

Supplemental Material

<i>Lmna</i> DCM Treatment	Age (weeks)	n	LVDD (mm)	P	LVWT (mm)	P	EF (%)	P	FS (%)	P
<i>EGFP</i> -Ctrl <i>shRNA</i>	5.5	5	4.41 ± 0.11		0.49 ± 0.09		13.91 ± 2.50		6.16 ± 1.15	
<i>Yy1</i> -Ctrl <i>shRNA</i>		5	4.16 ± 0.12	0.009	0.56 ± 0.09	0.25	31.70 ± 4.31	4E-05	14.81 ± 2.20	5E-05
<i>Yy1-Ccnd1 shRNA</i>		5	4.04 ± 0.15	0.002	0.58 ± 0.06	0.09	32.06 ± 2.88	5E-06	14.93 ± 1.47	5E-06

Online Table I. Effect of *Yy1-Ccnd1 shRNA* on *Lmna* DCM in mice

Effect of *Yy1-Ccnd1 shRNA*, *Yy1*-Ctrl *shRNA* or *EGFP*-Ctrl *shRNA* at a dose of 0.5E+13 vg/kg on *Lmna* DCM mice assessed at 5.5 weeks. P values represent comparisons to *Lmna* DCM mice treated with *EGFP*-Ctrl *shRNA*. LVDD, left ventricular diastolic dimension; LVWT, LV wall thickness; EF, ejection fraction; FS, fractional shortening.

<i>Lmna</i> DCM Treatment	Age (weeks)	n	LVDD (mm)	P	LVWT (mm)	P	EF (%)	P	FS (%)	P
<i>EGFP</i>	5.5	5	4.39 ± 0.10		0.46 ± 0.05		14.77 ± 5.30		6.48 ± 2.33	
<i>Ccnd1</i>		5	4.44 ± 0.11	0.44	0.52 ± 0.06	0.16	16.86 ± 1.84	0.43	7.54 ± 0.87	0.37

Online Table II. Effect of *Ccnd1* on *Lmna* DCM in mice

Effect of *Ccnd1* or *EGFP* at a dose of 0.5E+13 vg/kg on *Lmna* DCM mice assessed at 5.5 weeks. P values represent comparisons to *Lmna* DCM mice treated with *EGFP*. LVDD, left ventricular diastolic dimension; LVWT, LV wall thickness; EF, ejection fraction; FS, fractional shortening.

