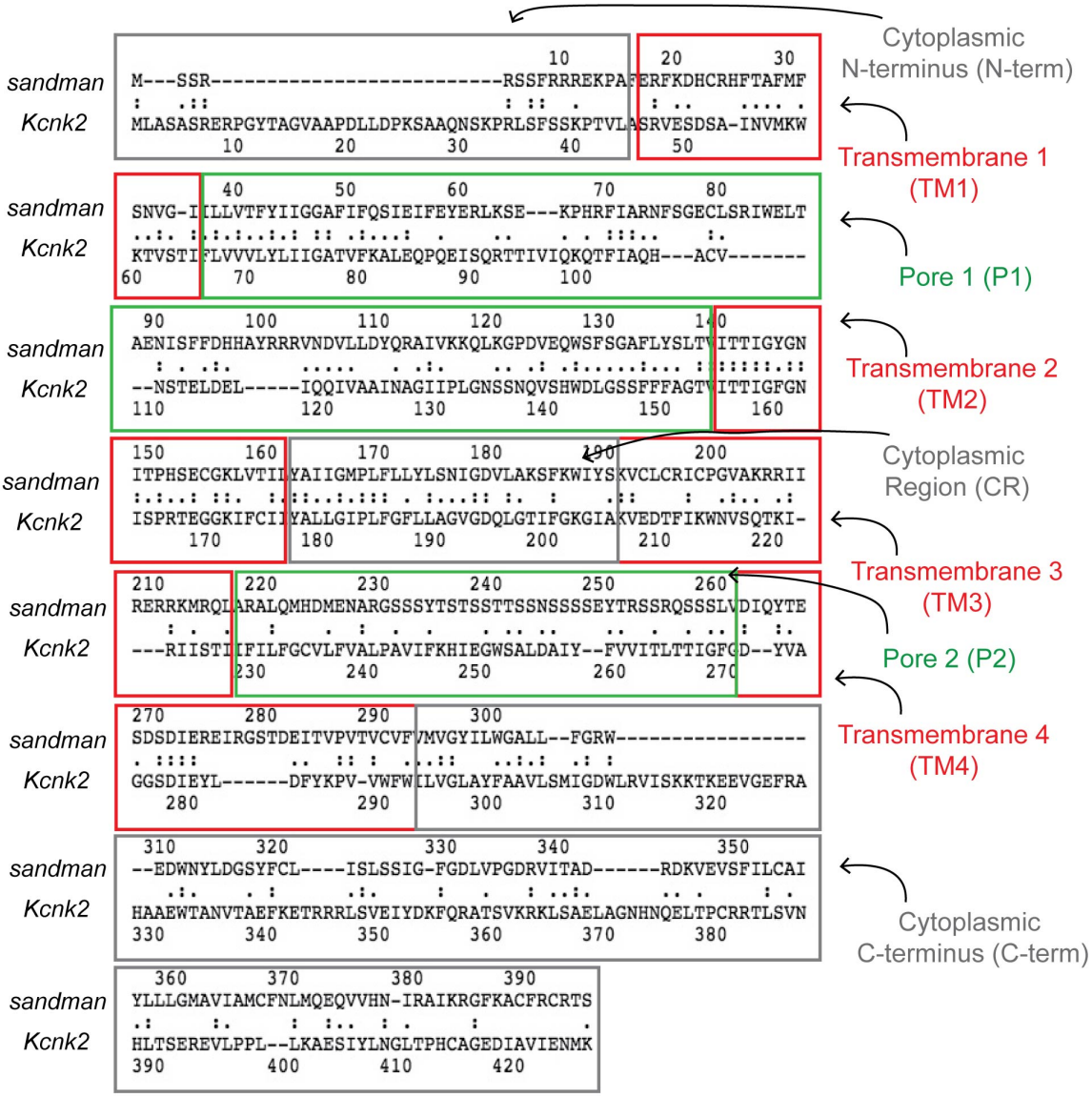
Fig. S1 A *Drosophila sandman* and Mouse TREK-1 (*Kcnk2*) Sequence Alignment



B Sequence Identity of *sandman* vs TREK-1 (*Kcnk2*): Global: 20% identity

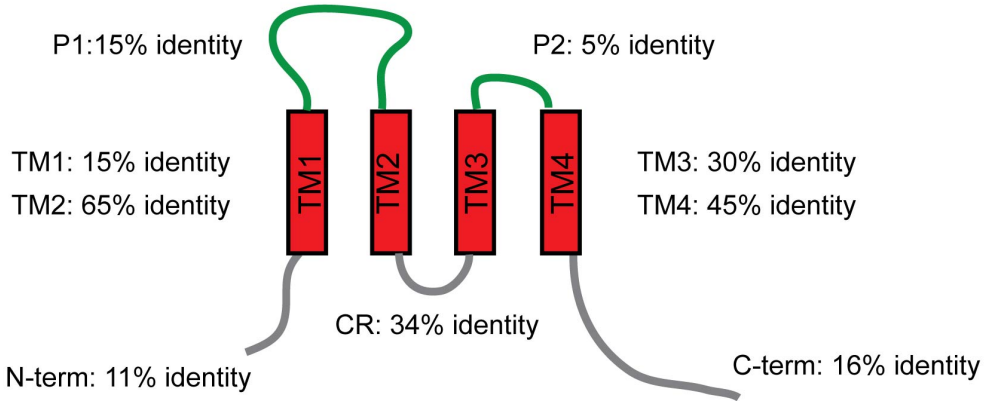


Fig. S1. *CG8713* (*sandman*) vs TREK-1 sequence alignment. (A) Amino acid sequence alignment of Drosophila CG8713 (top line) and Mouse TREK-1 or *Kcnk2* (bottom line) monomer, known structural domains of TREK-1 outlined in the following manner: Cytoplasmic domains (grey box), Transmembrane domains (red box) and Pore forming domains (green box), Sequence identity denoted by ":" sign; **(B)** Sequence identity between CG8713 and TREK-1 shown with depiction of known structural domains of TREK-1, Sequence identity in the entire sequence is 20%. Structural domain sequence identity for the 1) cytoplasmic N-terminus (N-term) is 11%, 2) transmembrane 1 (TM1) is 15%, 3) Pore 1 (P1) is 15%, 4) transmembrane 2 (TM2) is 65%, 5) Cytoplasmic region (CR) is 34%, 6) transmembrane 3 (TM3) is 30%; 7) Pore 2 (P2) is 5%, 8) transmembrane 4 (TM4) is 45% and 8) cytoplasmic C-terminus (C-term) is 16%.

Fig. S2

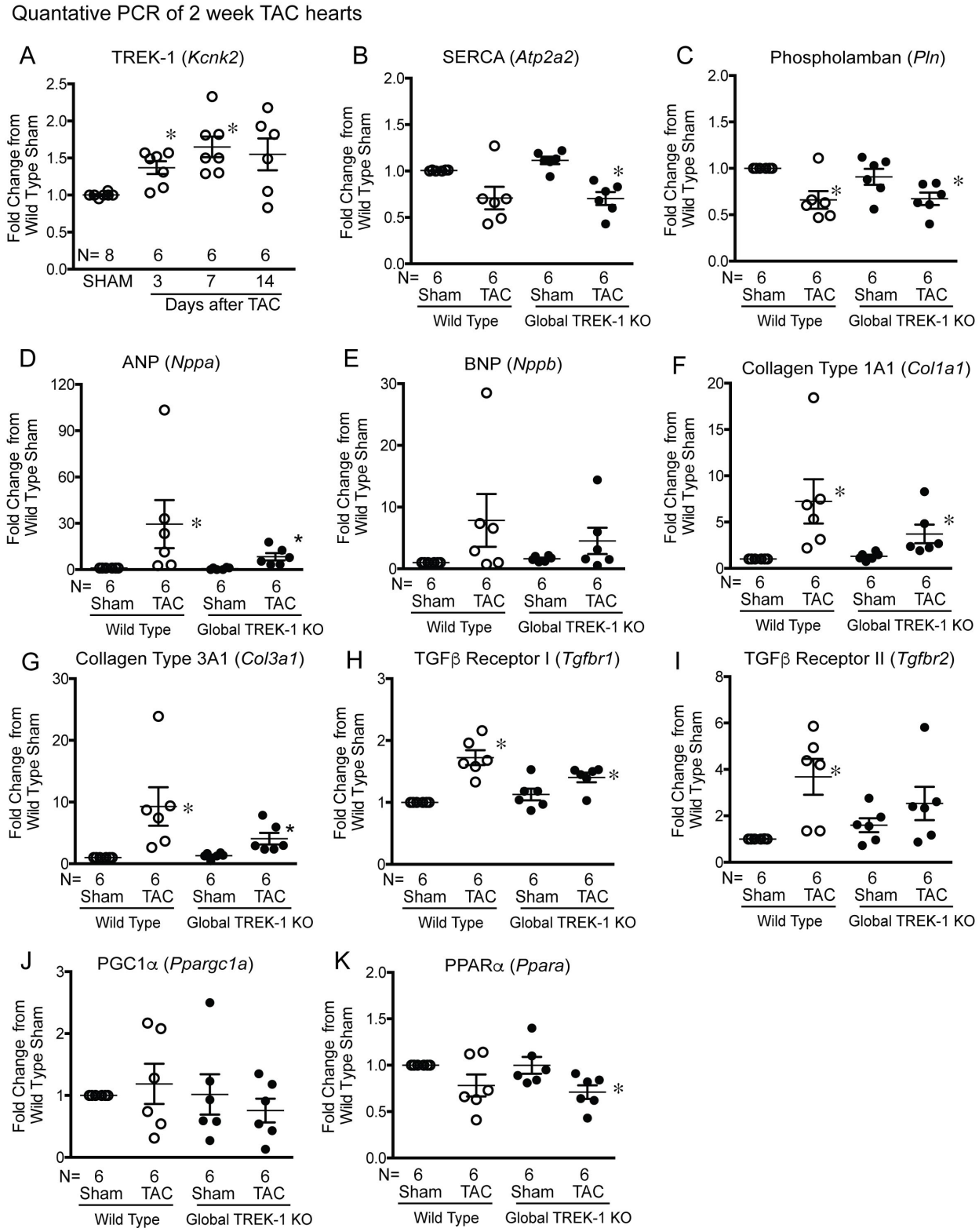

Quantative PCR of 2 week TAC hearts
A
TREK-1 (Kcnk2)
Fold Change from Wild Type Sham
N= 8 6 6 6
SHAM 3 7 14
Days after TAC
B
SERCA (Atp2a2)
C
Phospholamban (Pln)
D
ANP (Nppa)
E
BNP (Nppb)
F
Collagen Type 1A1 (Col1a1)
G
Collagen Type 3A1 (Col3a1)
H
TGFβ Receptor I (Tgfbr1)
I
TGFβ Receptor II (Tgfbr2)
J
PGC1α (Ppargc1a)
K
PPARα (Ppara)
N= 6 6 6 6
Sham TAC Sham TAC
Wild Type
Global TREK-1 KO

Fig. S2. TREK-1 KO 2-week TAC gene expression (A) Average TREK-1 gene expression (Mouse gene name shown in parentheses) in harvested left ventricles from Wild Type mice after Sham, 3 days, 7 days or 14 days of TAC, Average Gene expression of **(B)** SERCA and **(C)** Phospholamban, **(D)** Atrial Natriuretic Peptide (ANP), **(E)** Brain Natriuretic Peptide (BNP), **(F)** Collagen, type I, alpha (Col1A1), **(G)** Collagen, type III, alpha (Col3A1), **(H)** Transforming Growth Factor beta I receptor (TGFβ Receptor I), **(I)** Transforming Growth Factor beta II receptor (TGFβ Receptor II), **(J)** PGC1α and **(K)** PPARα after 2 week TAC in Wild type and Global TREK-1 KO by quantitative PCR; Statistical comparisons to Wild Type Sham, which has a theoretical mean of "1", were made with a "one sample" two-tailed t-test. *$p<0.05$ vs. Wild type Sham. Comparisons between all other groups excluding Wild Type Sham were made using a by Kruskal–Wallis test with Dunn's multiple comparisons test. The statistical comparisons between all other groups excluding Wild Type Sham were not statistically significant.

Fig. S3

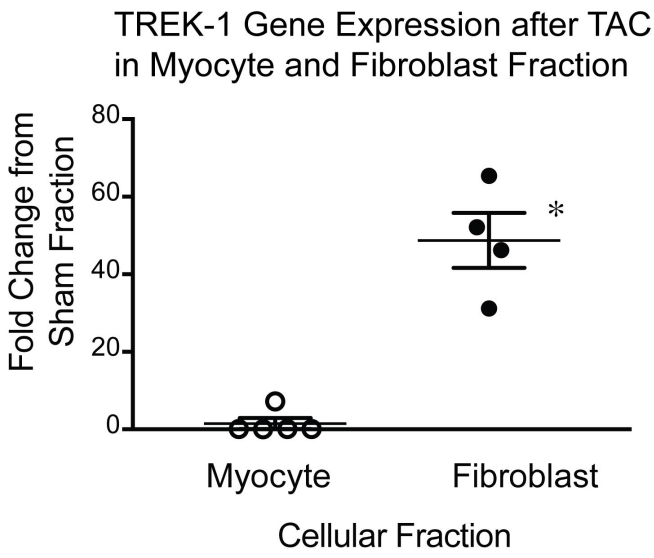


Fig. S3. TREK gene expression in Myocyte and Fibroblast Fraction after TAC

Average *TREK-1* gene expression in myocyte (n=5) and fibroblast (n=4) fractions obtained from harvested left ventricles from Wild Type mice after 7 days TAC. Data is expressed as a fold change from the corresponding cellular fraction under sham conditions. Data compared using a Mann Whitney test with two tailed p value. *$p<0.05$ vs myocyte fraction after TAC.

Fig. S4

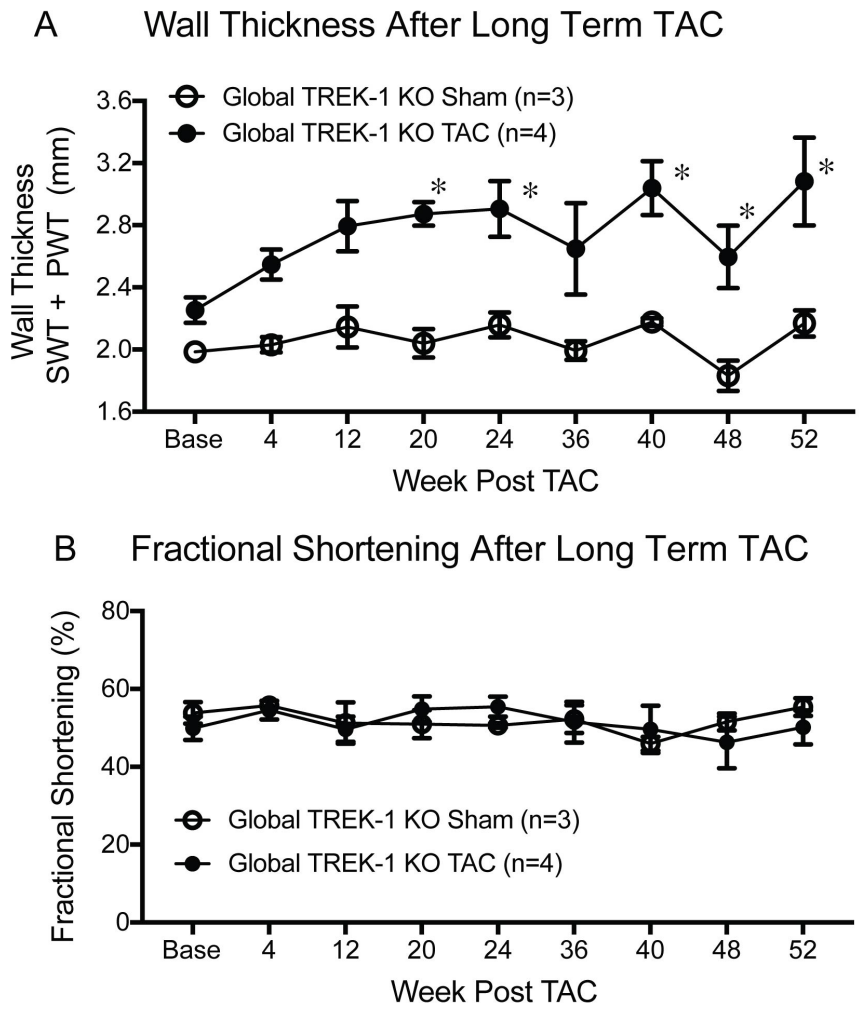


Fig. S4. Long-term maintenance of cardiac function in global TREK-1 KO mice after TAC.

