SUPPLEMENTAL MATERIAL

SUPPLEMENTARY METHODS

Diabetic rat model of heart failure. The Otsuka Long-Evans Tokushima Fatty (OLETF) and normal male Long-Evans Tokushima Otsuka (LETO) rats were obtained from Tokushima Research Institute, Otsuka Pharmaceutical Company (Tokushima, Japan). The OLETF is an established model of spontaneous non-insulin-dependent type 2 diabetes mellitus (DM) that manifests stable clinical and pathological features that resemble human type 2 DM[1]. Sixty to sixty five week-old OLETF rats develop systolic and diastolic dysfunction, leading to heart failure[2]. LETO rats served as control animals.

Pressure-Volume loop. *In vivo* hemodynamic analysis using pressure-conductance catheters LV pressure-volume loops (P-V) measurements were obtained as previously described[3]. Briefly, the mice were anesthetized with an intraperitoneal injection of a combination of urethane (1 mg/g), etomidate (10 μg/g), and morphine (1 μg/g), intubated via a tracheotomy and mechanically ventilated. The heart was exposed via thoracotomy and a Pressure-Volume conductance catheter (1.1 Fr, Scisense) was placed in the left ventricle via an apical stab approach. The animals were kept sedated with 0.75-1% isoflurane maintaining a stable heart rate (~450 beats/minute). Hemodynamic recordings were performed after 5-10 minutes after placement of catheter and confirmation of steady-state cardiac function, including heart rate, and achievement of appropriate pressure and volume raw-data waveforms. The load-independent P-V relationships measurements were obtained by transiently occluding the intra-

thoracic inferior vena cava to decrease venous return/preload. Volume measurements were initially obtained as blood conductance and calibrated using the Baan equation 3 and pressure sensors were calibrated according to manufacturer's instructions (Scisense). Hemodynamic measurements were acquired and analyzed using IOX software (EMKAtech).

Histology. Hematoxilin-Eosin (H&E) staining: Whole ventricular tissue was embedded in optimum cutting temperature compound (TissueTek). Frozen sections (10 µm) were mounted and subsequently stained with H&E using routine procedures. Cardiac fibrosis: Masson's trichrome staining was used to assess the fibrosis according to the manufacturer's protocol (Sigma-Aldrich).

Cardiomyocyte cross-sectional area. Heart LV tissue cryosections (10 µm) were fixed in 4% paraformaldehyde and incubated for 45 min at room temperature with Texas Red®-X conjugate of wheat germ agglutinin (5 µg/ml; Life Technologies). The cross-sectional area was measured in the LV free wall of each animal (ImageJ) in 100-200 cardiomyocytes with circular cell membrane shape.

Electron Microscopy. Mouse hearts were arrested in diastole with a bolus injection of potassium chloride (KCL, 1M), gently minced into ~1 mm^3 pieces and subsequently pre-fixed in a solution of 3% glutaraldehyde (overnight at 4 °C) followed by post-fixation in 1% osmium tetroxide (OsO_4). Finally, the tissue was

dehydrated in an alcohol gradient, and embedded in epoxy resin. Ultrathin sections were stained with uranylacetate and lead citrate, and high-resolution images were captured in a transmission electron microscope (HITACHI H-7650). Quantification of the mitochondria size and content was performed using NIH ImageJ software. Random fields were chosen and the surface area of 40-50 mitochondria per image was measured manually using ImageJ.

Cardiomyocyte contractility and intracellular Ca^{2+} measurements. Adult rat ventricular myocytes (ARVM) were isolated from Sprague-Dawley male rats (280–300 g) using a modified Langendorff perfusion system. ARVMs were plated onto laminin-pre-coated coverslips (1 μg/cm^2), infected with adenoviruses expressing either the miR-152 precursor Ad.miR-152 or Ad.GFP, and cultured in MEM media supplemented with penicillin (50 U/ml), streptomycin (100 μg/ml), 0.1% BSA, 10 mM 2,3-butanedione monoxime (Sigma-Aldrich) and 1× insulin/transferrin/selenium supplement (Life Technologies). After 48 hours the cardiomyocytes were loaded with Fura-2, a fluorescent Ca^{2+}-sensitive dye, and intracellular Ca^{2+} transients from individual cardiomyocytes electrically stimulated (0.5 Hz) together with sarcomeric shortening measurements were recorded using the IonOptix system (IonOptix).

Human heart tissue. Human heart tissue specimens were obtained from the National Disease Research Interchange (NDRI) through the Human Tissues and Organs for Research (HTOR) program.