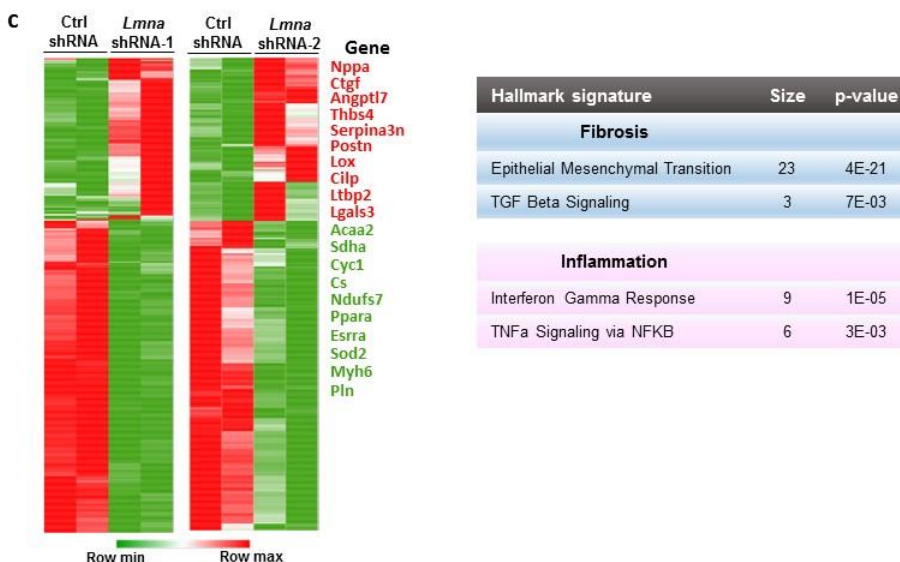
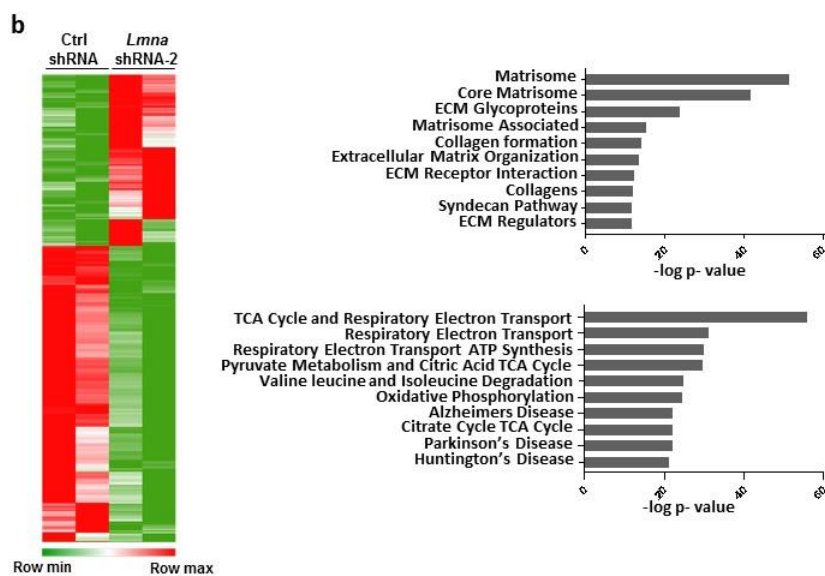
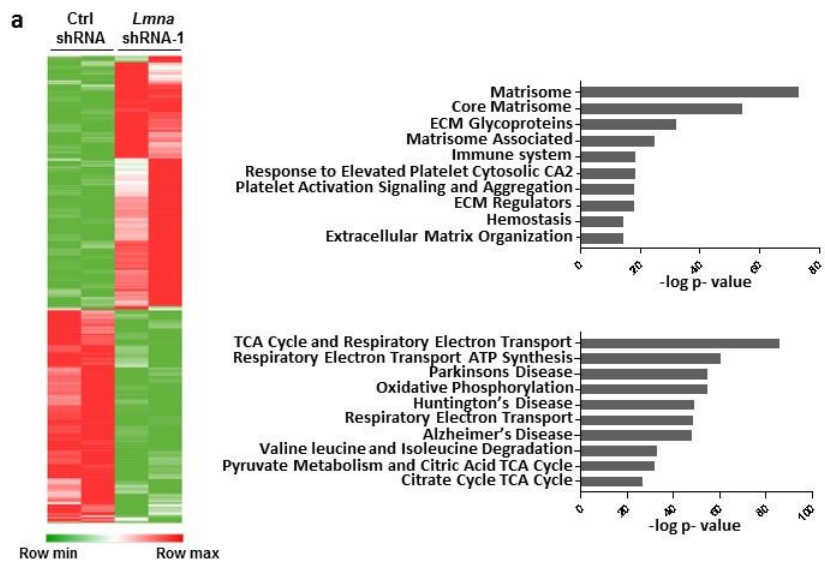
<i>Lmna</i> DCM Treatment	Age (weeks)	n	LVDD (mm)	P	LVWT (mm)	P	EF (%)	P	FS (%)	P
<i>EGFP</i>	5.5	5	4.25 ± 0.10		0.43 ± 0.11		14.38 ± 5.03		6.38 ± 2.32	
<i>Bmp7</i>		6	4.02 ± 0.22	0.07	0.45 ± 0.09	0.79	20.56 ± 8.94	0.21	9.31 ± 4.21	0.20

Online Table III. Effect of *Bmp7* on *Lmna* DCM in mice

Effect of *Bmp7* at a dose of 0.5E+13 vg/kg on *Lmna* DCM mice assessed at 5.5 weeks. P values represent comparisons to *Lmna* DCM mice treated with *EGFP*. LVDD, left ventricular diastolic dimension; LVWT, LV wall thickness; EF, ejection fraction; FS, fractional shortening.