(A) Serial echocardiographic measurements of average wall thicknesses [septal wall thickness (SWT) + posterior wall thickness (PWT)] and **(B)** Average Fractional Shortening from TREK-1 KO mice undergoing Sham (n=3) or TAC (n=4) at baseline and up to 52 weeks after TAC. Statistical comparisons between TREK-1 KO Sham and TAC data were made using two-way repeated measures ANOVA. Comparisons between genotypes at each time point was made using Bonferroni's test for multiple comparisons, *$p<0.05$ vs. TREK KO Sham at each time point

Fig. S5

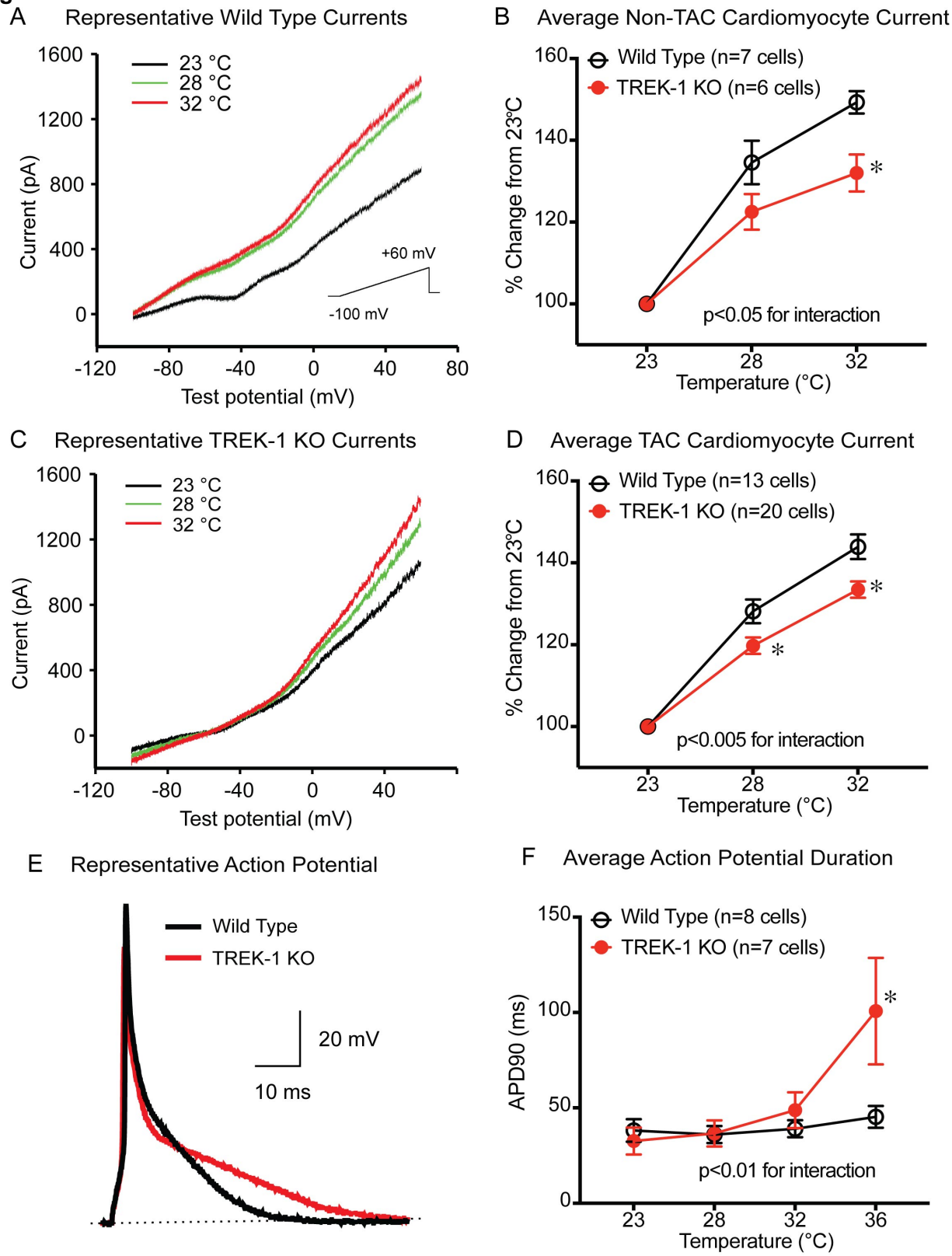

A
Representative Wild Type Currents
23 °C
28 °C
32 °C
Current (pA)
1600
1200
800
400
0
+60 mV
-100 mV
-120
-80
-40
0
40
80
Test potential (mV)
B
Average Non-TAC Cardiomyocyte Current
Wild Type (n=7 cells)
TREK-1 KO (n=6 cells)
% Change from 23°C
160
140
120
100
*
p<0.05 for interaction
23
28
32
Temperature (°C)
C
Representative TREK-1 KO Currents
23 °C
28 °C
32 °C
Current (pA)
1600
1200
800
400
0
-120
-80
-40
0
40
Test potential (mV)
D
Average TAC Cardiomyocyte Current
Wild Type (n=13 cells)
TREK-1 KO (n=20 cells)
% Change from 23°C
160
140
120
100
*
*
p<0.005 for interaction
23
28
32
Temperature (°C)
E
Representative Action Potential
Wild Type
TREK-1 KO
20 mV
10 ms
F
Average Action Potential Duration
Wild Type (n=8 cells)
TREK-1 KO (n=7 cells)
APD90 (ms)
150
100
50
0
*
p<0.01 for interaction
23
28
32
36
Temperature (°C)

Fig. S5: TREK-1 isolated myocyte electrophysiology. **(A)** and **(C)** Representative potassium current recordings from cardiac myocytes isolated from wild type mice and TREK-1 KO mice. TREK-1 is activated by temperature. Potassium current increases in wild cardiac myocytes exposed to 28°C and 32°C. A temperature dependent increase in current was blunted in TREK-1 KO, suggesting that TREK-1 contributes significantly to the measured current. **(B)** Average current change in cardiac myocytes obtained from Wild Type and TREK-1 KO non-TAC mice (Wild Type=7, TREK-1 KO= 6 myocytes). **(D)** Average current change in cardiac myocytes obtained from Wild Type and TREK-1 KO mice after TAC (Wild Type=13, TREK-1 KO=20 myocytes). **(E)** Representative ventricular myocyte action potential from cells isolated from Wild Type and TREK-1 KO mice. **(F)** Average Action Potential Duration in Wild Type and TREK-1 KO myocytes (Wild Type=13, TREK-1 KO=20 myocytes). N=4-5 mice used for each protocol. Statistical comparisons between Wild Type and TREK-1 KO electrophysiologic recordings were made using two-way repeated measures ANOVA. The p value for the interaction between genotype and temperature is shown. Comparisons between genotypes at each temperature was made using Bonferroni's test for multiple comparisons, *$p<0.05$ vs. Wild Type.

Fig. S6

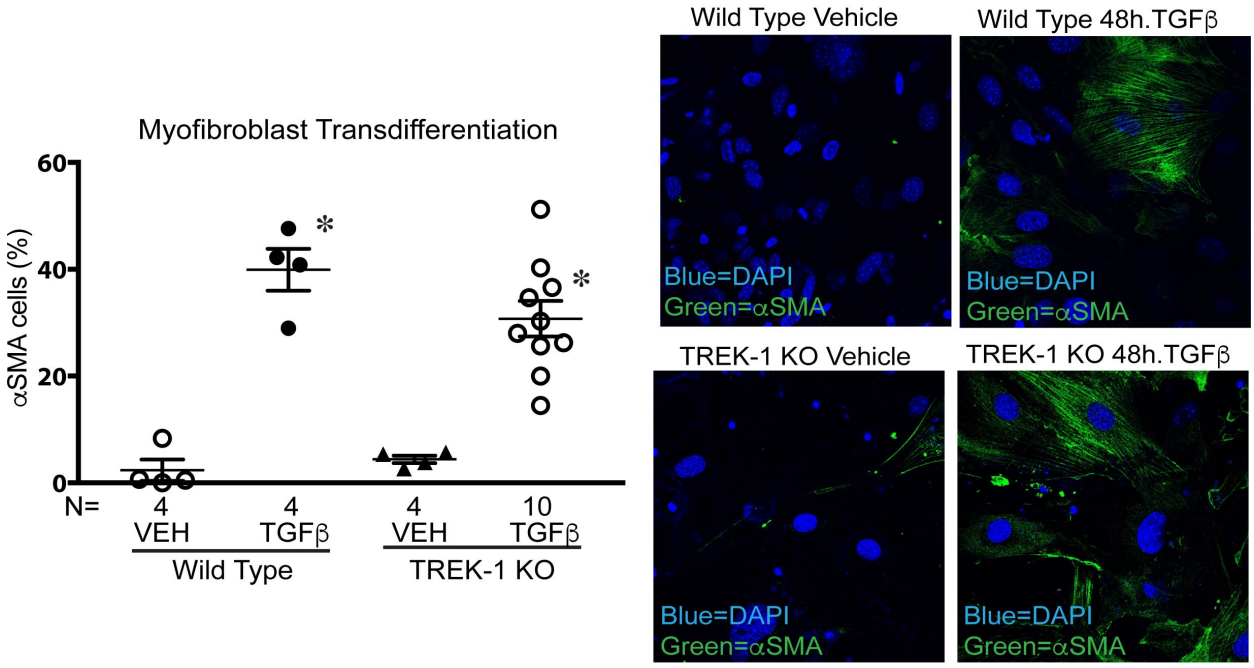


Fig. S6. Effect of TREK-1 on Myofibroblast transdifferentiation. Myofibroblast transdifferentiation in isolated wild type & global TREK-1 KO lung fibroblasts was quantified by assessing the % of isolated fibroblasts that express alpha smooth muscle actin (αSMA) stress fibers after 48-hour treatment with either Vehicle (VEH) or 10ng/ml transforming growth factor beta (TGFβ). Blue= DAPI and Green=αSMA fibers, Statistical comparisons made using a by Kruskal–Wallis test with Dunn's multiple comparisons test, *$p<0.05$ vs Wild Type Vehicle

Fig. S7

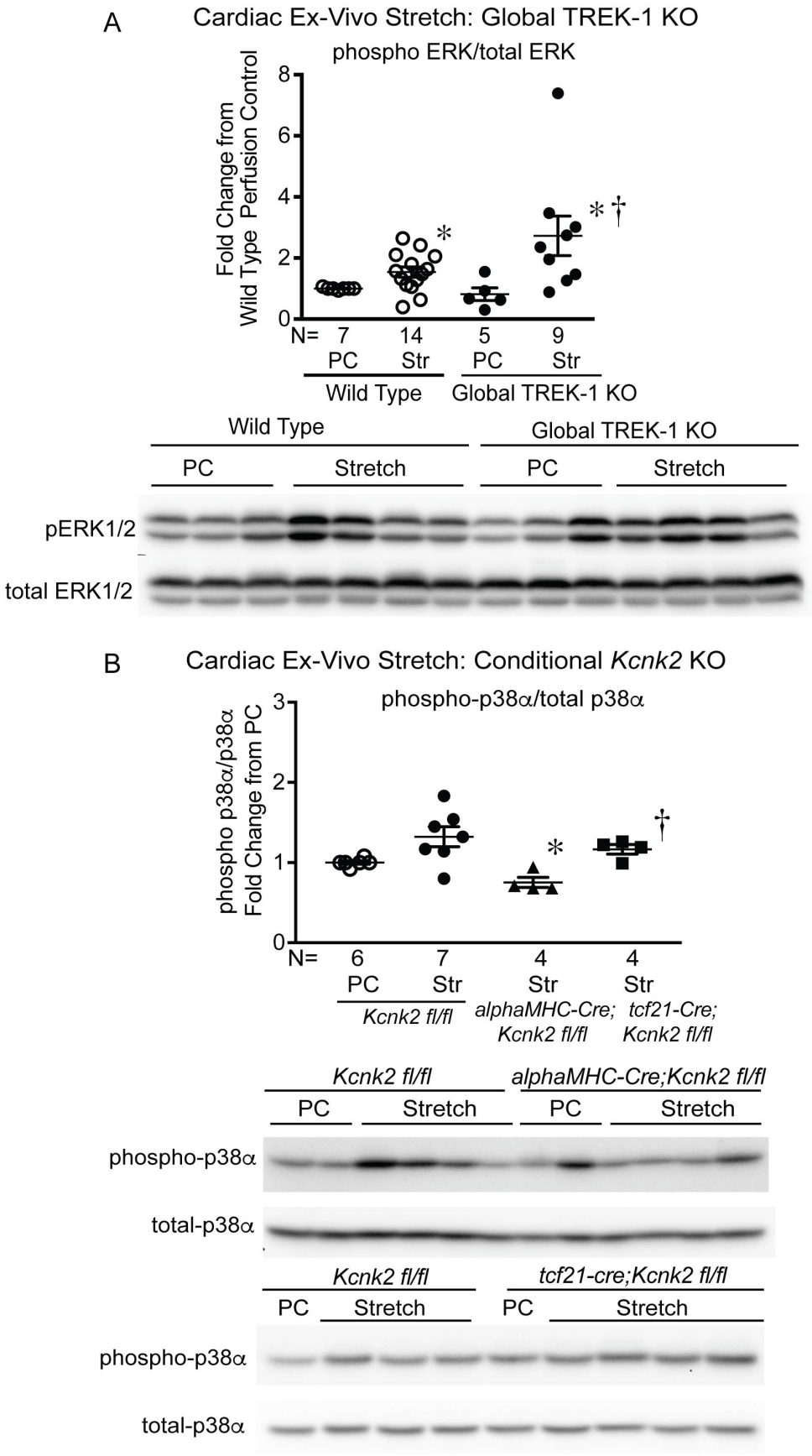

A
Cardiac Ex-Vivo Stretch: Global TREK-1 KO
phospho ERK/total ERK
Fold Change from Wild Type Perfusion Control
8
6
4
2
0
N= 7 14 5 9
PC Str PC Str
Wild Type
Global TREK-1 KO
Wild Type
Global TREK-1 KO
PC
Stretch
PC
Stretch
pERK1/2
total ERK1/2
B
Cardiac Ex-Vivo Stretch: Conditional Kcnk2 KO
phospho-p38α/total p38α
phospho p38α/p38α Fold Change from PC
3
2
1
0
N= 6 7 4 4
PC Str Str Str
Kcnk2 fl/fl
alphaMHC-Cre; Kcnk2 fl/fl
tcf21-Cre; Kcnk2 fl/fl
Kcnk2 fl/fl
alphaMHC-Cre;Kcnk2 fl/fl
PC
Stretch
PC
Stretch
phospho-p38α
total-p38α
Kcnk2 fl/fl
tcf21-cre;Kcnk2 fl/fl
PC
Stretch
PC
Stretch
phospho-p38α
total-p38α

Fig. S7. ERK and p38α phosphorylation in global and conditional TREK-1 KO cardiac *ex vivo* stretch. **(A)** Immunoblotting results for phosphorylated ERK 1/2 in Wild Type and Global TREK-1 KO hearts harvested after either a Perfusion control (PC) or *ex-vivo* stretch (Str). Representative array blots shown in the lower panel, Statistical comparisons to Wild Type PC, which has a theoretical mean of "1", were made with a Wilcoxon Signed Rank test. *p<0.05 vs. Wild type PC. Comparisons between all other groups excluding Wild Type PC were made using a by Kruskal–Wallis test with Dunn's multiple comparisons test. †p<0.05 vs Global TREK-1 KO PC. **(B)** Immunoblotting results for phosphorylated p38α in *Kcnk2 fl/fl*, *alphaMHC-cre*; *Kcnk2 fl/fl* and *tcf21-icre*; *Kcnk2 fl/fl* hearts harvested after either a Perfusion control (PC) or *ex-vivo* stretch (Str). Data reported as Fold Change from the PC samples within a gel; all PCs (n=6) for respective genotype shown together (*Kcnk2 fl/fl* n=3, *alphaMHC-cre*;*Kcnk2 fl/fl* n=2 and *tcf21-icre*;*Kcnk2 fl/fl* n=1). Representative blots shown in the lower panel. Statistical comparisons to *Kcnk2 fl/fl* PC, which has a theoretical mean of "1", were made with a Wilcoxon Signed Rank test and no significant differences from *Kcnk2 fl/fl* PC were noted. Comparisons between all other groups excluding *Kcnk2 fl/fl* PC were made using a by Kruskal–Wallis test with Dunn's multiple comparisons test. †p<0.05 vs. *alphaMHC-cre*; *Kcnk2 fl/fl* and *p<0.05 vs *Kcnk2 fl/fl* Str