Transcriptome profiling: Total RNA was isolated from Tg152 and control heart tissue with the RNeasy Isolation kit (Qiagen) with on-column DNase I treatment to eliminate contaminating genomic DNA using the RNase-free DNase Set according to the manufacturer's instructions (Qiagen). The purified total RNA (200ng) was converted to biotinynated amplified RNA (aRNA) using the Illumina Total Prep RNA Amplification Kit according to the manufacturer's recommendation (Life Technologies). A total of 700 ng of aRNA was hybridized at 58°C for 16 hours to the MouseWG-6 v2.0 Expression BeadChips (Illumina). The BeadChip arrays were then scanned with the HiScan System (Illumina) and the data generated were normalized using BeadStudio (Illumina). Spurious probes were filtered by translating the detection p-values into q-values[4,5] and removing any probe with maximum q-value across all samples greater than or equal to 10%. The resulting data were then analyzed for differential expression with SAM using its default parameters[6,7], and genes assigned a false discovery rate less than 5% were considered differentially expressed. The enriched Gene Ontology terms and pathways in the resultant lists of differentially expressed genes were identified using the DAVID[8] and Ingenuity Pathway Analysis (Ingenuity Systems, www.ingenuity.com) applications respectively.

Quantification of mature miRNAs. Total RNA was isolated with miRVana isolation kit followed by a DNase treatment to eliminate contaminating genomic DNA (Life Technologies). Mature miR-152 expression was quantified by real-time

qRT-PCR using the Taqman® MicroRNA Assays according to the manufacturer's instructions (Life Technologies). Gene expression levels were normalized to U6 rRNA endogenous control and fold changes were calculated using the ΔΔCt method.

Quantitative Real-Time RT-PCR. Relative gene expression was determined using two-step quantitative qRT-PCR (Supplemental Table 4). Quantitative PCR reactions were performed with Power SYBR Green Master Mix (Life Technologies) on an ABI Prism 7500 Real Time PCR System. Fold changes were calculated using the ΔΔCt method with normalization to 18S rRNA housekeeping gene.

Protein expression analyses. Protein expression was evaluated in LV lysates by Western blot analysis according to standard procedure. The following antibodies were used: mouse monoclonal anti-Pln and anti-phospho S16 Pln (Badrilla), rabbit polyclonal anti-Serca2a (custom made), rabbit polyclonal anti-Glrx5 (Sigma-Aldrich), mouse monoclonal anti-Sdhb (Abcam) and mouse monoclonal anti-Gapdh (Sigma-Aldrich). The proteins were detected with ECL-Plus chemiluminescence detection kit (Pierce) or with the ODYSSEY Infrared Imaging System (Li-CoR).

Dual Luciferase Reporter Assays. The mouse 3-'UTR sequences of Glrx5 was amplified from genomic DNA by PCR and cloned downstream of the *Renilla* translational stop codon of the psiCHECK-2 dual luciferase vector (Promega). A

3’ UTR without the predicted miR152 binding site was synthesized by GeneArt (Thermofisher Scientific) and cloned to the psiCHECK-2 vectror. The psiCHECK-3’UTR constructs (50 ng) and 10 pmoles of synthetic pre-miR-152 mimic (Ambion) or 10 pmoles of pre-miR negative control (Ambion) were co-transfected in HEK293FT cells (Life Technologies) using the DharmaFECT-Duo transfection reagent (ThermoFisher Scientific). After 48h, the normalized *Renilla* luciferase activity (Renilla/Firefly) was measured using the Dual-Glo™ Luciferase Assay System according to the manufacturer’s instructions (Promega). For the miR-152 reporter construct, the mature miR152 sequence (x3) was synthesized as double-stranded DNA (GeneArt) and was cloned downstream of the *Renilla* translational stop codon of the psiCHECK-2 dual luciferase vector. The psiCHECK-miR152 vector (50 ng) and the LNA-152 or LNA-control oligonucleotides were co-transfected in HEK293FT cells (Life Technologies) using the DharmaFECT-Duo transfection reagent (ThermoFisher Scientific). After 48h, the normalized *Renilla* luciferase activity (Renilla/Firefly) was measured using the Dual-Glo™ Luciferase Assay System according to the manufacturer’s instructions (Promega).