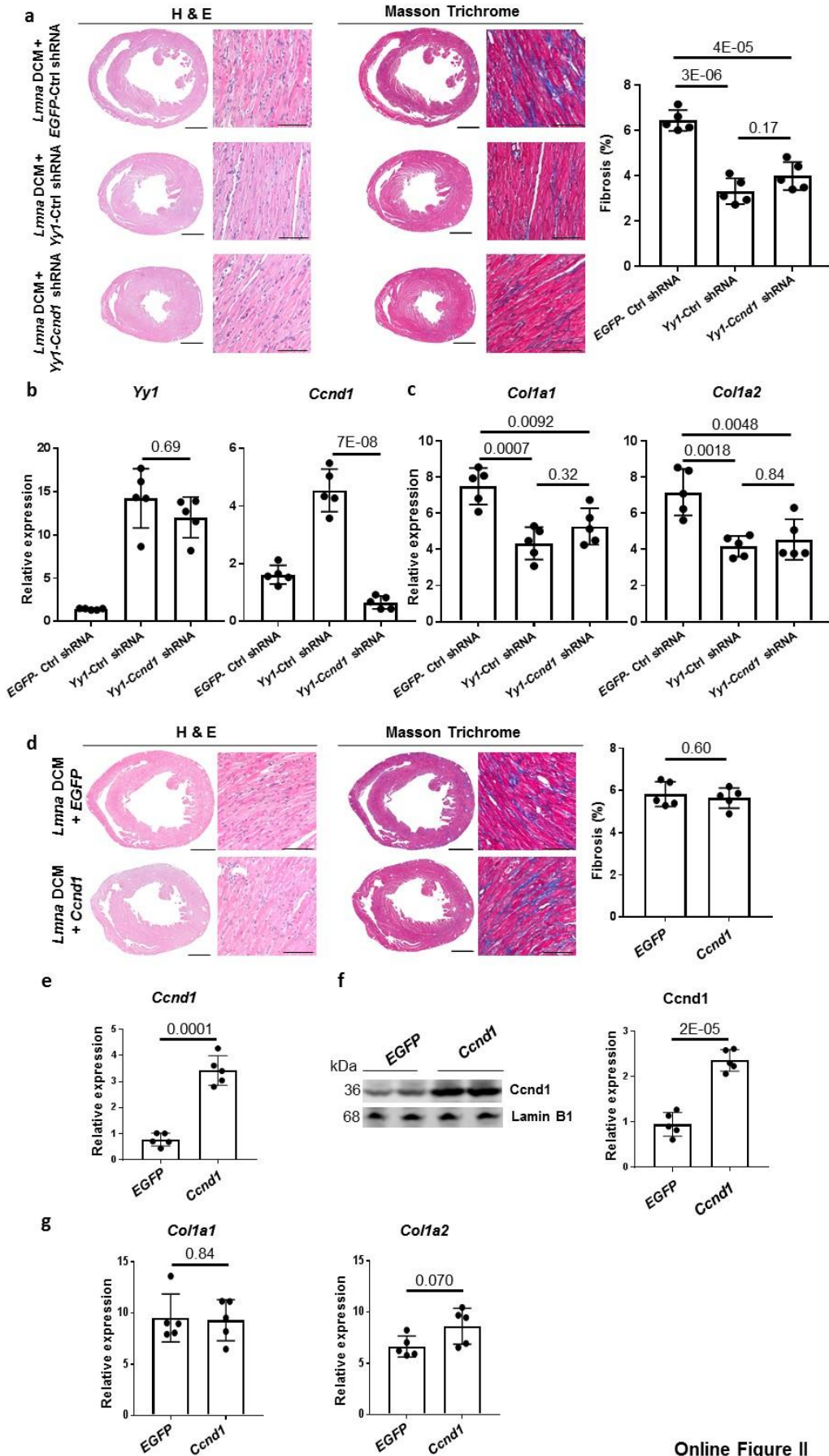
<i>Lmna</i> DCM Treatment	Age (weeks)	n	LVDD (mm)	P	LVWT (mm)	P	EF (%)	P	FS (%)	P
Ctrl <i>shRNA</i>	5.5	6	4.28 ± 0.12		0.47 ± 0.08		17.34 ± 9.80		7.86 ± 4.76	
<i>Ctgf shRNA</i>		7	4.16 ± 0.13	0.10	0.51 ± 0.06	0.26	23.79 ± 4.52	0.15	10.83 ± 2.20	0.17

18 **OnlineTable IV. Effect of *Ctgf* shRNA on *Lmna* DCM in mice**
19 Effect of *Ctgf* shRNA at a dose of 2.0E+13 vg/kg on *Lmna* DCM mice assessed at 5.5 weeks. P values represent
20 comparisons to *Lmna* DCM mice treated with Ctrl shRNA. LVDD, left ventricular diastolic dimension; LVWT,
21 LV wall thickness; EF, ejection fraction; FS, fractional shortening.
22