Fig. S8

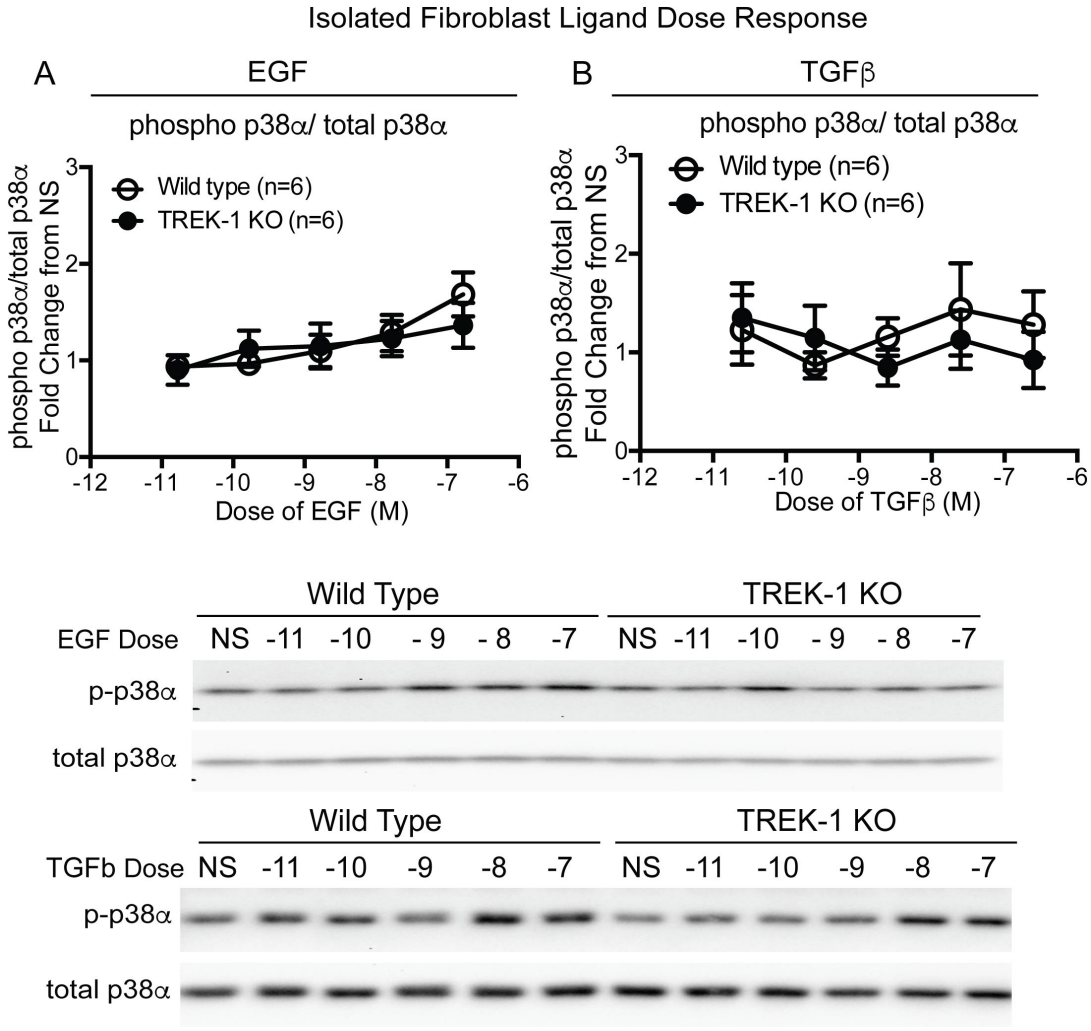


Fig. S8. p38α phosphorylation response to EGF and TGFβ. (A) Average p38α phosphorylation/total p38α in response to 20 minutes of treatment with epidermal growth factor (EGF) and **(B)** 40 minutes of treatment with Transforming Growth Factor beta (TGFβ) in isolated wild type and global TREK-1 KO lung fibroblasts (n=6 separate experiments). Doses of either EGF or TGFβ were tested from over a range of concentrations for 10^{-11}M to 10^{-7}M. Data is expressed as fold change from a non-stimulated (NS) condition. Data compared by 2-way ANOVA with Bonferroni's multiple comparisons test. No significant change in p38α phosphorylation was seen after either EGF or TGFβ stimulation

Fig. S9

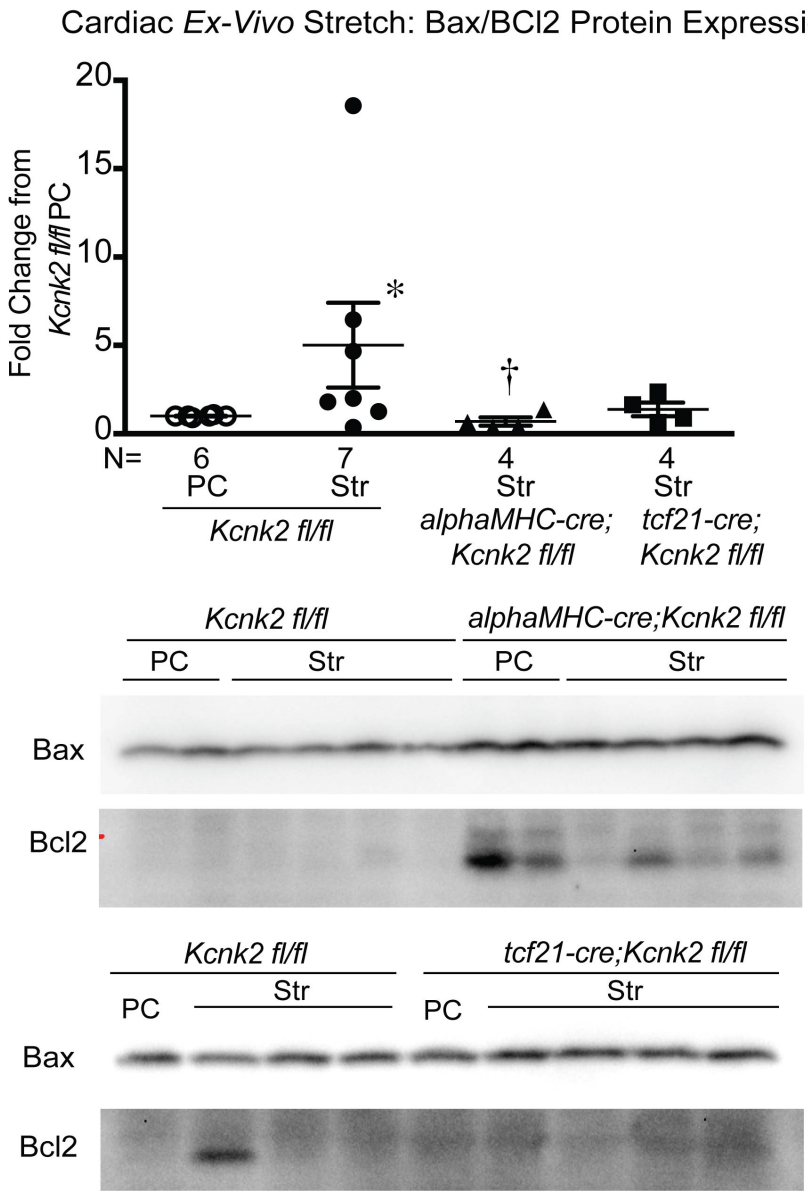


Fig. S9- Bax/BCl2 protein expression in conditional myocyte and fibroblast TREK-1 KO before and after Ex-Vivo cardiac Stretch. Immunoblotting results for proapoptotic Bax and antiapoptotic Bcl2 (Data represented as Fold Change in Bax/BCl2) in *Kcnk2 fl/fl*, *alphaMHC-cre*;*Kcnk2 fl/fl* and *tcf21-iCre*;*Kcnk2 fl/fl* hearts harvested after either a Perfusion control (PC) or ex-vivo stretch (Str). Data reported as Fold Change from the PC samples within a gel; all PCs (n=6) for respective genotype shown together (*Kcnk2 fl/fl* n=3, *alphaMHC-cre* ;*Kcnk2 fl/fl* n=2 and *tcf21-icre*;*Kcnk2 fl/fl* n=1). Representative

array blots shown in the lower panel. Statistical comparisons to *Kcnk2 fl/fl* PC, which has a theoretical mean of “1”, were made with a Wilcoxon Signed Rank test. *p<0.05 vs. Wild type PC. Comparisons between all other groups excluding *Kcnk2 fl/fl* PC were made using a by Kruskal–Wallis test with Dunn’s multiple comparisons test. †p<0.05 vs *Kcnk2 fl/fl* Str.

Fig S10

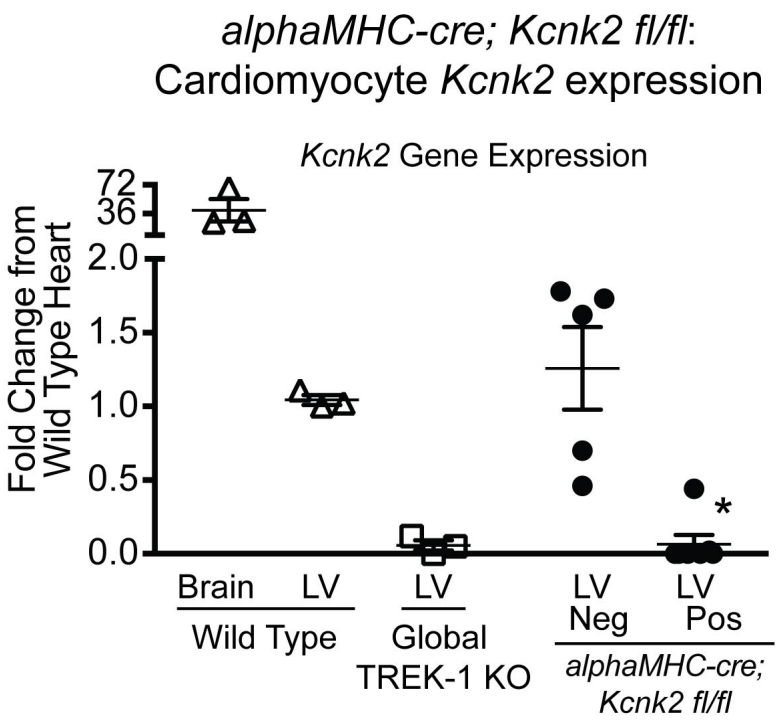


Fig. S10. Confirmation of TREK-1 Conditional Knockout. TREK-1 (*Kcnk2*) gene expression in isolated cardiac myocytes obtained from mice bearing the conditional TREK-1 KO allele alone (*Kcnk2 fl/fl*) or in combination with Cre recombinase under the control of an alpha myosin heavy chain promoter (*alphaMHC-cre*). Data is expressed as a fold change from wild type heart. Wild type brain and global TREK KO hearts were used as positive and negative controls, respectively. Statistical comparisons to Wild Type Heart (LV), which has theoretical mean of "1", were made with a one sample two-tailed t-test. *$p<0.05$ vs. *Kcnk2 fl/fl* (Cre negative). Comparisons between all other groups excluding Wild Type Heart were made using a by Kruskal–Wallis test with Dunn's multiple comparisons test, which were not significantly different.

Table S1 **Baseline Left Ventricular Hemodynamic Parameters after 2 week TAC**

	Wild Type		Global TREK-1 KO	
	Sham	2 week TAC	Sham	2 week TAC
N=	19	15	16	19
Heart Rate (BPM)	398 ± 17	401 ± 14	414 ± 12	434 ± 17
LVESV (μl)	16.24 ± 2.46	22.49 ± 2.75*	9.30 ± 2.00	10.13 ± 1.02†
LVEDV (μl)	33.04 ± 2.44	35.12 ± 2.14	24.46 ± 2.03†	29.46 ± 2.26
LVESP (mm Hg)	111.20 ± 5.08	143.65 ± 12.67*	110.73 ± 5.26	147.84 ± 6.74*
LVEDP (mm Hg)	6.45 ± 0.81	13.89 ± 3.06*	5.44 ± 1.06	8.64 ± 1.62†
Stroke Volume (μl)	20.93 ± 1.40	17.42 ± 1.67	20.73 ± 0.89	22.78 ± 1.90
Ejection Fraction (%)	60.62 ± 3.91	47.17 ± 4.76*	77.21 ± 4.27†	69.85 ± 2.63†
Cardiac Output (μl/min)	8360.99 ± 666.33	7028.19 ± 764.32	8565.73 ± 446.40	10097.68 ± 1109.86
Stroke Work (mm Hg*μl)	1911.26 ± 178.68	1861.67 ± 218.89	1992.88 ± 135.83	3063.89 ± 342.16*†
dP/dt_{max} (mm Hg/seconds)	8556.89 ± 649.37	7912.93 ± 550.49	9582.63 ± 616.23	10209.79 ± 659.94
dP/dt_{min} (mm Hg/seconds)	-7870.53 ± 613.56	-6928.60 ± 507.50	-8723.13 ± 770.77	-10240.89 ± 638.92†
dV/dt_{max} (μl /seconds)	738.21 ± 58.02	746.27 ± 77.03	678.00 ± 30.10	877.84 ± 118.65
Tau [Weiss] (ms)	8.19 ± 0.42	9.07 ± 0.44	7.46 ± 0.33	7.13 ± 0.52†
Tau [Glantz] (ms)	12.73 ± 0.65	17.95 ± 2.82*	11.97 ± 0.52	11.69 ± 0.75†
Tau [Log] (ms)	6.43 ± 0.27	7.75 ± 0.61*	6.14 ± 0.23	5.99 ± 0.36†

Table S1. Basal Hemodynamic Parameters after 2-week TAC. Pressure-volume loop analysis data obtained from basal loops from Wild type and TREK KO mice undergoing 2-week TAC procedure. Statistical comparisons performed using a one-way ANOVA with Neumann Keuls test for multiple comparisons. *$p<0.01$ vs. Sham of same genotype; †$p<0.05$ vs. Wild type TAC.

Error indicates standard error of the mean. Statistical comparisons performed using a one-way ANOVA with Neumann Keuls test for multiple comparisons.

Table S2

Cardiac Chamber Weights in 2 weeks and 16 weeks after TAC

		Wild Type			Global TREK-1 KO		
		Sham	2 week TAC	16 week TAC	Sham	2 week TAC	16 week TAC
	N=	12	22	12	13	36	9
Body weight (g)		25.37 ± 1.41	23.97 ± 1.07	26.25 ± 1.57	21.82 ± 1.28	24.40 ± 0.86	27.83 ± 1.21
Heart weight (mg)		149.82 ± 3.99	191.00 ± 8.65	186.57 ± 29.16	131.41 ± 7.06	185.34 ± 7.04*	247.40 ± 19.10*†
LV weight (mg)		87.48 ± 4.32	128.60 ± 5.49*	125.99 ± 17.85*	85.41 ± 4.72	125.53 ± 4.50*	165.19 ± 11.02*†
RV weight (mg)		55.05 ± 5.41	51.38 ± 3.43	45.68 ± 6.55	38.77 ± 2.90	49.02 ± 2.52	68.39 ± 6.49*†
L. Atria weight (mg)		3.99 ± 0.30	7.14 ± 0.56	7.53 ± 2.47	3.92 ± 0.35	6.52 ± 0.40	6.56 ± 0.32
R. Atria weight (mg)		3.29 ± 0.38	3.87 ± 0.37	7.36 ± 3.14	3.31 ± 0.26	4.28 ± 0.24	4.98 ± 0.51
LV/Body weight (mg/g)		3.47 ± 0.08	5.45 ± 0.20*	4.87 ± 0.60*	3.93 ± 0.06	5.30 ± 0.23*	6.04 ± 0.54*
LV/Tibia length (mg/mm)		4.99 ± 0.21	7.41 ± 0.31*	7.06 ± 0.99*	4.94 ± 0.26	7.22 ± 0.27*	9.16 ± 0.58*†

Table S2. Heart weights after TAC. Heart weight and body weight measurements on mice undergoing a TAC or Sham procedure. Data for Wild type and Global TREK-1 KO genotype after Sham, 2-week TAC or 16-week TAC listed. Statistical comparisons performed using a one-way ANOVA with Neumann Keuls test for multiple comparisons. *$p<0.01$ vs. Sham of same genotype; †$p<0.05$ vs. Wild type 16-week TAC. Error indicates standard error of the mean. Statistical comparisons performed using a one-way ANOVA with Neumann Keuls test for multiple comparisons.

Table S3

Load Independent Hemodynamic Parameters after 2 week TAC.

	Wild Type		Global TREK-1 KO	
	Sham	2 week TAC	Sham	2 week TAC
ESPVR	4.88 ± 0.43	7.66 ± 1.28	5.97 ± 0.55	11.11 ± 2.43*
E_{max}	11.16 ± 1.30	15.30 ± 3.07	12.88 ± 1.67	30.67 ± 5.34*†
EDPVR	0.32 ± 0.04	0.62 ± 0.10*	0.27 ± 0.03	0.37 ± 0.03†
PRSW	37.94 ± 4.41	54.56 ± 12.85	53.68 ± 4.58	79.10 ± 10.02*
dP/dt vs. EDV	154.58 ± 45.31	180.13 ± 37.43	240.53 ± 28.95	236.44 ± 38.29

Table S3: Load Independent Hemodynamic Parameters after 2-week TAC. Hemodynamic parameters obtained after aortic and inferior vena cava constriction for each animal, to assess effect of changing afterload and preload, respectively. The following are the number of Wild Type (WT) Sham, Wild Type 2-week TAC, Global TREK-1 KO Sham and Global TREK-1 KO 2-week TAC are listed for each parameter: ESPVR and Emax (n=9,7,9,5); EDPVR, PRSW and dP/dt/EDV (n=11, 6, 11, 10). Statistical comparisons performed using a one-way ANOVA with Neumann Keuls test for multiple comparisons. *$p<0.01$ vs. Sham of same genotype; †$p<0.05$ vs. Wild type 2 week TAC. Error indicates standard error of the mean.

