis in young mice**

m	Healthy	Healthy+ CD5/ β LNP- FAPCAR 2.2	BLM	BLM +IgG/ β LNP- FAPCAR 2.2	BLM +CD5/ β LNP- FAPCAR 2.2	BLM +PFD
ALB2 (g/L)	32.37 $\pm$ 2.34	29.7 $\pm$ 1.13	35.2 $\pm$ 1.03	34.73 $\pm$ 1.57	34.87 $\pm$ 1.72	31.48 $\pm$ 1.54
ALTL (U/L)	29.75 $\pm$ 5.93	28.34 $\pm$ 5.23	41.11 $\pm$ 19.81*	28.21 $\pm$ 9.52	29.77 $\pm$ 5.67	24.34 $\pm$ 4.56
UA2 (mg/dL)	0.42 $\pm$ 0.13	0.62 $\pm$ 0.54	0.41 $\pm$ 0.14	0.43 $\pm$ 0.09	0.38 $\pm$ 0.06	0.28 $\pm$ 0.12
ASTL (U/L)	95.58 $\pm$ 33.39	112.66 $\pm$ 53.57	135.36 $\pm$ 46.5*	81.24 $\pm$ 14.38	108.56 $\pm$ 31.28	117.34 $\pm$ 25.85
CREA2 (μ mol/L)	13.50 $\pm$ 0.50	15.4 $\pm$ 1.02	17.7 $\pm$ 0.9	15.67 $\pm$ 1.05	15.5 $\pm$ 0.81	14.2 $\pm$ 2.93
CKMB2 (U/L)	289.20 $\pm$ 38.88	429.28 $\pm$ 93.8	360.44 $\pm$ 85.46	275.1 $\pm$ 55.52	306.57 $\pm$ 30.69	402.94 $\pm$ 74.89
U-BUN (mmol/L)	7.97 $\pm$ 1.07	7.42 $\pm$ 0.91	8.13 $\pm$ 0.81	8.6 $\pm$ 0.79	8.48 $\pm$ 0.91	8.32 $\pm$ 1.01
CK2(U/L)	1301 $\pm$ 703.12	1595 $\pm$ 587.97	1422 $\pm$ 454.46	1402 $\pm$ 322.22	1515 $\pm$ 296.65	2972 $\pm$ 690.92*
ALP2L (U/L)	0	0	0.44 $\pm$ 0.95*	0	0	0

2 ALTL: glutamic pyruvic transaminase level, ASTL: glutamic oxaloacetic transaminase level,
3 ALB2: albumin 2, UREA/BUN: urea/urea nitrogen, CREA2: creatinine 2, UA2: uric acid 2,
4 CK2: creatine kinase 2, CKMB2: creatine kinase-MB 2, ALP2: alkaline phosphatase 2
5 n=6,7,10,9,10,9
6 Numbers are mean $\pm$ SDs
7 *compared to Healthy group, $P < 0.05$
8 P -value determined by two tailed unpaired Student's t -test
9

Supplementary Table 4: Blood biochemical analysis in aged mice

Index	Healthy	Healthy+ CD5/ β LNP- FAPCAR 2.2	BLM	BLM +IgG/ β LNP- FAPCAR 2.2	BLM +CD5/ β LNP- FAPCAR 2.2
ALB2(g/L)	32.53 $\pm$ 0.78	32.45 $\pm$ 0.95	27.92 $\pm$ 0.53	31.77 $\pm$ 0.79	29.83 $\pm$ 1.89
ALTL(U/L)	27.77 $\pm$ 3.73	30.4 $\pm$ 0.41	52.95 $\pm$ 15.4*	36.7 $\pm$ 7.62*	29.53 $\pm$ 4.01 [#]
UA2(mg/dL)	0.43 $\pm$ 0.26	0.39 $\pm$ 0.08	0.65 $\pm$ 0.38*	0.57 $\pm$ 0.39	0.27 $\pm$ 0.09
ASTL(U/L)	98.56 $\pm$ 7.24	101.2 $\pm$ 7.64	161.17 $\pm$ 62.3*	137.61 $\pm$ 34.9*	158.53 $\pm$ 28.6*
CREA2(μ mol/L)	14.33 $\pm$ 0.94	14.12 $\pm$ 1.63	12.75 $\pm$ 2.58	13.57 $\pm$ 1.62	13.33 $\pm$ 0.94
CKMB2(U/L)	415.43 $\pm$ 69.2	439.55 $\pm$ 73.25	436.9 $\pm$ 43.58	507.69 $\pm$ 91.3	512.87 $\pm$ 55.72
U-BUN(mmol/L)	10.5 $\pm$ 2.79	11.75 $\pm$ 2.65	8.02 $\pm$ 0.43	11.83 $\pm$ 1.74	8.8 $\pm$ 1.31
CK2(U/L)	2045 $\pm$ 734.08	2291 $\pm$ 792.3	2155 $\pm$ 683.07	2623 $\pm$ 655.3	2695 $\pm$ 527.5
ALP2L(U/L)	0	0	0	0	0

n=4,4,8,8,8

Numbers are mean $\pm$ SDs

*compared to Healthy group; #compared to BLM group, $P < 0.05$

P-value determined by two tailed unpaired Student's *t*-test

Supplementary Table 5. The sequences of primers used in IVT plasmid construction and mRNA copy number assay.

Gene	Sequence (5'-3')	
IVT vector	F: GCTGGAGCCTCGGTGGCCTA	R: GGTGGCGCCGGGGTCTTATA
FAPCAR	F: TATAAGACCCCGGCGCCACCATGGCC CTCCCTGTCACCG	R: TAGGCCACCGAGGCTCCAGCCTATTATCA CTCTGTGGCCTCCTTG
EGFP	F: TATAAGACCCCGGCGCCACCATGGTG AGCAAGGGCGAGG	R: TAGGCCACCGAGGCTCCAGCCTATTATCA CTTGTACAGCTCGTCCA
Luciferase	F: TATAAGACCCCGGCGCCACCATGGA AGATGCCAAAAACATTAAGAAGG	R: TAGGCCACCGAGGCTCCAGCCTATTATCA CACGGCGATCTTGC
tdTomato	F: GTTGAAGAAAACCCCGGGCCTATGG TGAGCAAGGGCGAGG	R: ACCGAGGCTCCAGCCTATTATCACTACTT GTACAGCTCGTCCATGCC
FAPCAR (scFV)	F: AGCAACGGCAACACCTACCT	R: AGGTCCTCGGCTTCCACTCT
FAPCAR (4-1BB)	F: CTCAAGAGGAGGACGGCTGTAG	R: TGTTGGTAGGCTGGAGCATCTG
FAPCAR 2.2 (TMD)	F: TAGTCGCCTTATTGGCGCTGC	R: TGTTGGTAGGCTGGAGCATCTGC