Supplementary References

1. Kawano K, Hirashima T, Mori S, Saitoh Y, Kurosumi M, Natori T. Spontaneous long-term hyperglycemic rat with diabetic complications. Otsuka long-evans tokushima fatty (oletf) strain. *Diabetes*. 1992;41:1422-1428
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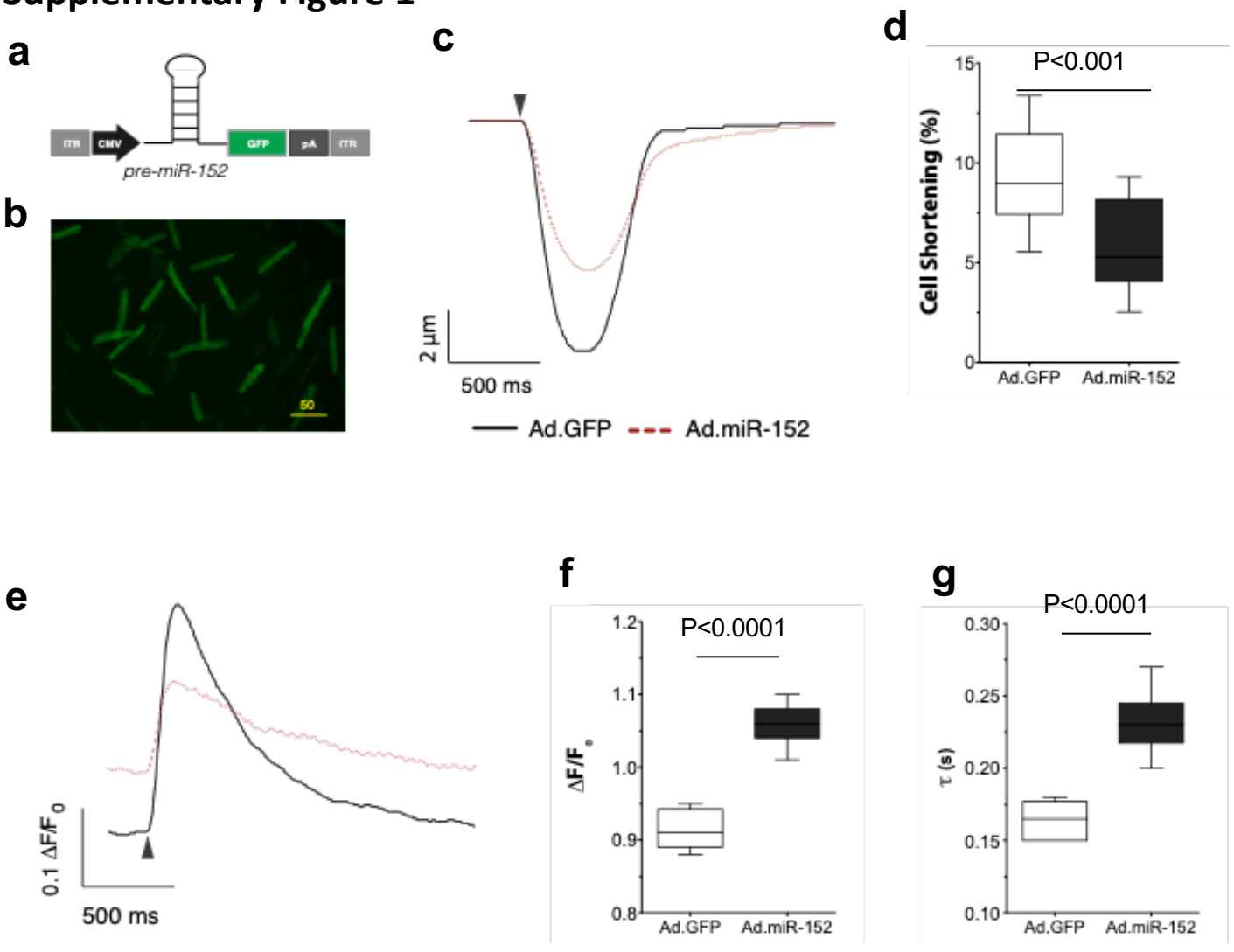
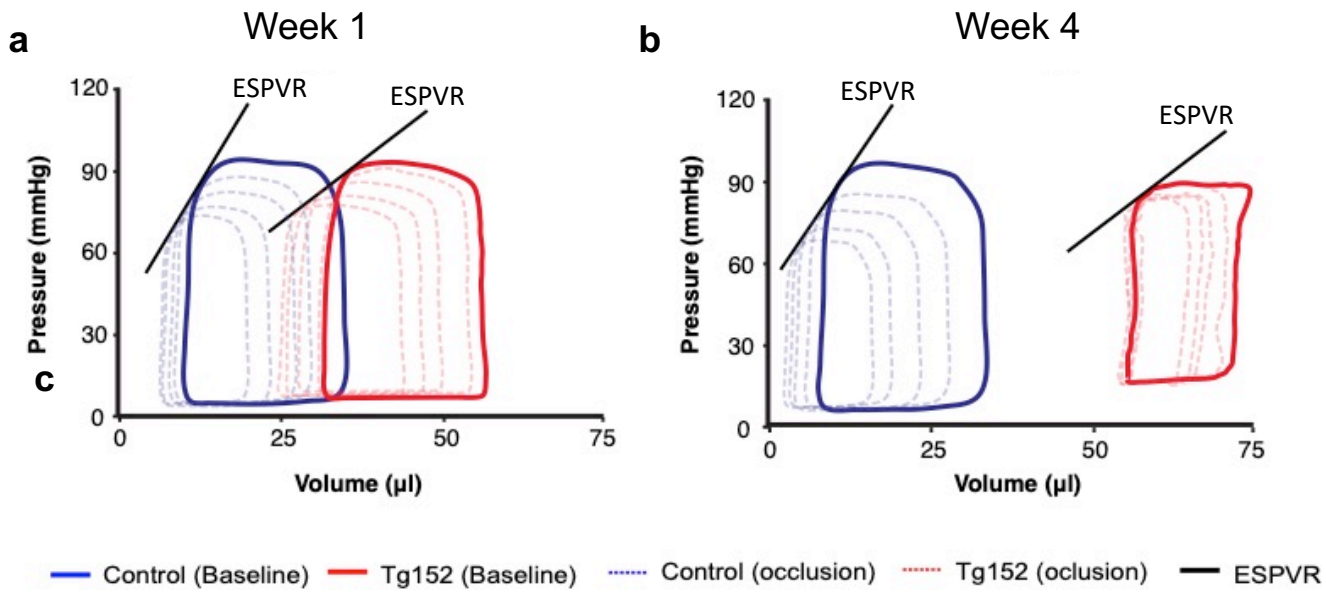
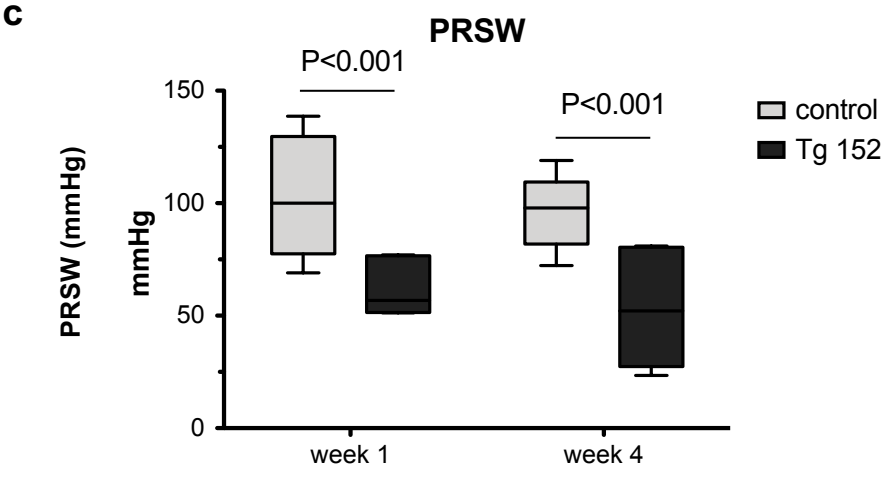
Supplementary Figure 1