Table S4

Tissue Specific TREK-1 KO TAC Serial Echocardiography

Base Sham	LVEDD (mm)	LVESD (mm)	SWT (mm)	PWT (mm)	HR (BPM)	LV mass (mg)	FS (%)	mVcFc (circ/s)
Kcnk2 fl/fl Sham (n=3)	3.52 ± 0.22	2.04 ± 0.21	0.82 ± 0.05	0.80 ± 0.03	634 ± 43	77.5 ± 8.5	42.1 ± 3.8	3.3 ± 0.3
aMHC-Cre;Kcnk2 fl/fl Sham (n=3)	3.35 ± 0.24	1.81 ± 0.23	0.89 ± 0.03	0.90 ± 0.09	684 ± 5	83.7 ± 12.0	46.4 ± 2.9	3.7 ± 0.1
Base TAC								
aMHC-Cre TAC (n=4)	3.13 ± 0.06	1.49 ± 0.09	0.85 ± 0.04	0.86 ± 0.06	656 ± 7	71.5 ± 4.4	52.4 ± 2.7	4.1 ± 0.3
tcf21-Cre TAC (n=8)	3.10 ± 0.10	1.62 ± 0.06	0.93 ± 0.03	0.99 ± 0.03	613 ± 40	83.6 ± 6.2	47.9 ± 0.8	3.5 ± 0.1
Kcnk2 fl/fl TAC (n=24)	3.12 ± 0.07	1.57 ± 0.06	0.89 ± 0.02	0.87 ± 0.02	634 ± 17	73.6 ± 3.2	50.1 ± 1.0	3.9 ± 0.1
aMHC-Cre;Kcnk2 fl/fl TAC (n=17)	3.24 ± 0.05	1.67 ± 0.06	0.93 ± 0.02	0.89 ± 0.02	657 ± 24	81.7 ± 4.0	48.6 ± 1.2	4.0 ± 0.1
tcf21-Cre;Kcnk2 fl/fl TAC (n=12)	3.13 ± 0.07	1.65 ± 0.07	0.86 ± 0.03	0.88 ± 0.02	629 ± 15	72.0 ± 3.1	47.7 ± 1.3	3.4 ± 0.2†

2 week Sham	LVEDD (mm)	LVESD (mm)	SWT (mm)	PWT (mm)	HR (BPM)	LV mass (mg)	FS (%)	mVcFc (circ/s)
Kcnk2 fl/fl Sham (n=3)	3.43 ± 0.29	2.11 ± 0.10	0.82 ± 0.04	0.81 ± 0.07*†	680 ± 44	74.6 ± 4.7	37.7 ± 3.6	2.9 ± 0.3
aMHC-Cre;Kcnk2 fl/fl Sham (n=3)	3.48 ± 0.12	2.00 ± 0.16	0.84 ± 0.02	0.92 ± 0.04	709 ± 2	85.9 ± 8.3	42.8 ± 2.6	3.3 ± 0.2
2 week TAC								
aMHC-Cre TAC (n=4)	3.16 ± 0.13	2.15 ± 0.21	1.18 ± 0.10	1.19 ± 0.01	708 ± 23	115.0 ± 6.8	32.1 ± 4.9	2.6 ± 0.4
tcf21-Cre TAC (n=5)	2.91 ± 0.33	1.88 ± 0.42	1.14 ± 0.04	1.25 ± 0.07	661 ± 16	106.0 ± 12.2	37.9 ± 5.6	2.9 ± 0.5
Kcnk2 fl/fl TAC (n=20)	3.48 ± 0.13	2.40 ± 0.19	1.08 ± 0.03	1.07 ± 0.03	656 ± 19	117.0 ± 6.9	33.0 ± 2.9	2.5 ± 0.3
aMHC-Cre;Kcnk2 fl/fl TAC (n=13)	3.48 ± 0.14	2.52 ± 0.19	1.09 ± 0.04	1.14 ± 0.03	604 ± 33	123.0 ± 7.7	28.4 ± 2.8	2.3 ± 0.3
tcf21-Cre;Kcnk2 fl/fl TAC (n=9)	3.16 ± 0.11	1.90 ± 0.12	1.07 ± 0.06	1.13 ± 0.05	649 ± 14	103.0 ± 5.2	40.2 ± 1.9	2.9 ± 0.2

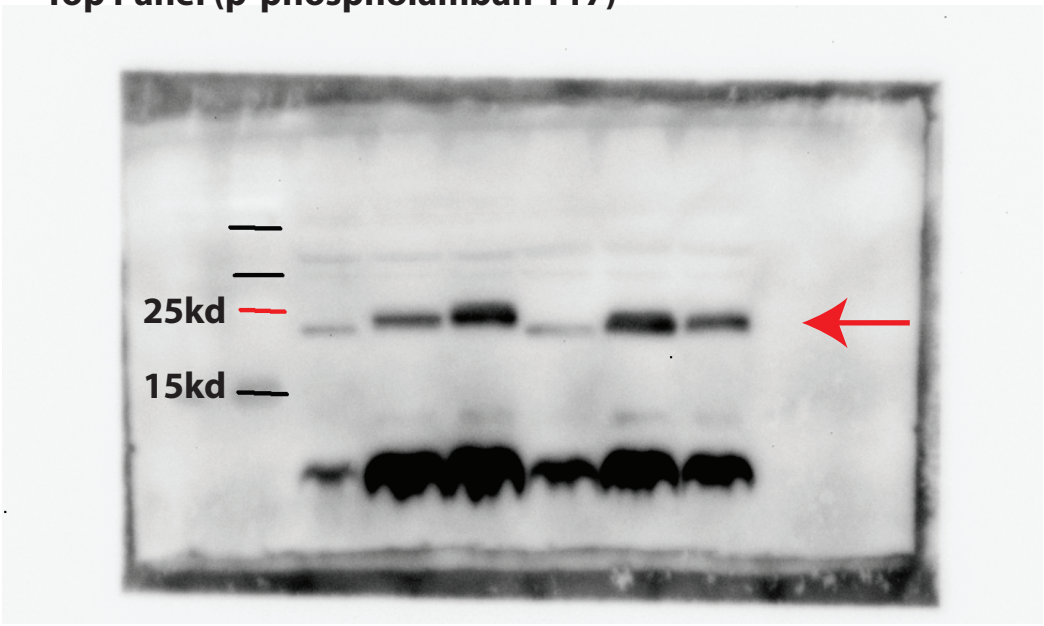
4 week Sham	LVEDD (mm)	LVESD (mm)	SWT (mm)	PWT (mm)	HR (BPM)	LV mass (mg)	FS (%)	mVcFc (circ/s)
Kcnk2 fl/fl Sham (n=3)	3.54 ± 0.09	2.07 ± 0.10	0.81 ± 0.06	0.80 ± 0.02*	629 ± 83	78.2 ± 7.0	41.6 ± 2.0	3.3 ± 0.3
aMHC-Cre;Kcnk2 fl/fl Sham (n=3)	3.27 ± 0.32	1.73 ± 0.33	0.91 ± 0.02	0.90 ± 0.05	701 ± 31	81.4 ± 12.0	48.1 ± 5.1	3.8 ± 0.4
4 week TAC								
aMHC-Cre TAC (n=4)	3.61 ± 0.31	2.64 ± 0.44	0.96 ± 0.10	1.07 ± 0.10	643 ± 36	111.0 ± 7.0	27.9 ± 6.9	2.3 ± 0.6
tcf21-Cre TAC (n=5)	2.95 ± 0.22	1.82 ± 0.25	1.17 ± 0.08	1.25 ± 0.05	661 ± 7	111.0 ± 16.8	39.4 ± 4.0	2.9 ± 0.3
Kcnk2 fl/fl TAC (n=18)	3.72 ± 0.18	2.66 ± 0.26	1.07 ± 0.02	1.07 ± 0.03	632 ± 17	130.0 ± 10.5	30.9 ± 3.6	2.3 ± 0.3
aMHC-Cre;Kcnk2 fl/fl TAC (n=11)	3.98 ± 0.18	3.08 ± 0.26	1.07 ± 0.04	1.02 ± 0.04	605 ± 27	137.0 ± 9.9	23.9 ± 3.5	1.8 ± 0.3
tcf21-Cre;Kcnk2 fl/fl TAC (n=9)	3.08 ± 0.14†	1.81 ± 0.16†	1.10 ± 0.05	1.13 ± 0.04	651 ± 15	103.0 ± 9.0	41.8 ± 2.8†	3.1 ± 0.2

8 week Sham	LVEDD (mm)	LVESD (mm)	SWT (mm)	PWT (mm)	HR (BPM)	LV mass (mg)	FS (%)	mVcFc (circ/s)
Kcnk2 fl/fl Sham (n=3)	3.09 ± 0.36	1.80 ± 0.22	0.86 ± 0.06*	0.88 ± 0.04*	660 ± 32	72.8 ± 16.1	41.8 ± 1.2	3.3 ± 0.2
aMHC-Cre;Kcnk2 fl/fl Sham (n=3)	3.29 ± 0.15	1.81 ± 0.19	0.91 ± 0.07	0.96 ± 0.05	695 ± 13	86.7 ± 11.2	45.3 ± 3.4	3.7 ± 0.1
8 week TAC								
aMHC-Cre TAC (n=4)	3.95 ± 0.49	3.13 ± 0.68	1.05 ± 0.04	1.11 ± 0.07	575 ± 43	141.0 ± 19.5	23.7 ± 8.0	1.9 ± 0.7
tcf21-Cre TAC (n=5)	3.23 ± 0.34	2.05 ± 0.44	1.19 ± 0.07	1.26 ± 0.04	710 ± 16	128.0 ± 18.5	39.0 ± 6.3	3.2 ± 0.6
Kcnk2 fl/fl TAC (n=17)	3.72 ± 0.26	2.70 ± 0.35	1.14 ± 0.04	1.17 ± 0.04	602 ± 29	146.0 ± 14.7	31.7 ± 4.2	2.5 ± 0.3
MHC-Cre;Kcnk2 fl/fl TAC (n=9)	4.41 ± 0.24	3.62 ± 0.36	0.94 ± 0.04*	0.96 ± 0.03*	583 ± 38	143.0 ± 11.9	20.0 ± 3.8	1.6 ± 0.3
tcf21-Cre;Kcnk2 fl/fl TAC (n=9)	2.88 ± 0.11†	1.60 ± 0.14†	1.20 ± 0.05†	1.21 ± 0.05†	676 ± 14	106.0 ± 8.9	44.8 ± 3.0†	3.2 ± 0.2

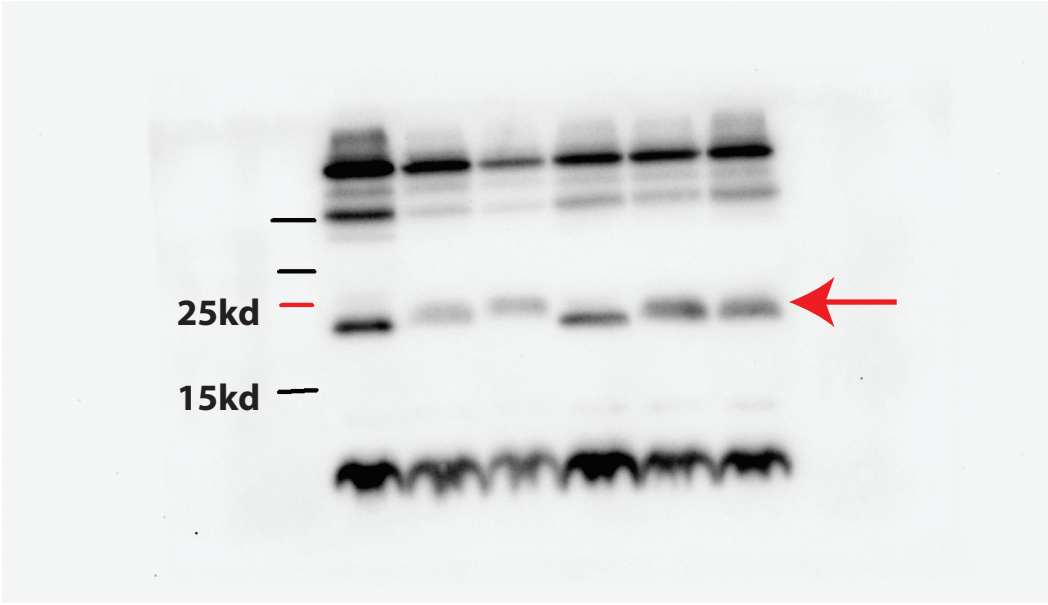
Table S4: Tissue Specific TREK-1 KO Echocardiography data. Echocardiography data from all mice tested in Tissue Specific TREK-1 KO. The number of mice shown reflects the number of mice available at each time point. LVEDD= LV End Diastolic Dimension; LVESD= LV End Systolic Dimension; SWT= Septal Wall Thickness; PWT= Posterior Wall Thickness; AET=Aortic Ejection Time; HR= Heart Rate; BPM=Beats Per Minute; LVEDV= LV End Diastolic Volume; LVESV= LV End Systolic Volume, FS=Fractional Shortening, mVcFc = mean velocity of circumferential shortening corrected for heart rate calculated as (mVcFc = Fractional Shortening/(Aortic Ejection Time/(√60/Heart Rate)) ; Statistical comparisons performed using a one-way ANOVA with Bonferroni's multiple comparisons test. *p<0.05 vs *KCNK fl/fl* TAC, †p<0.05 vs *alphaMHC-cre; KCNK fl/fl* TAC. Error indicates standard error of the mean.

Figure 2I

Top Panel (p-phospholamban-T17)



Middle Panel (total phospholamban)



Bottom Panel (GAPDH)

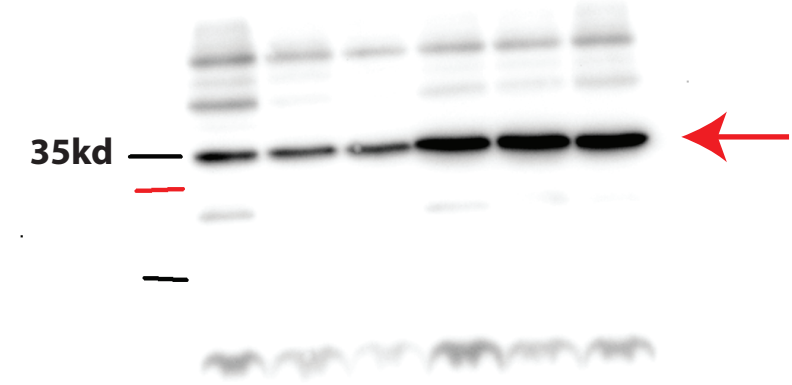
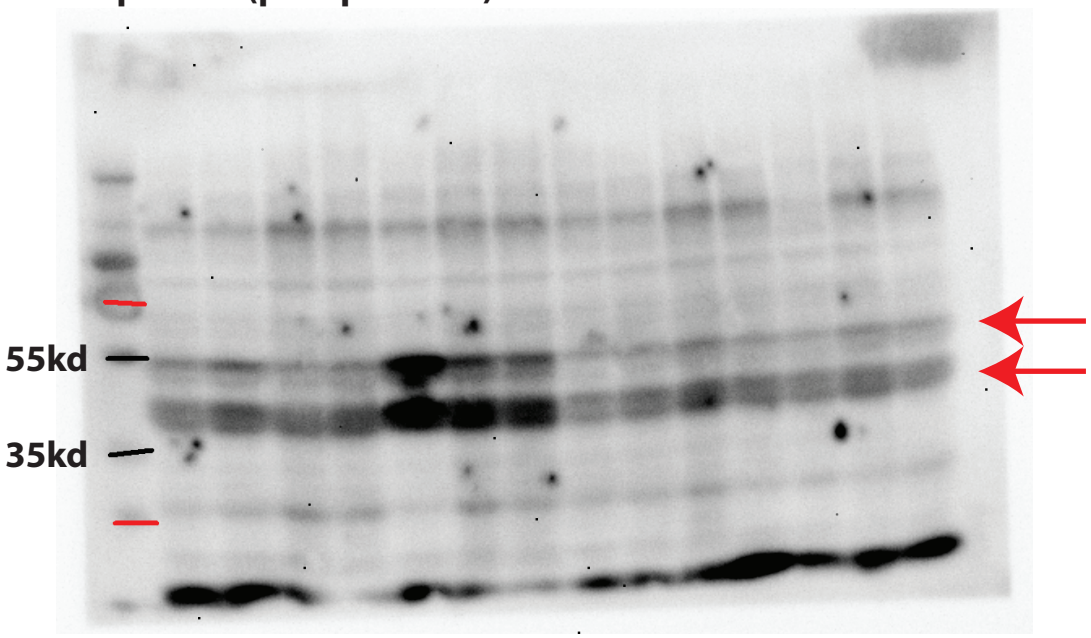


Figure 6B

Top Panel (phospho-JNK)



Second Panel (total JNK)