Online Figure 1

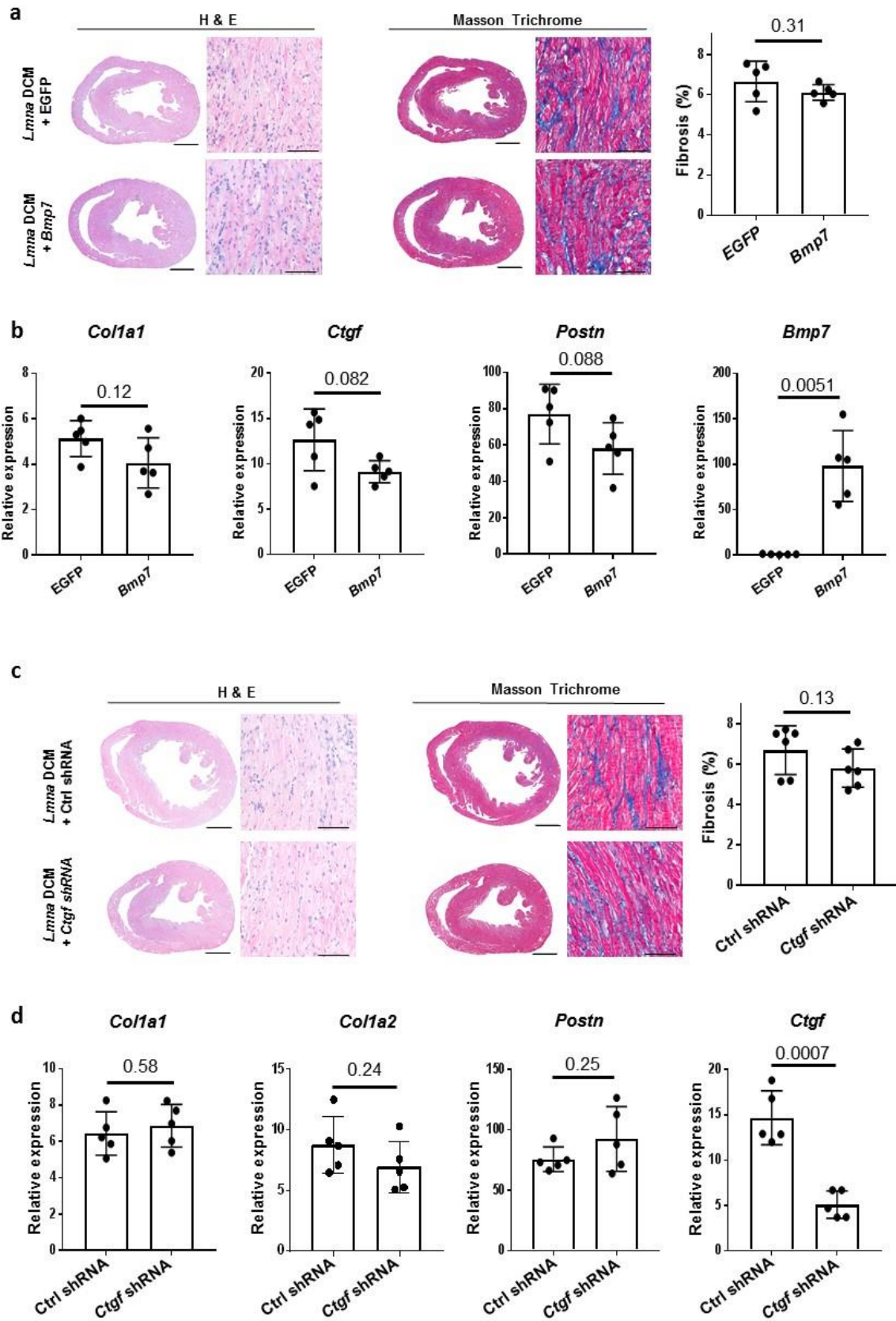
24 **Online Figure I. *Lmna* shRNAs result in dysregulated downstream signaling pathways**
25 **(a, b, c)** Heat map representing color-coded expression level of genes that significantly changed in *Lmna*
26 shRNA-1 **(a)** or *Lmna* shRNA-2 **(b)** transduced group or common dysregulated genes for both groups **(c)** in
27 comparison to control shRNA group or. Virus dose, 2.0E+13 vg/kg. Mice were harvest four weeks after
28 transduction, n = 2. Top 10 gene sets in canonical pathway of each category **(a, b)** or representative hallmark
29 signature **(c)** as designated by GSEA, arranged by -log P value.
30