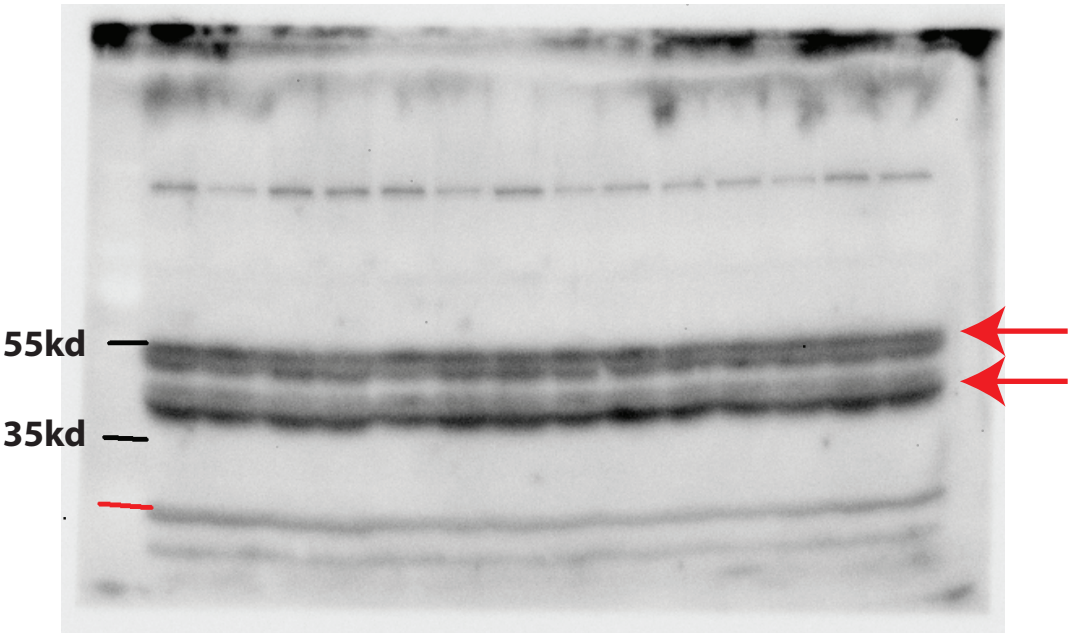


Figure 6B

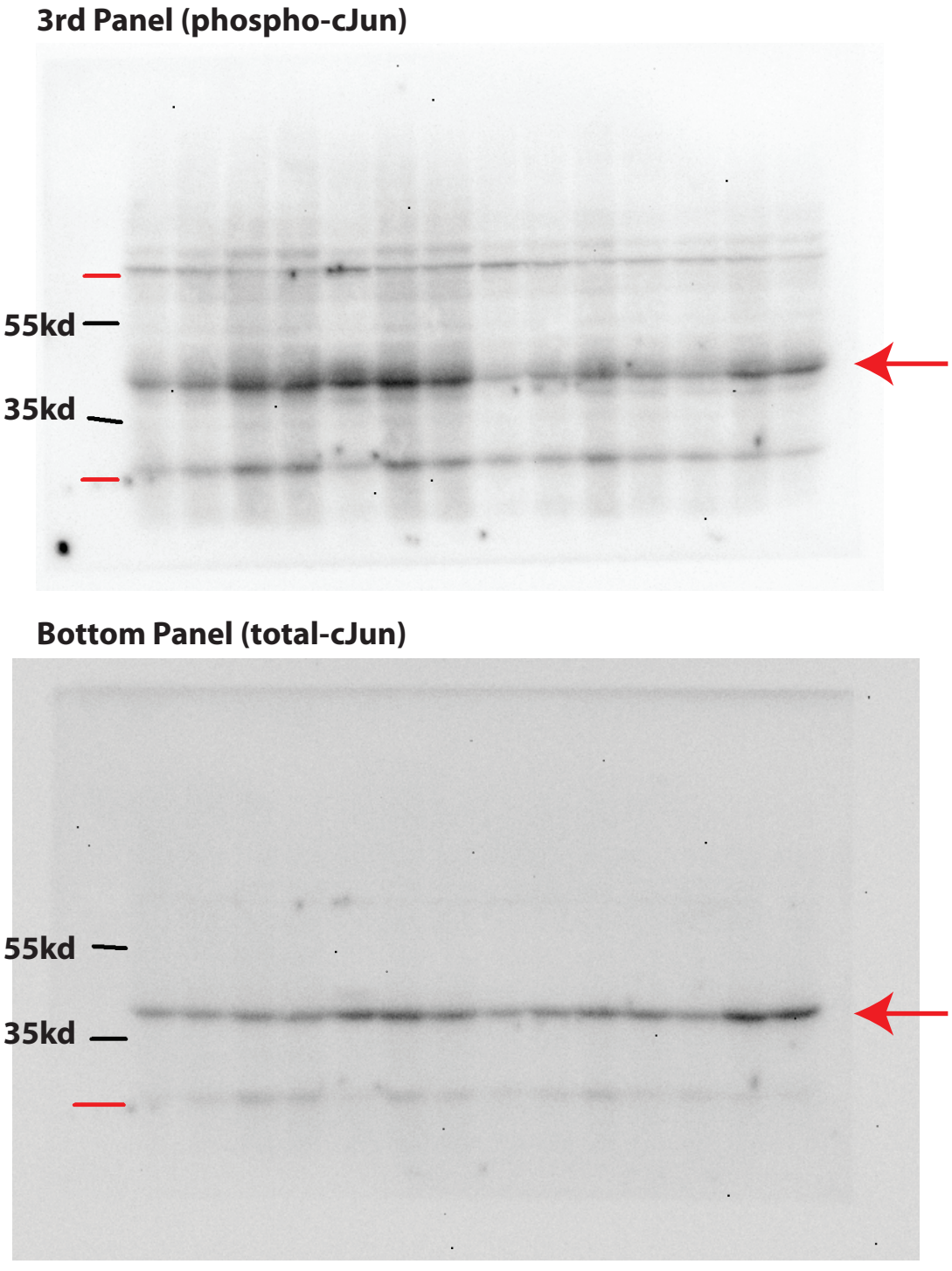
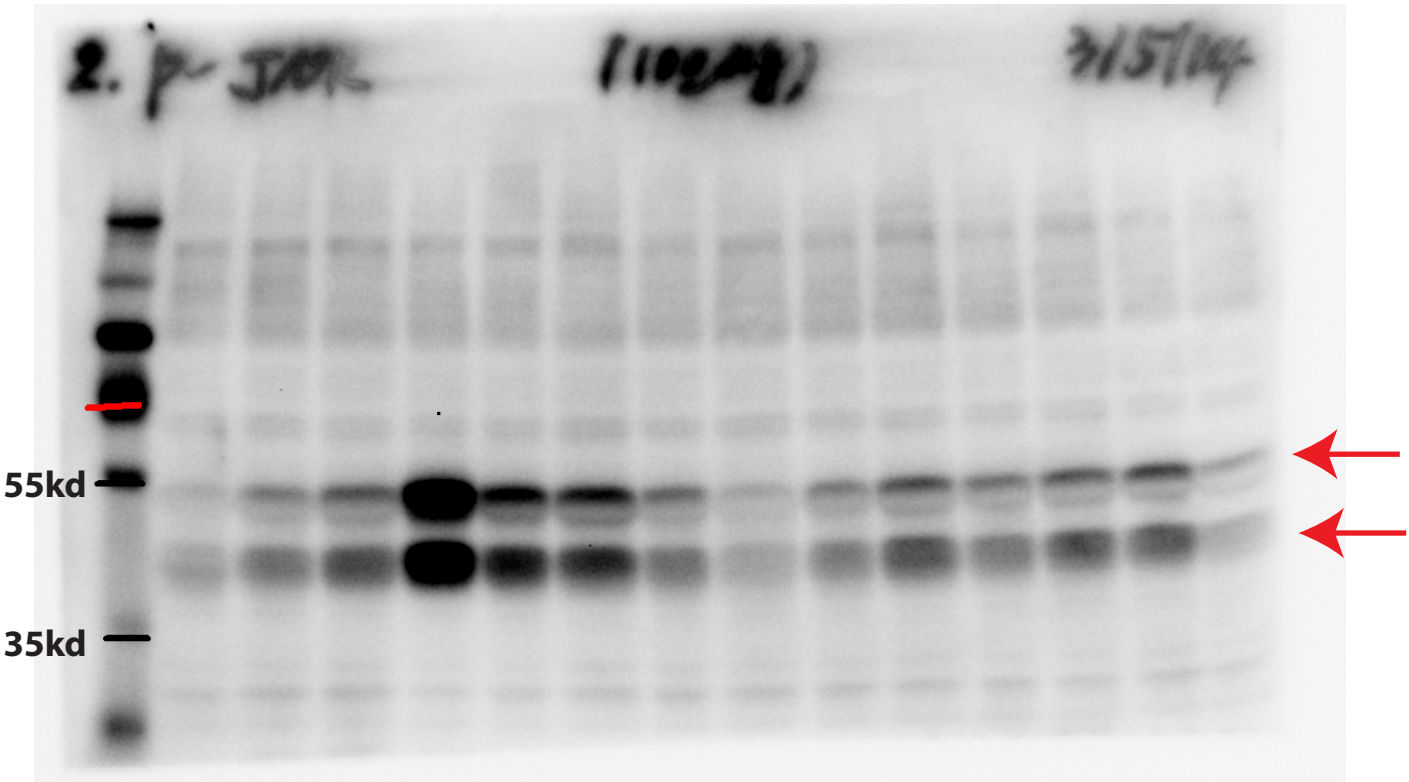

3rd Panel (phospho-cJun)
55kd
35kd
Bottom Panel (total-cJun)
55kd
35kd

Figure 6C

Top Panel (phospho-JNK)



Bottom Panel (total-JNK)

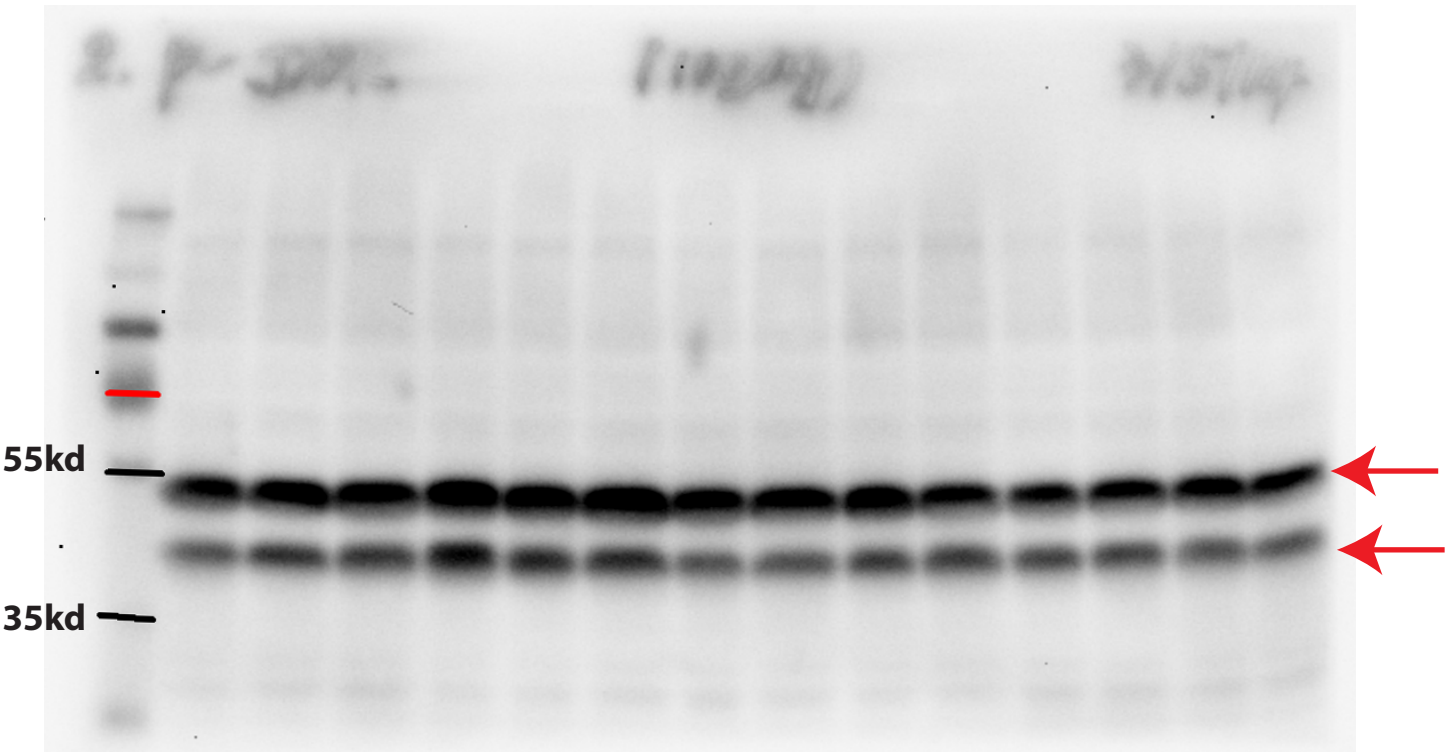
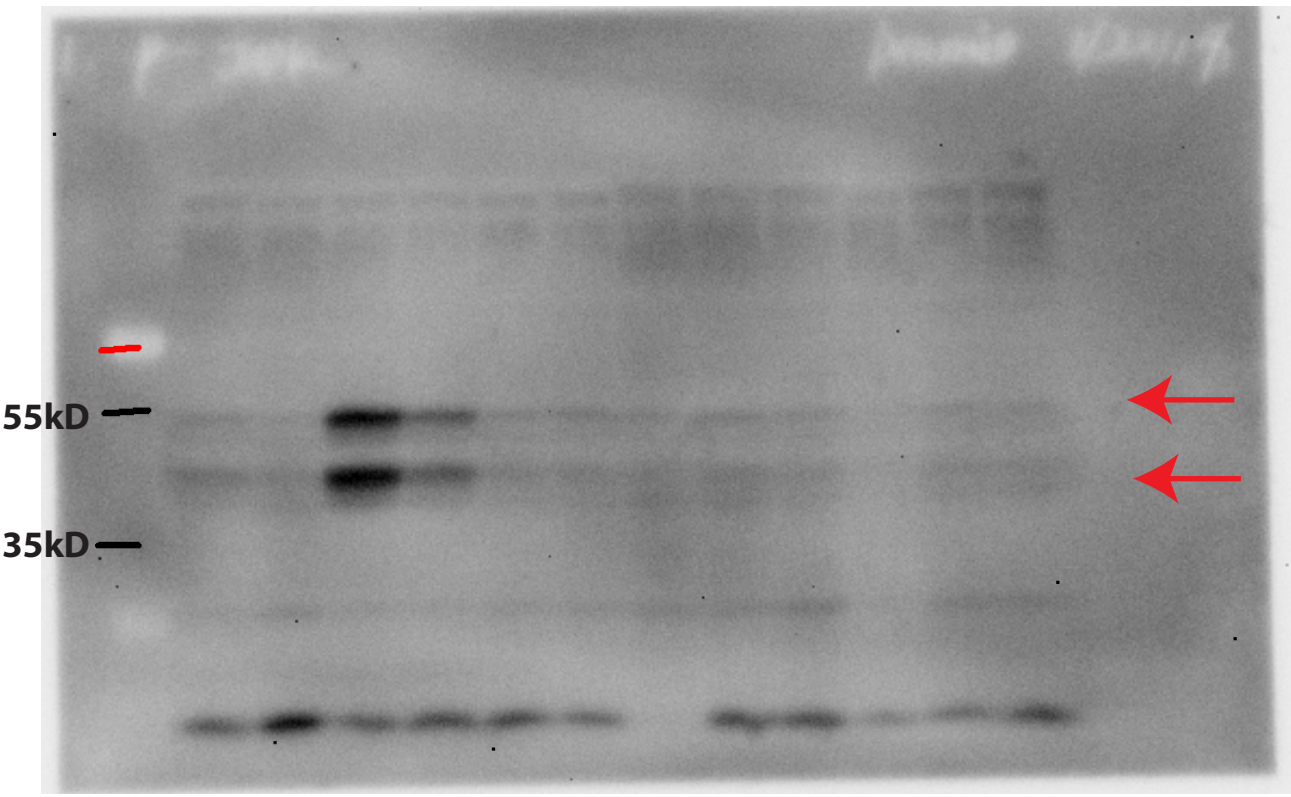


Figure 6D

1st panel (pJNK)



2nd panel (tJNK)