Online Figure II

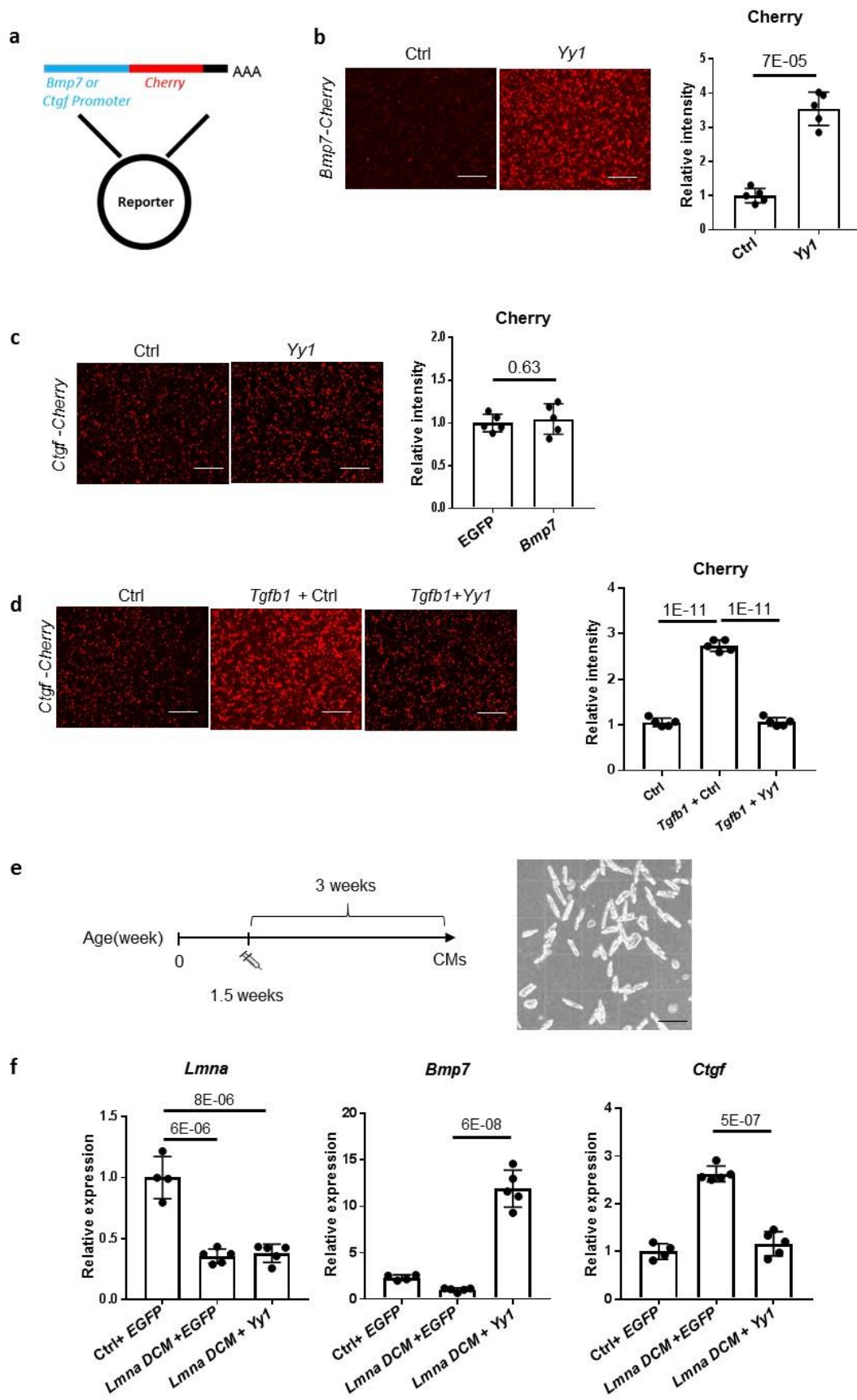
33 **Online Figure II. Modulation of *Ccnd1* does not affect the suppressive effect of *Yy1* on *Lmna* DCM and**
34 **cardiac fibrosis**

35 (a) H&E and MT staining of paraffin heart sections from *Lmna* DCM mice taken 4 weeks after *EGFP*-Ctrl
36 shRNA, *Yy1*-Ctrl shRNA or *Yy1-Ccnd1* shRNA transduction. Quantification of myocardial fibrosis of MT
37 sections is shown, n = 5. Scale bars: 1000 μ m for complete heart images; 100 μ m for enlarged images. (b)
38 Quantitative real-time PCR analyses of *Yy1* and *Ccnd1* levels in cardiomyocytes (CM) from mice transduced
39 with *EGFP*-Ctrl shRNA, *Yy1*-Ctrl shRNA or *Yy1-Ccnd1* shRNA, n = 5. (c) Quantitative real-time PCR analyses
40 of *Colla1* and *Colla2* expression in *Lmna* DCM heart tissue from groups treated with *EGFP*-Ctrl shRNA, *Yy1*-
41 Ctrl shRNA or *Yy1-Ccnd1* shRNA, n = 5. (d) H&E and MT stained paraffin heart sections of *Lmna* DCM mice
42 treated with *EGFP* or *Ccnd1*. Quantification of myocardial fibrosis of MT sections is shown, n = 5. Scale bars:
43 1000 μ m for complete heart images; 100 μ m for enlarged images. (e) Quantitative real-time PCR analyses of
44 *Ccnd1* levels and (f) Western blot and quantitative analysis of *Ccnd1* protein levels in mouse heart tissue from
45 *EGFP* and *Ccnd1* treated groups. Mouse hearts were harvested 4 weeks after transduction, n = 5. (g)
46 Quantitative real-time PCR analyses of *Colla1* and *Colla2* in *Lmna* DCM heart tissue from mice treated with
47 *EGFP* and *Yy1*, n = 5.
48