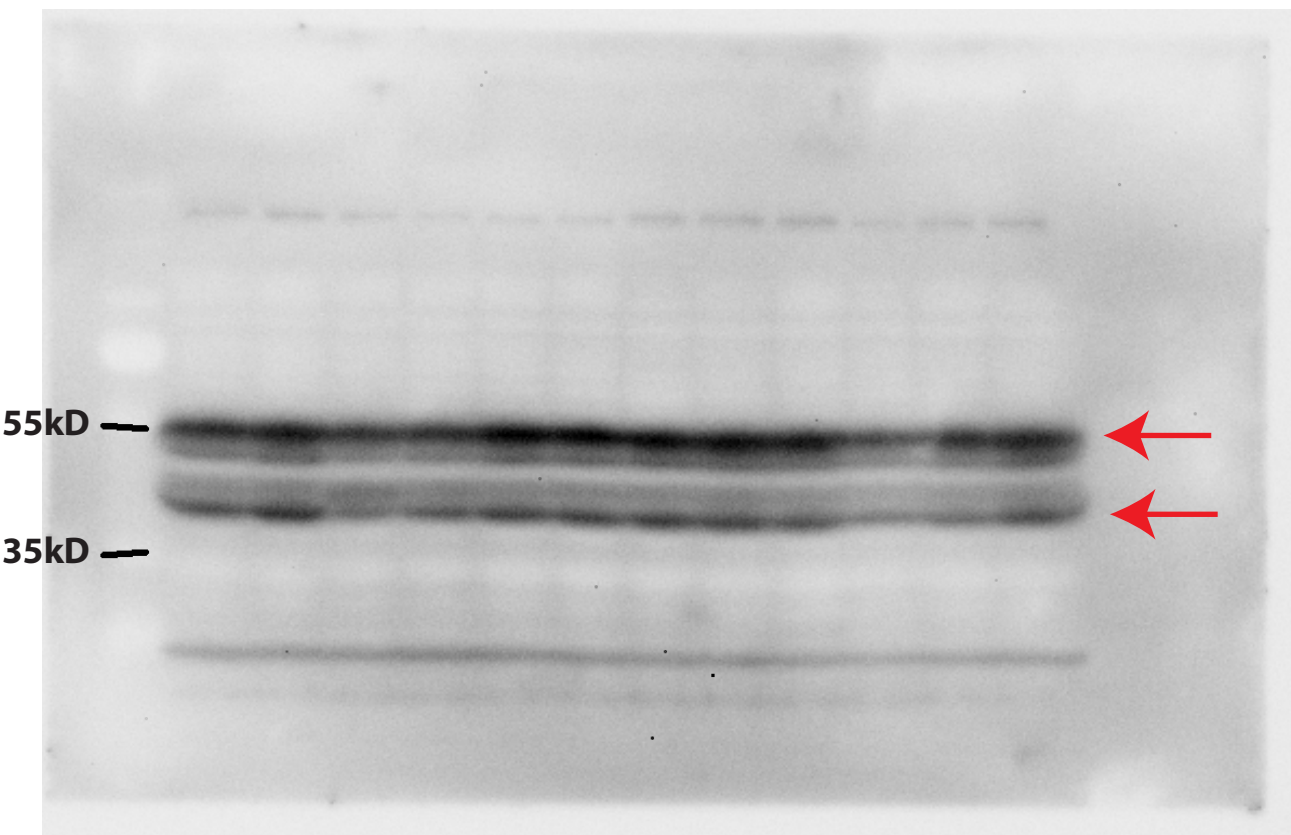
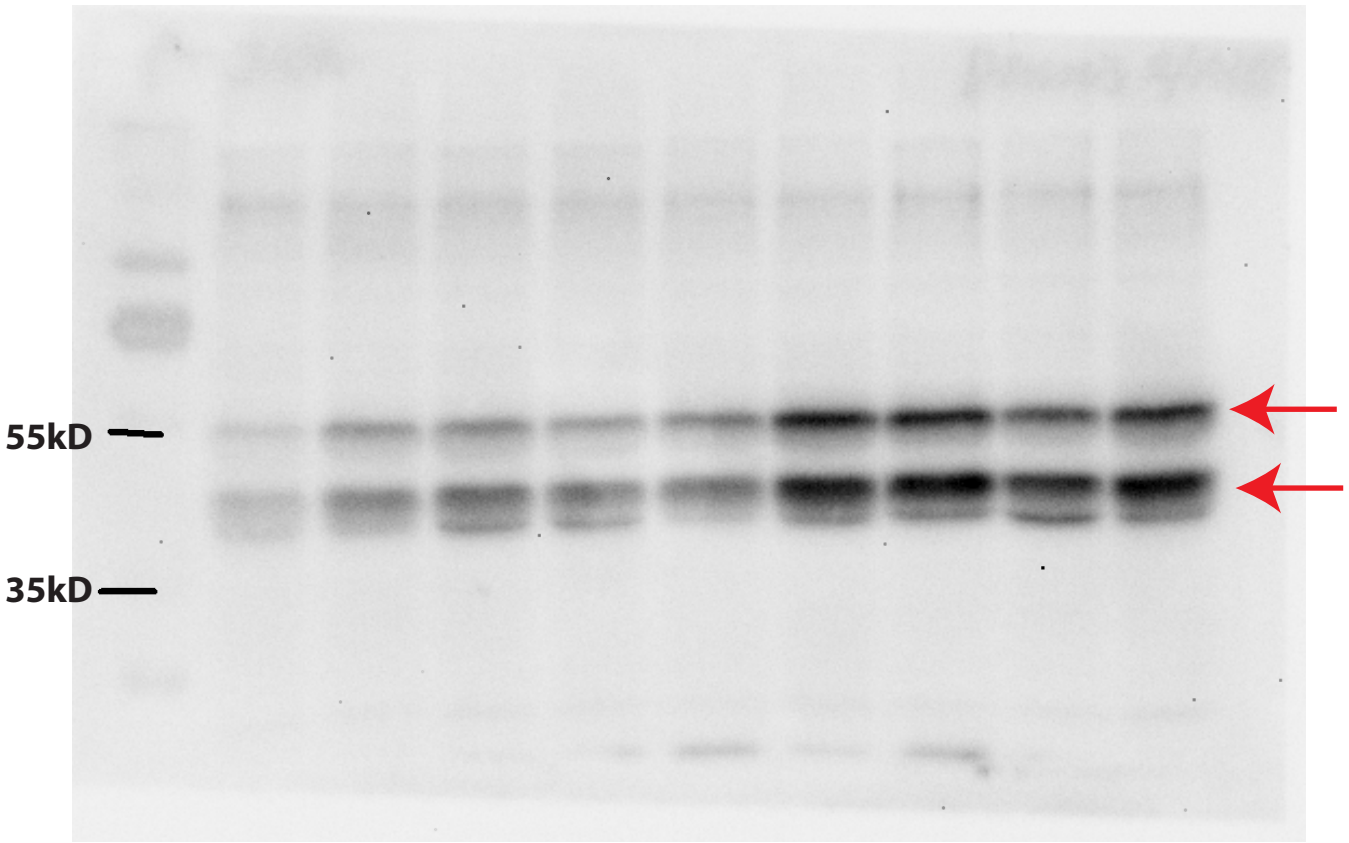


Figure 6D

3rd panel (pJNK)



4th panel (tJNK)

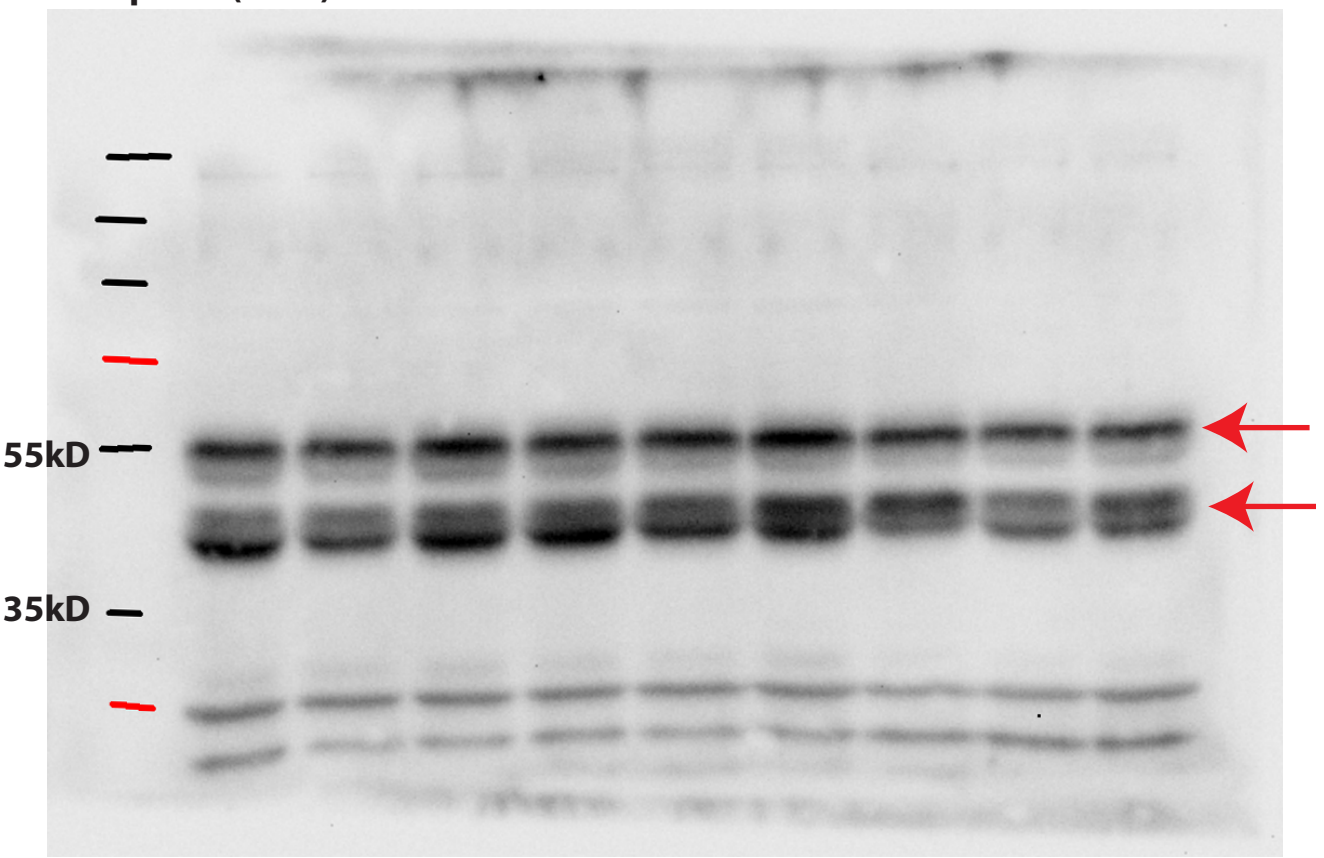
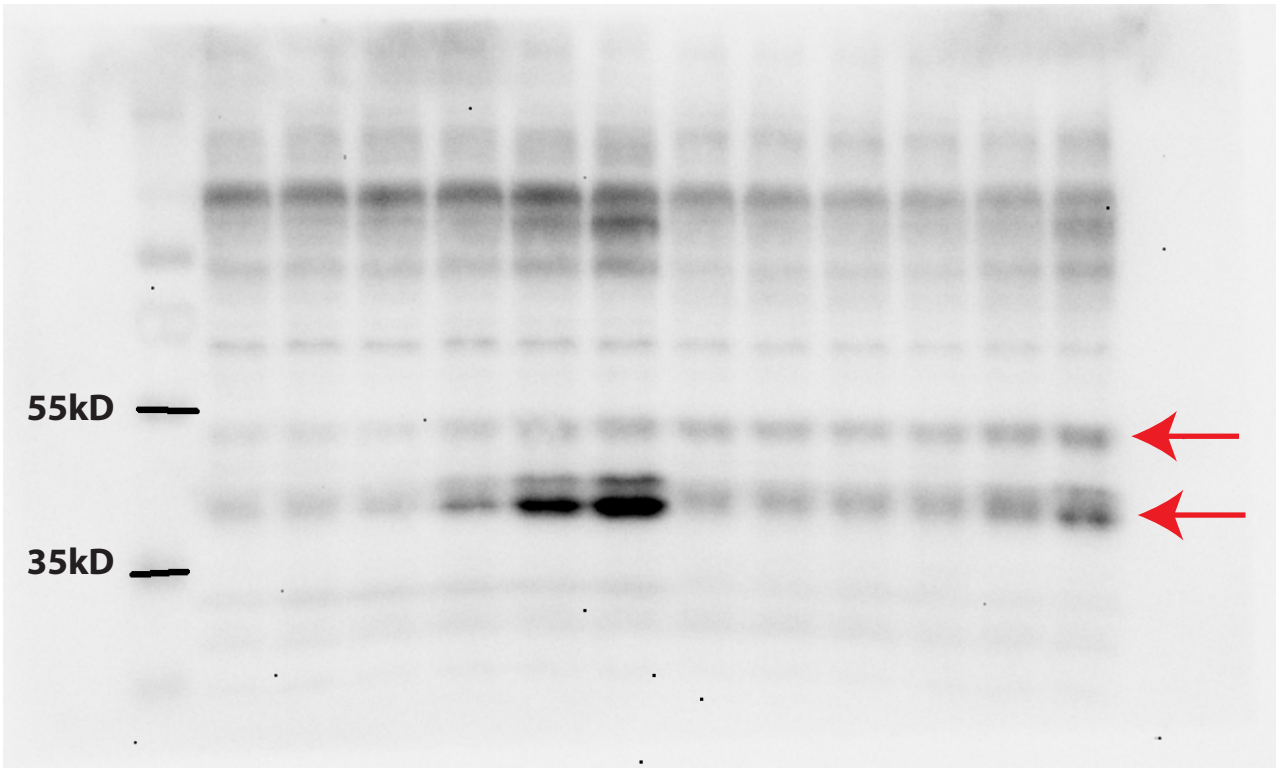


Figure 6E

1st panel (pJNK)



2nd panel (tJNK)

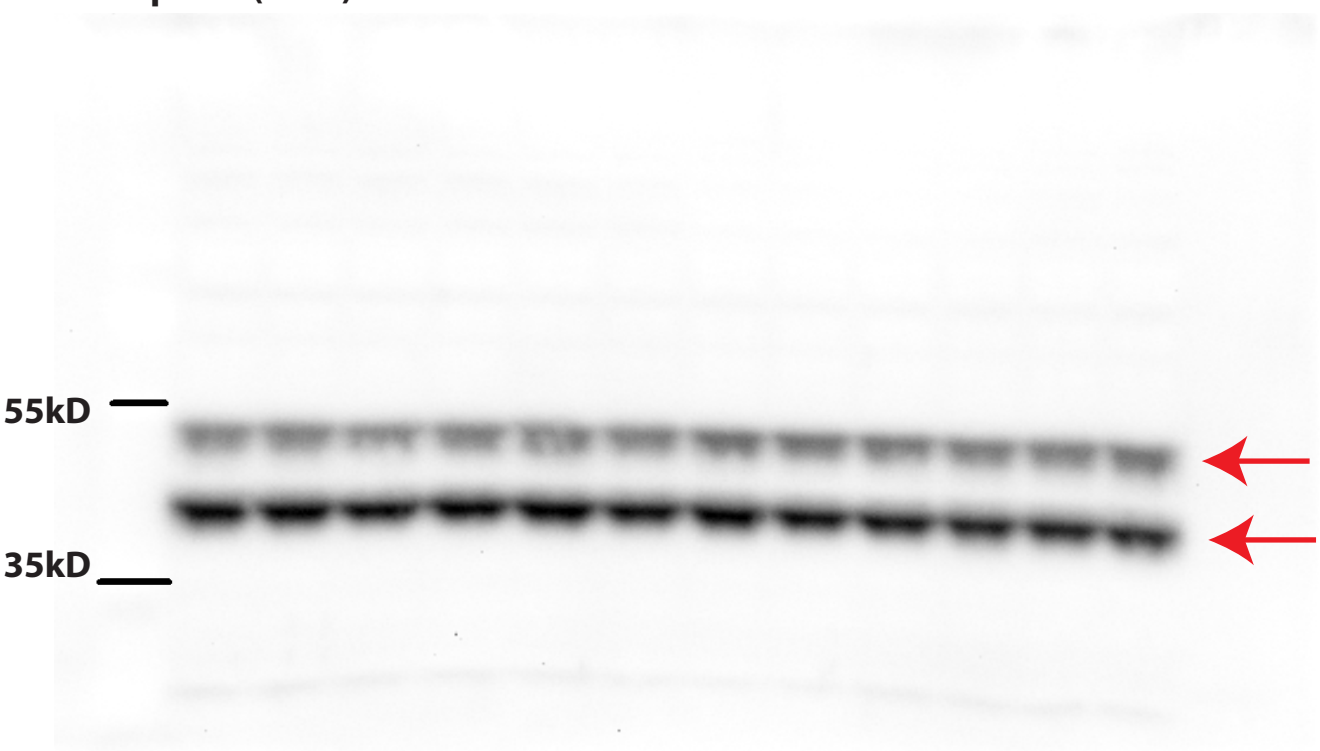
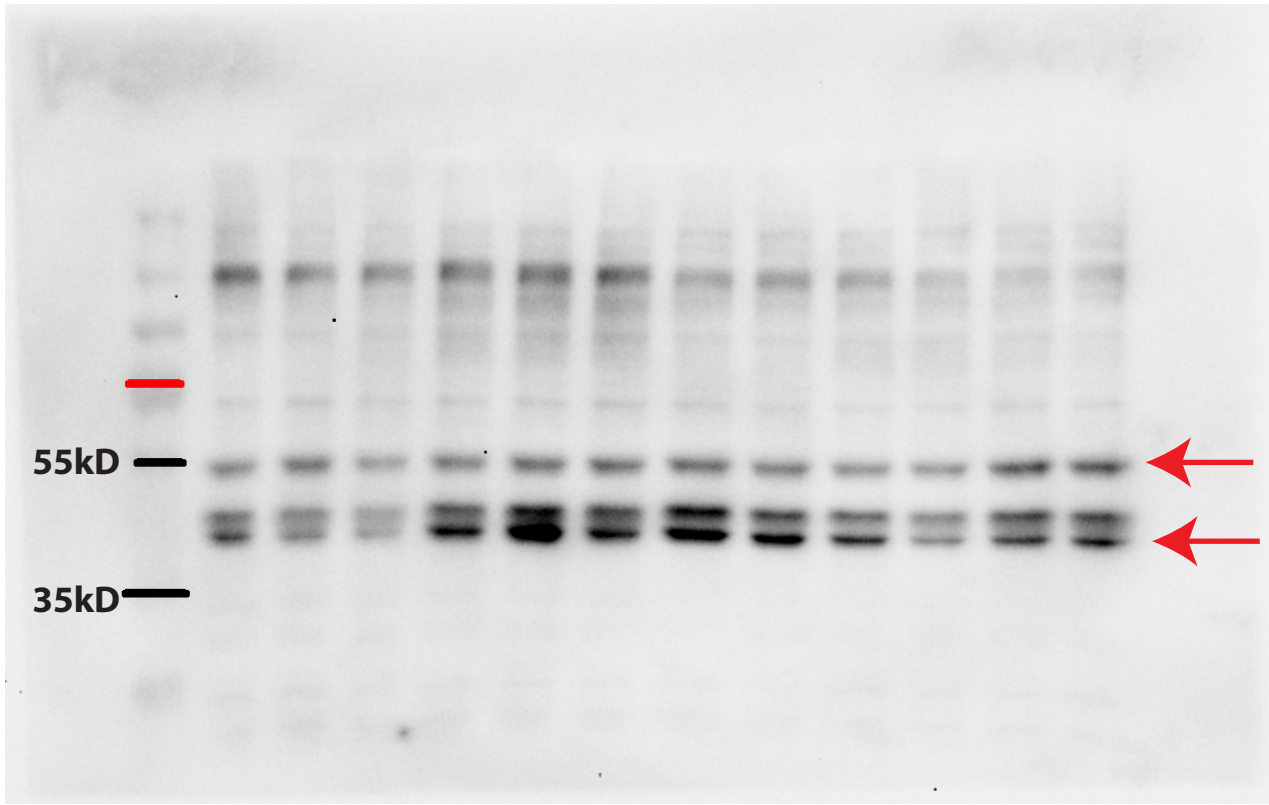