Online Figure III

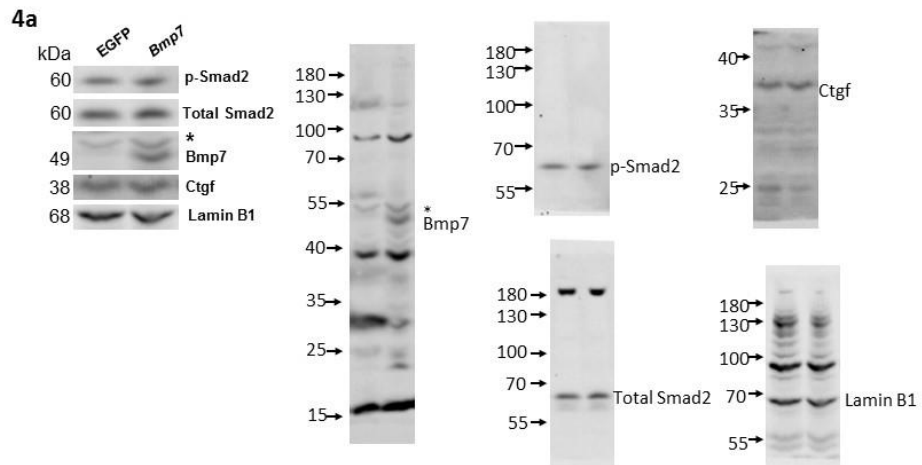
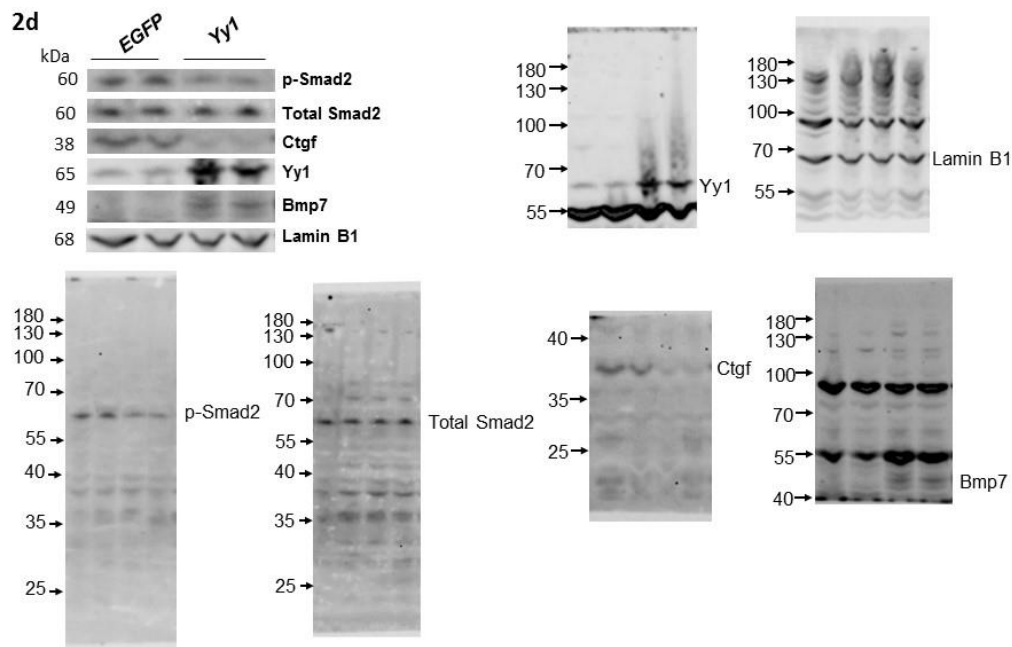
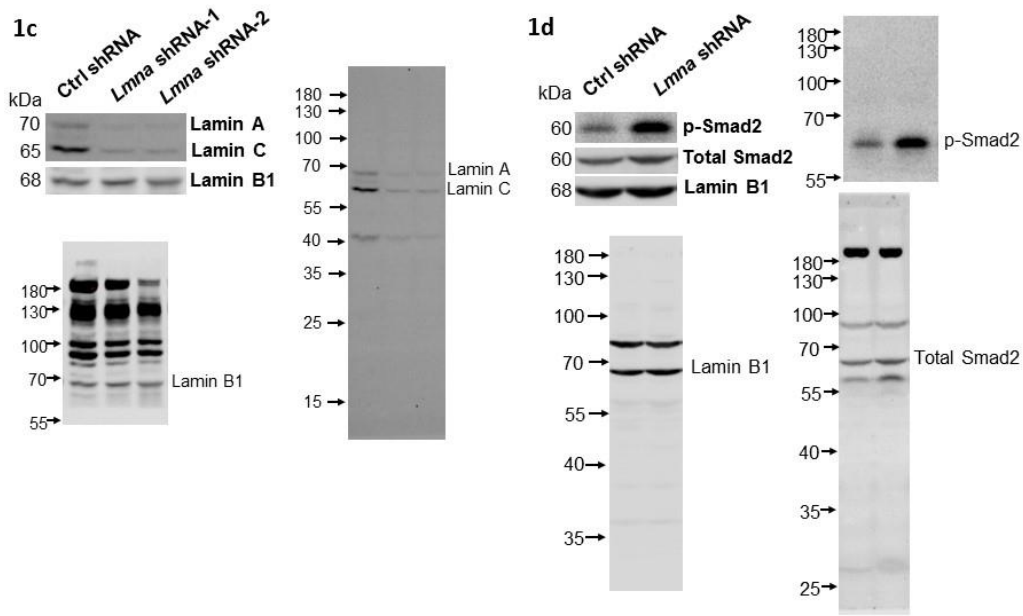
50 **Online Figure III. Upregulation of *Bmp7* or *Ctgf* silencing alone is not sufficient to suppress *Lmna* DCM**
51 **and cardiac fibrosis**
52 (a and c) H&E and MT staining of paraffin heart sections from *Lmna* DCM mice 4 weeks after (a) *EGFP* or
53 *Bmp7* transduction and (c) Ctrl shRNA or *Ctgf* shRNA transduction. Quantification of myocardial fibrosis of
54 MT sections is shown, $n \geq 5$. Scale bars: 1000 μm for complete heart images; 100 μm for enlarged images. (b
55 and d) Quantitative real-time PCR analyses of *Colla1*, *Colla2*, *Ctgf*, *Bmp7* and *Postn* expression in *Lmna*
56 DCM groups treated with (a) *EGFP*, *Bmp7*, $n = 5$ or (b) Ctrl shRNA, *Ctgf* shRNA, $n = 5$.