Figure 6E

3rd panel (pJNK)



4th panel (tJNK)

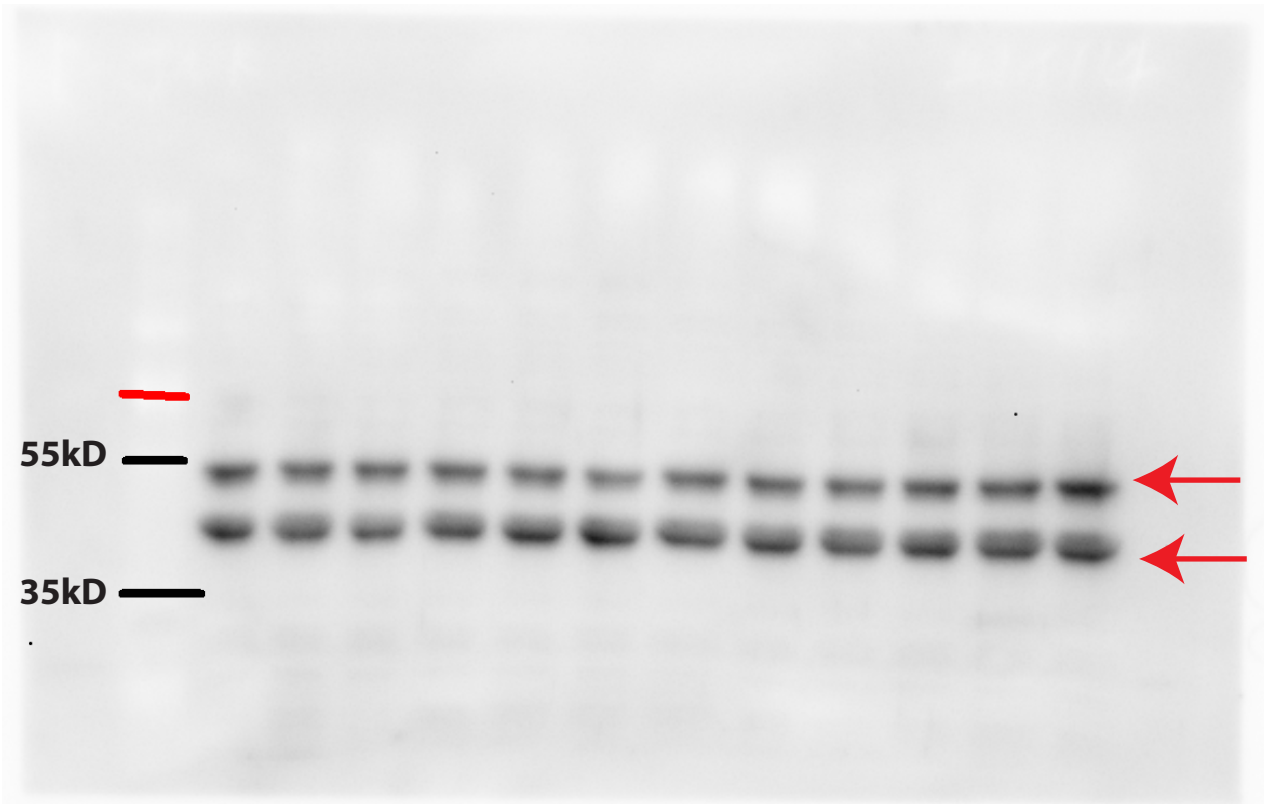
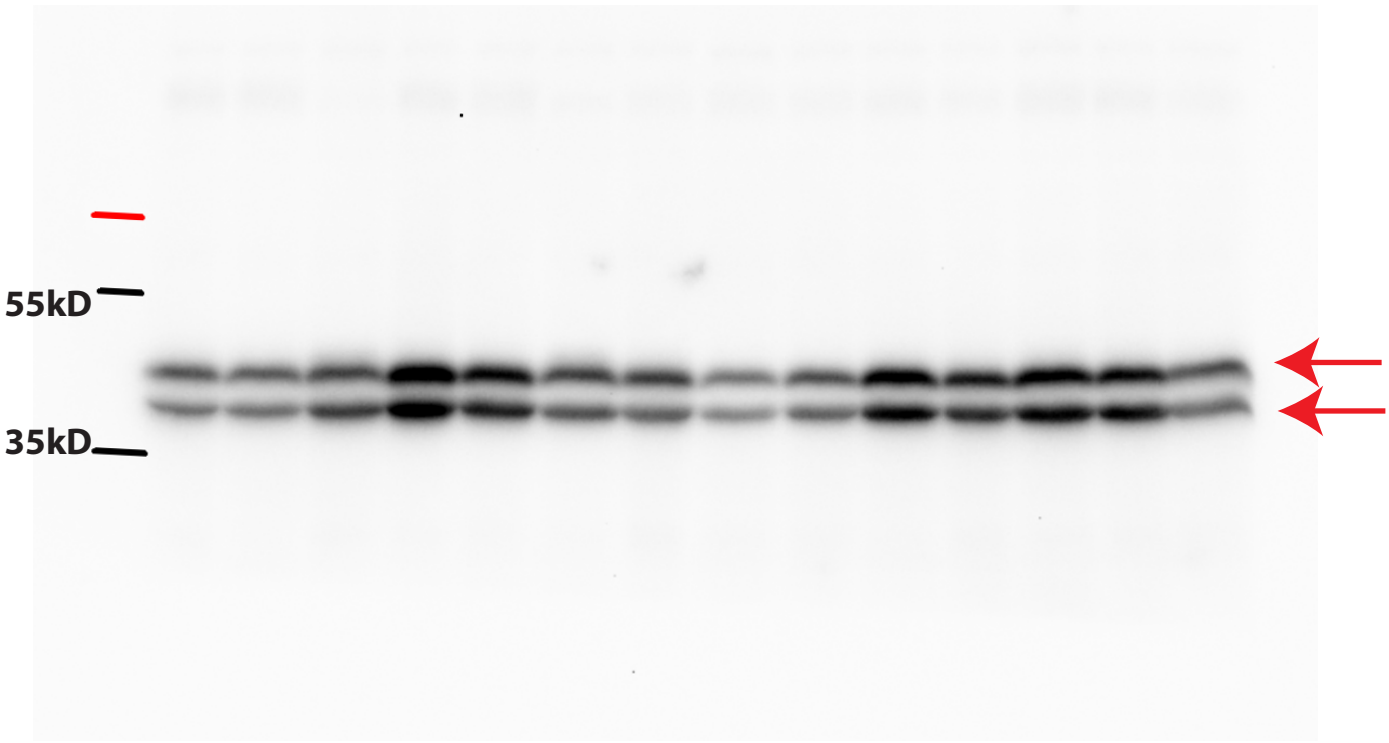


Figure S7A

1st panel (pERK1/2)



2nd panel (Total ERK1/2)

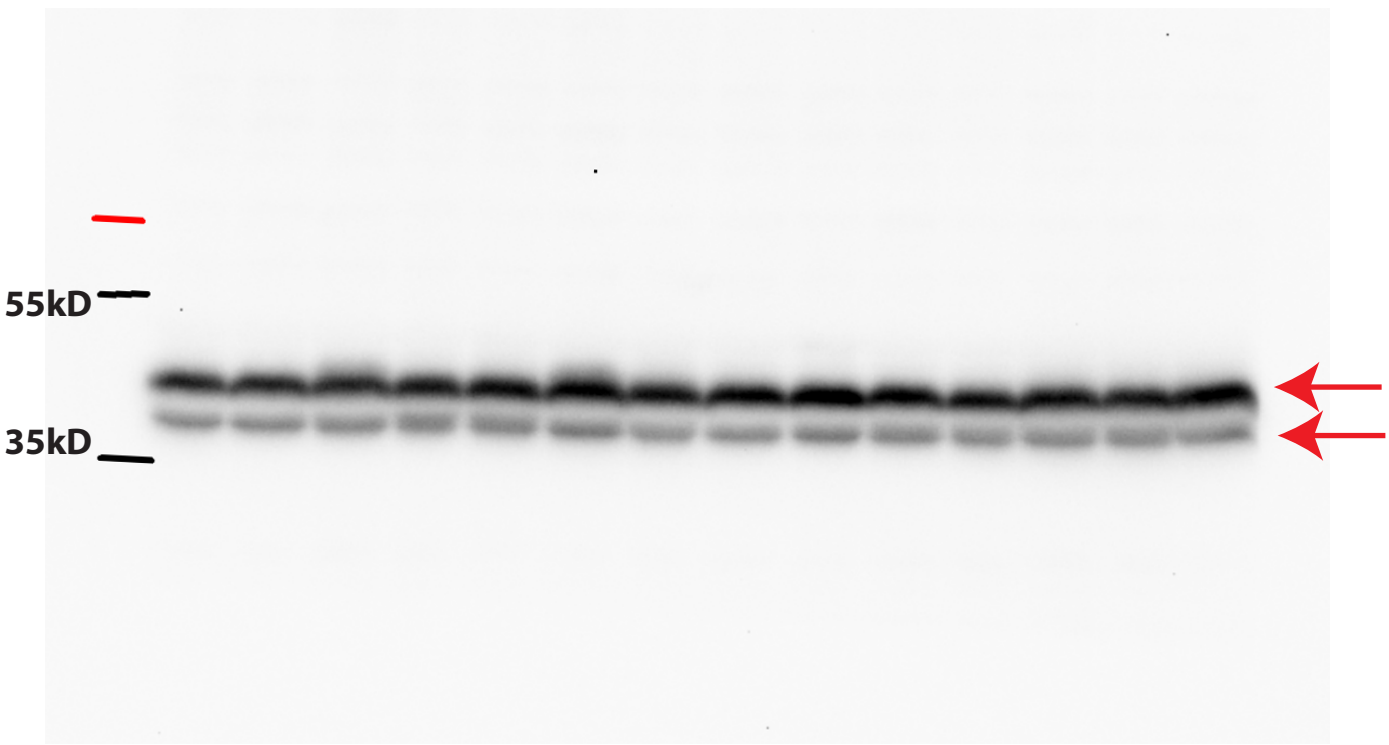
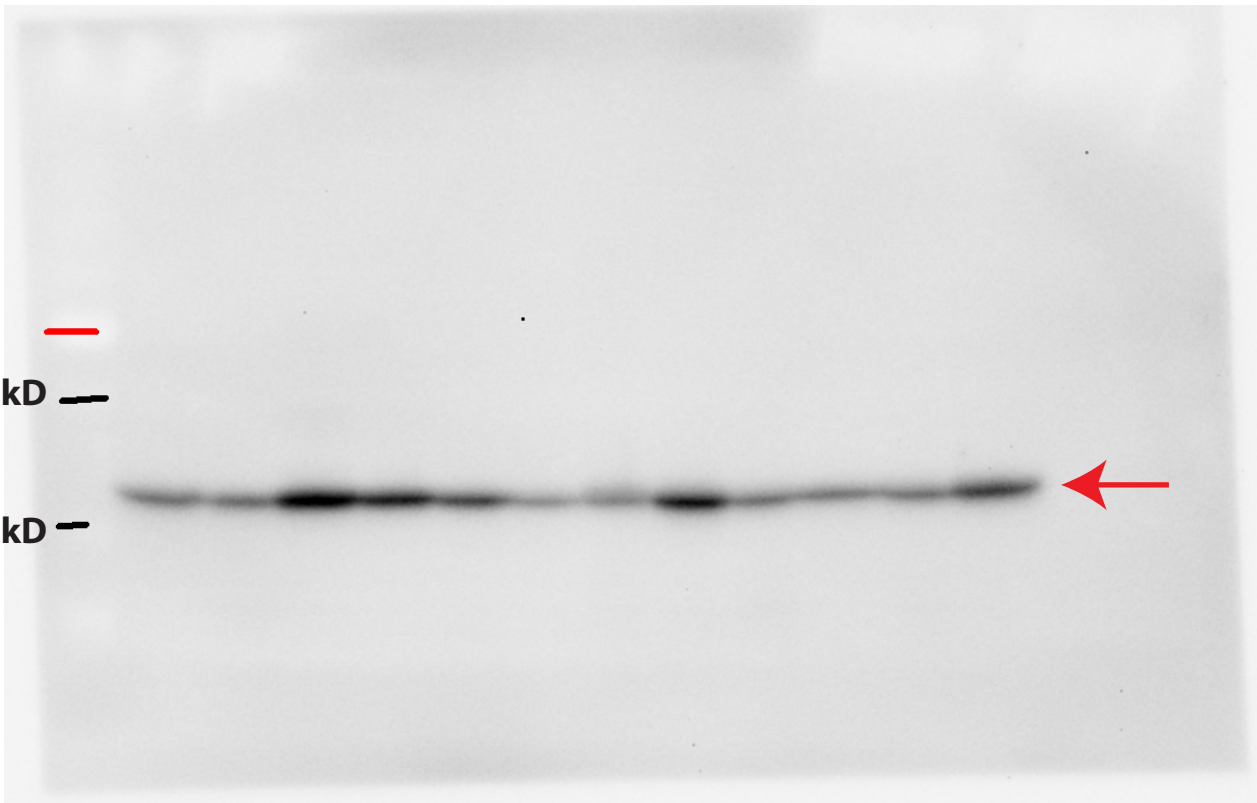


Figure S7B

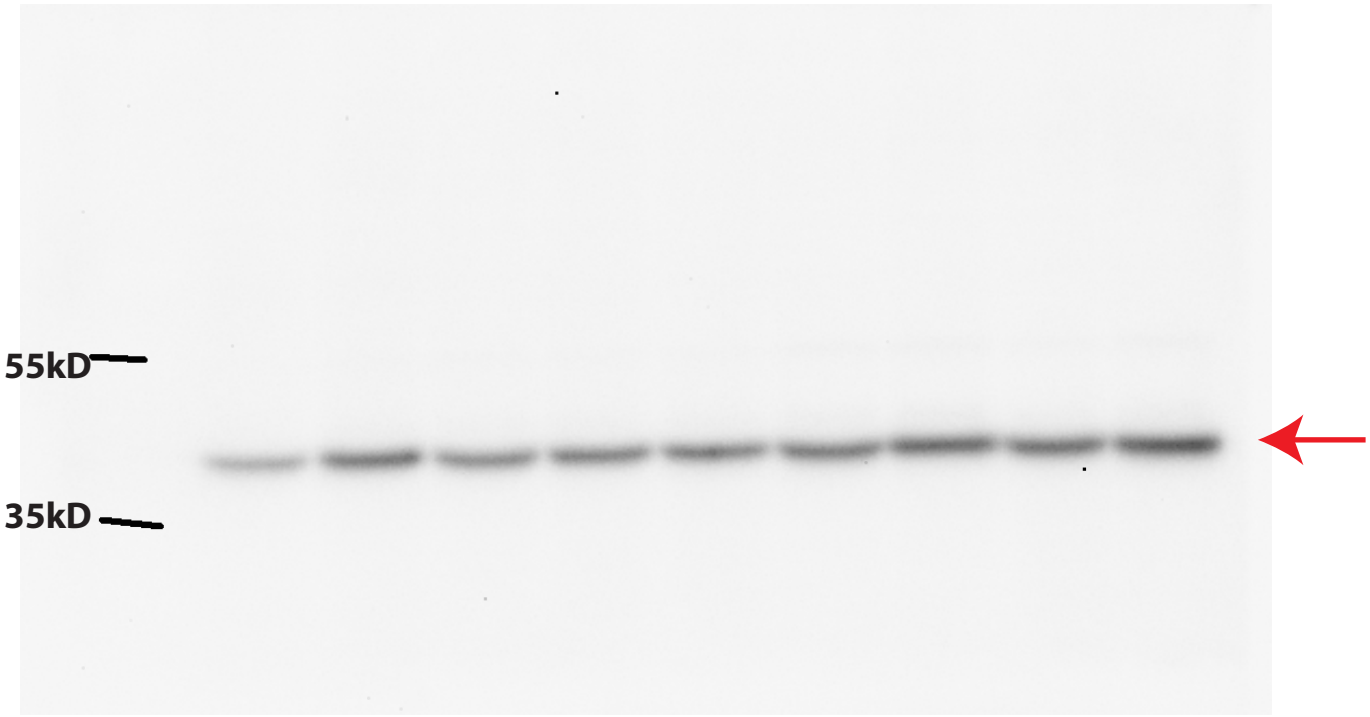
1st panel (p-p38 alpha)



2nd panel (total- p38 alpha)