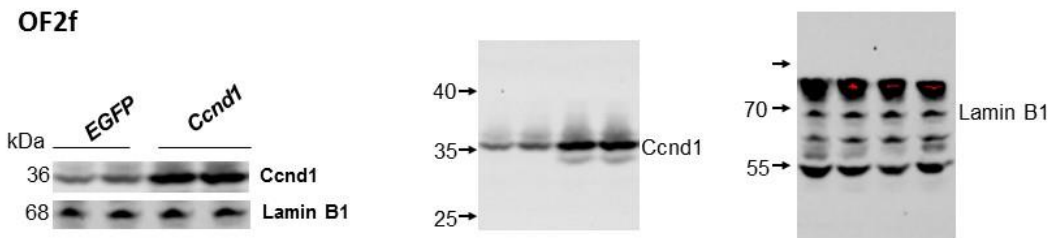
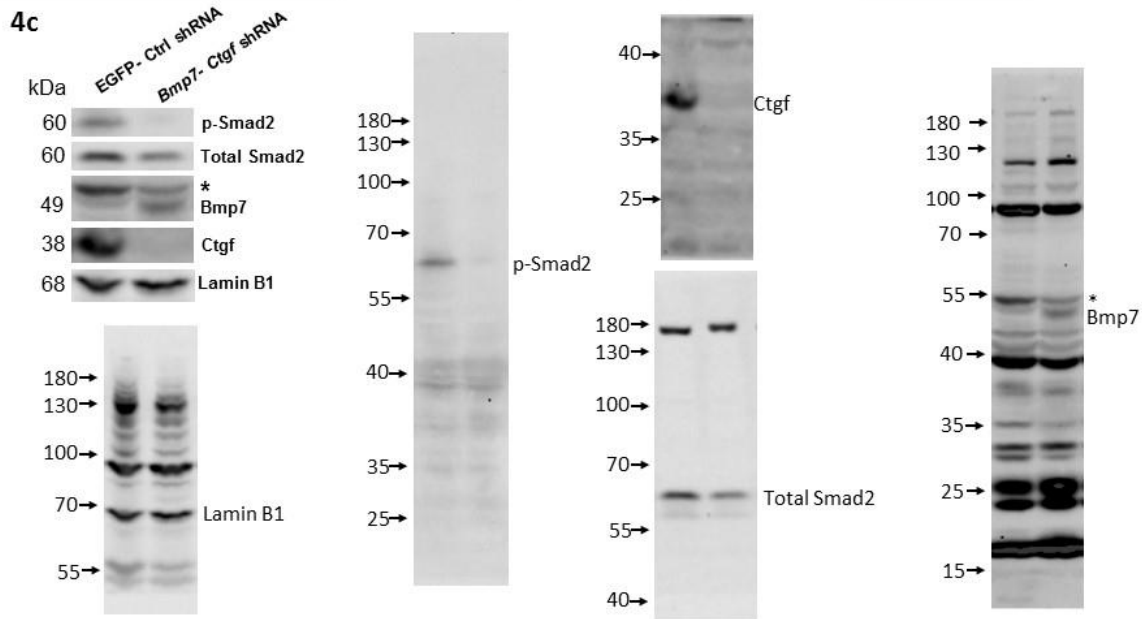
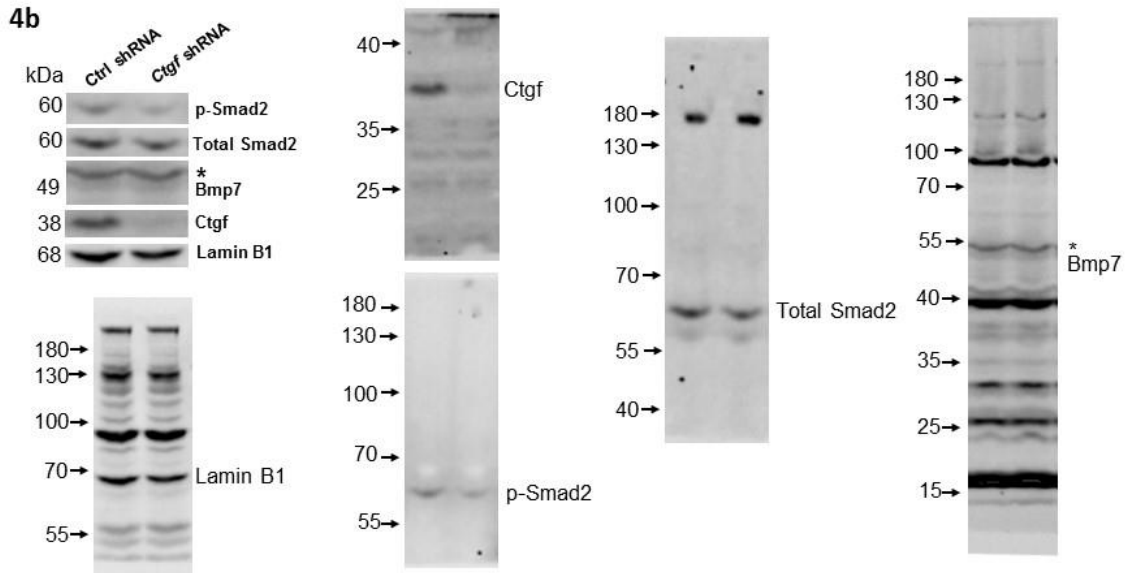
Online Figure IV

58 **Online Figure IV. Upregulation of *Yy1* regulates gene expression of *Bmp7* and *Ctgf***

59 (a) Schematic diagram of reporter plasmid with either a *Bmp7* or *Ctgf* promoter followed by a *Cherry* gene. (b,
60 c and d) HEK293T cells co-transfected with (b) *Yy1* plasmid and *Bmp7-Cherry* reporter plasmid (Red), (c) *Yy1*
61 plasmid and *Ctgf-Cherry* reporter plasmid and (d) *Tgfb1* plasmid + control, *Tgfb1* plasmid + *Yy1* plasmid and
62 *Ctgf-Cherry* reporter plasmid. Scale bar = 1000 μ m. Graph on the right shows the relative intensity of *Cherry*
63 expression (red) in respective groups, n = 5. (e) Experimental timeline showing timepoints of virus injection and
64 CMs isolation. Brightfield image of isolated CMs is shown, scale bar = 200 μ m. (f) Quantitative real-time PCR
65 analyses of *Lmna*, *Bmp7* and *Ctgf* expression in ctrl wildtype group treated with *EGFP* or *Lmna* DCM groups
66 treated with *EGFP* or *Yy1*, n \geq 4.
67



Online Figure V



Online Figure VI

Online Figure V and VI. Immunoblots containing markers