Figure S7B

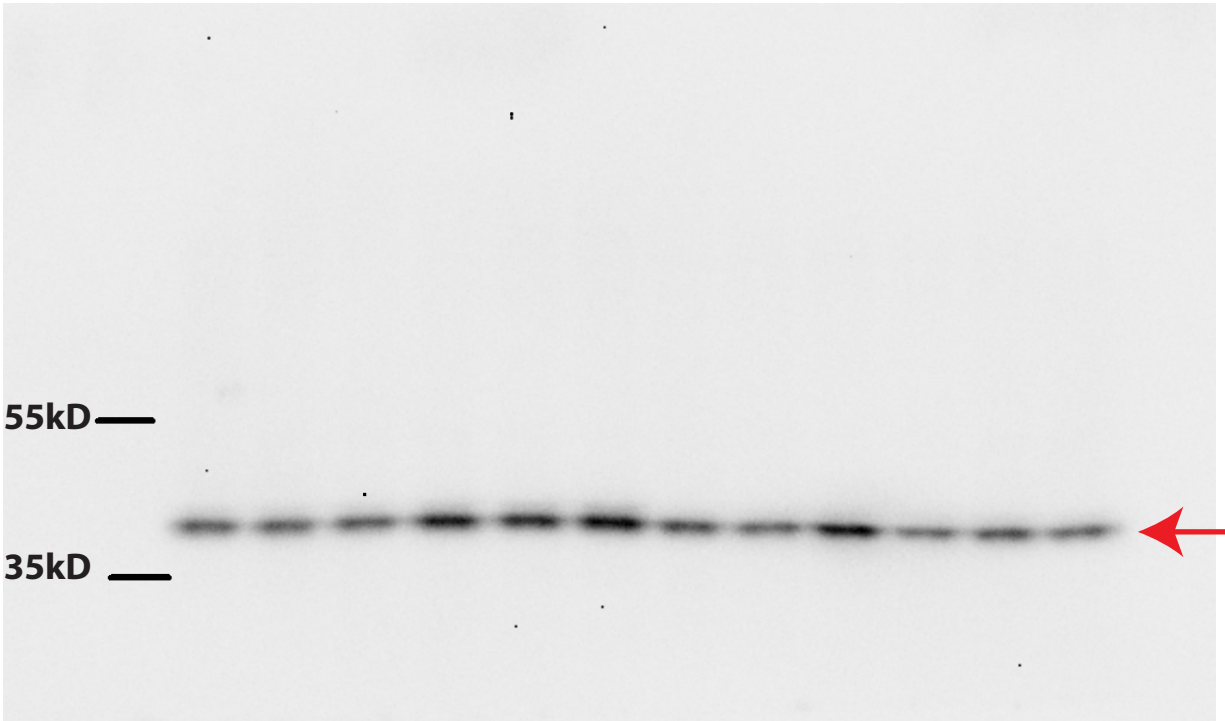
3rd panel (p-p38 alpha)



4th panel (total- p38 alpha)

Figure S8

1st panel (p-p38 alpha)



2nd panel (total- p38 alpha)

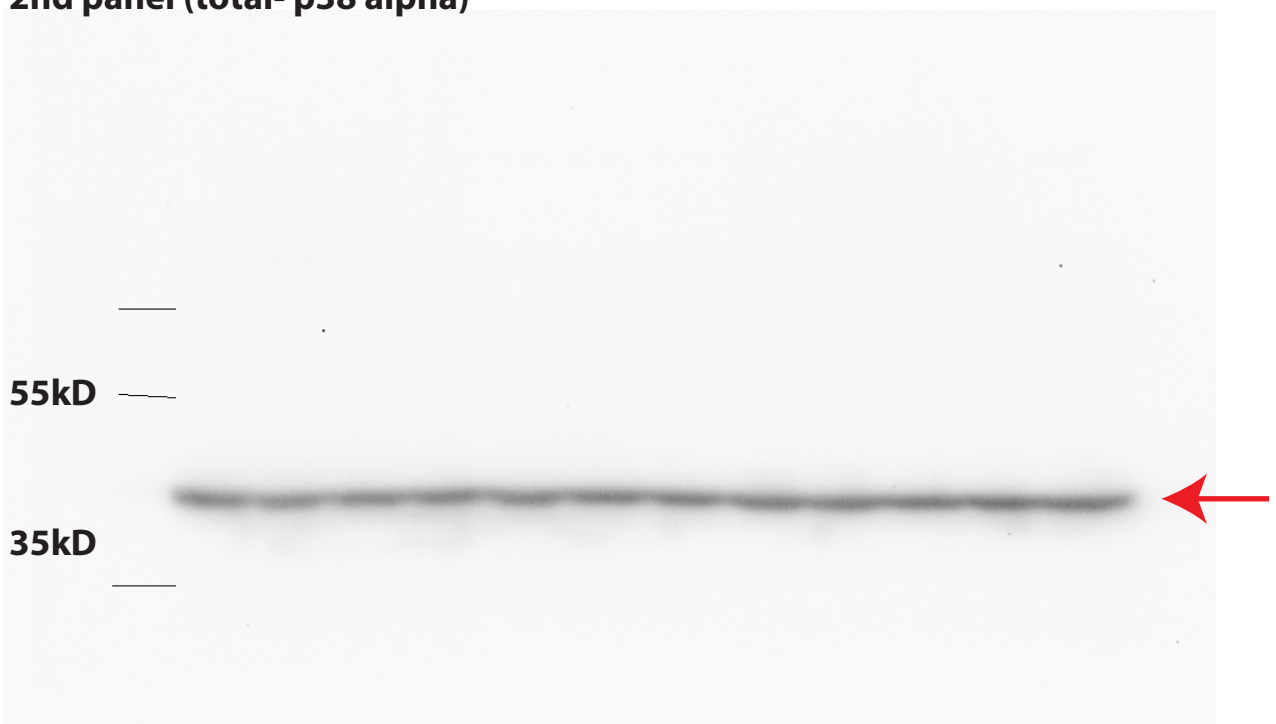
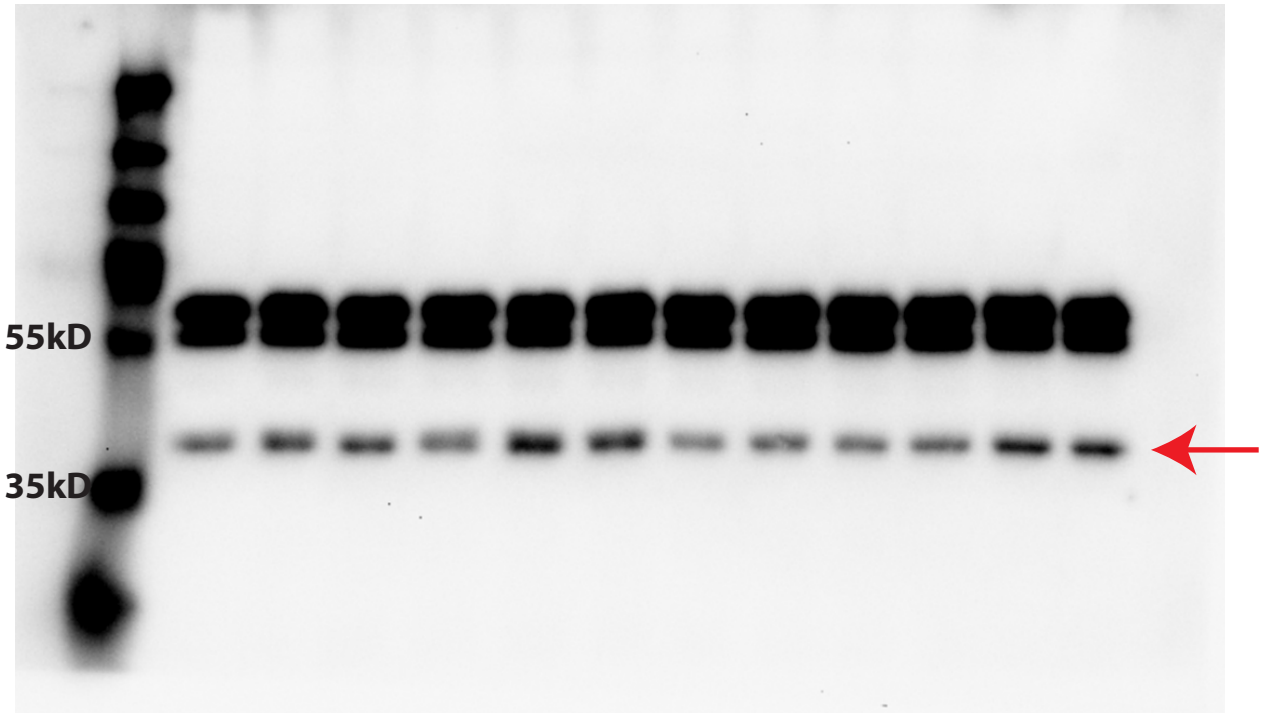


Figure S8

3rd panel (p-p38 alpha)



4th panel (total- p38 alpha)

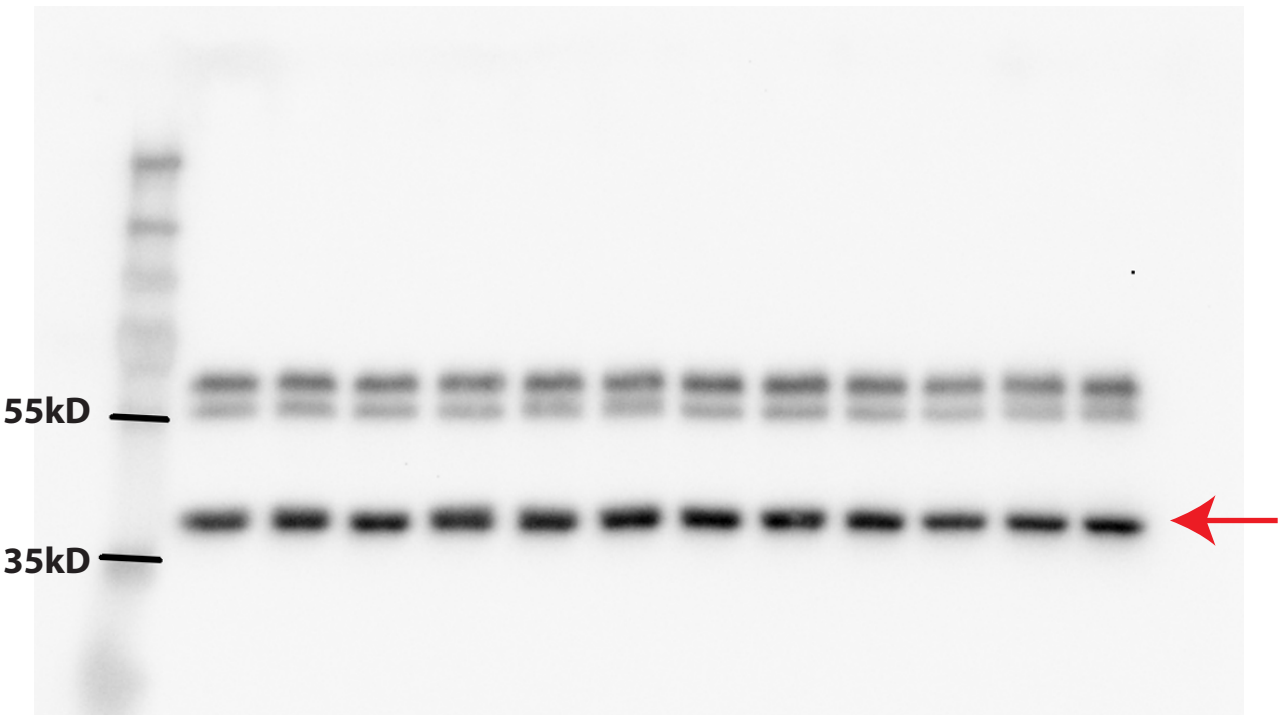
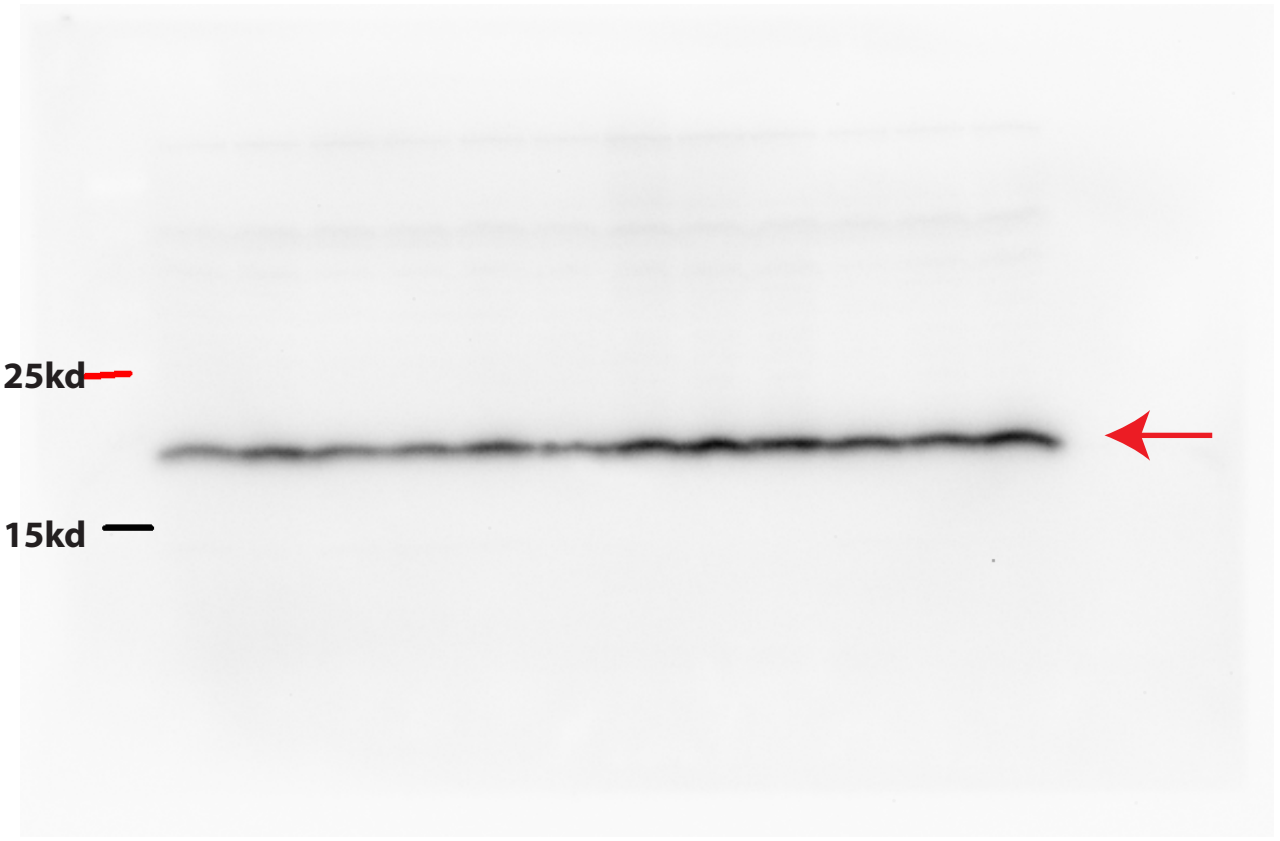


Figure S9

1st panel (Bax)



2nd panel (BCl2)

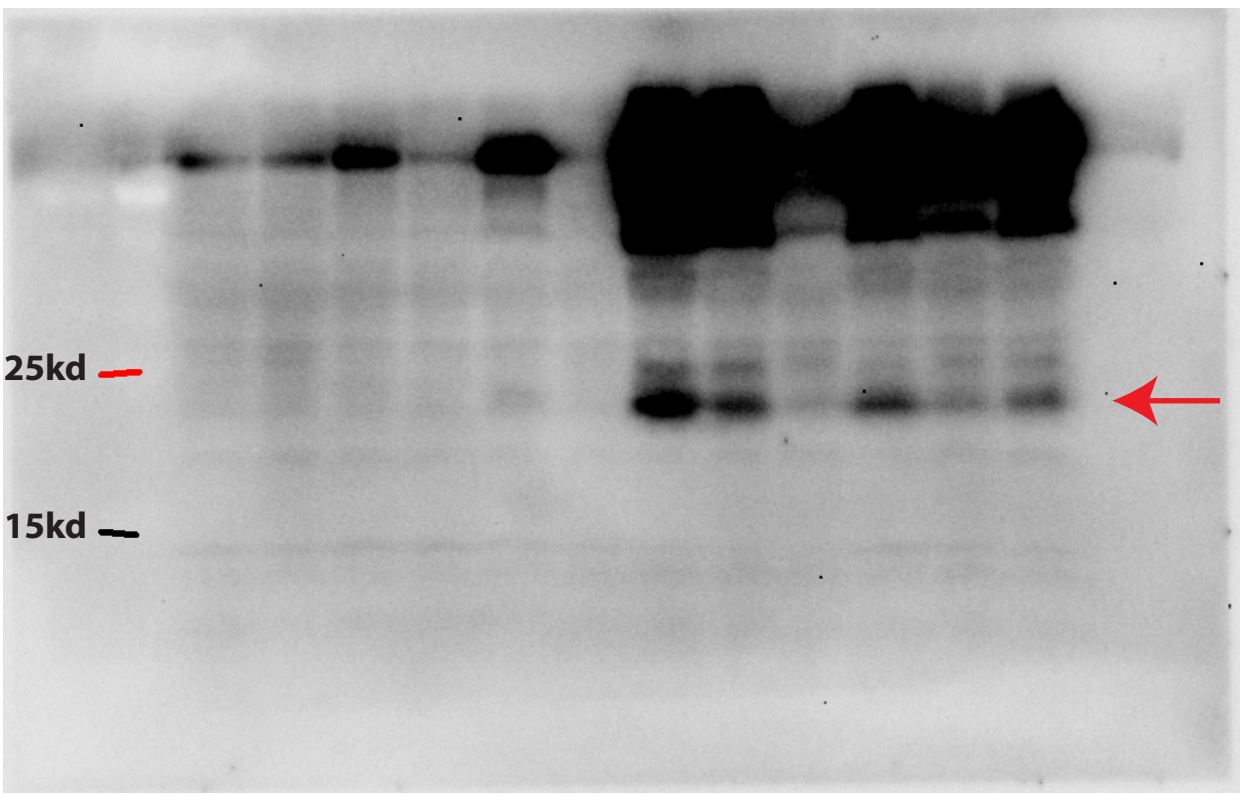


Figure S9