Supplementary Figure 1 . Effect of miR152 gain-of-function on cardiomyocyte contractility and calcium cycling *in vitro*. a) Schematic of adenoviral miR-152 construct. The expression cassette is comprised of the miR-152 stem-loop flanked by its native intron sequence. **b**) Transduction of adult rat ventricular cardiomyocytes (ARVMs) with an adenoviral vector expressing the miR-152 precursor cassette (MOI 10). Scale bar = 50µm**. c-d**) Contractility assessment. ARVMs were infected with either Ad.GFP (MOI=10) or Ad.miR152 (MOI=10) and the cell shortening of individual cells was analyzed by video-edge detection 48h post infection. **c**) Representative cell length displacement transient recordings. Traces represent the average of 15 shortening/re-lengthening cycles. **d**) Cardiomyocyte contractility assessed as percent change of cell length. **e-g**) Intracellular calcium [(Ca2+)i] analysis. ARVMs were infected with an adenovirus expressing either miR-152 (Ad.miR-152) or a control adenovirus (Ad.GFP). After 48h the cardiomyocytes were loaded with Fura-2, a fluorescent Ca^{2+} sensitive dye, and the ratio of the fluorescence intensities (excited at 340 nm and 380 nm) were recorded using the IonOptix system. **e**) Representative [(Ca2+)i] transient recordings of Fura-2 loaded ARVMs electrically stimulated at 0.5 Hz. **f**) Quantitative analysis of diastolic ([Ca2+]i) levels shown as Fura-2 ratio (F/F_0) at baseline. **g**) Ca^{2+} re-uptake kinetics measured by the exponential decay time constant (τ). Data are mean values ± se (n=21 Ad.GFP, n=25 Ad.miR152). *P<0.05. MOI=multiplicity of infection**.** Box-and-whisker plots show the minimum, the 25th percentile, the median, the 75th percentile, and the maximum. All comparison by unpaired Student's t-test.

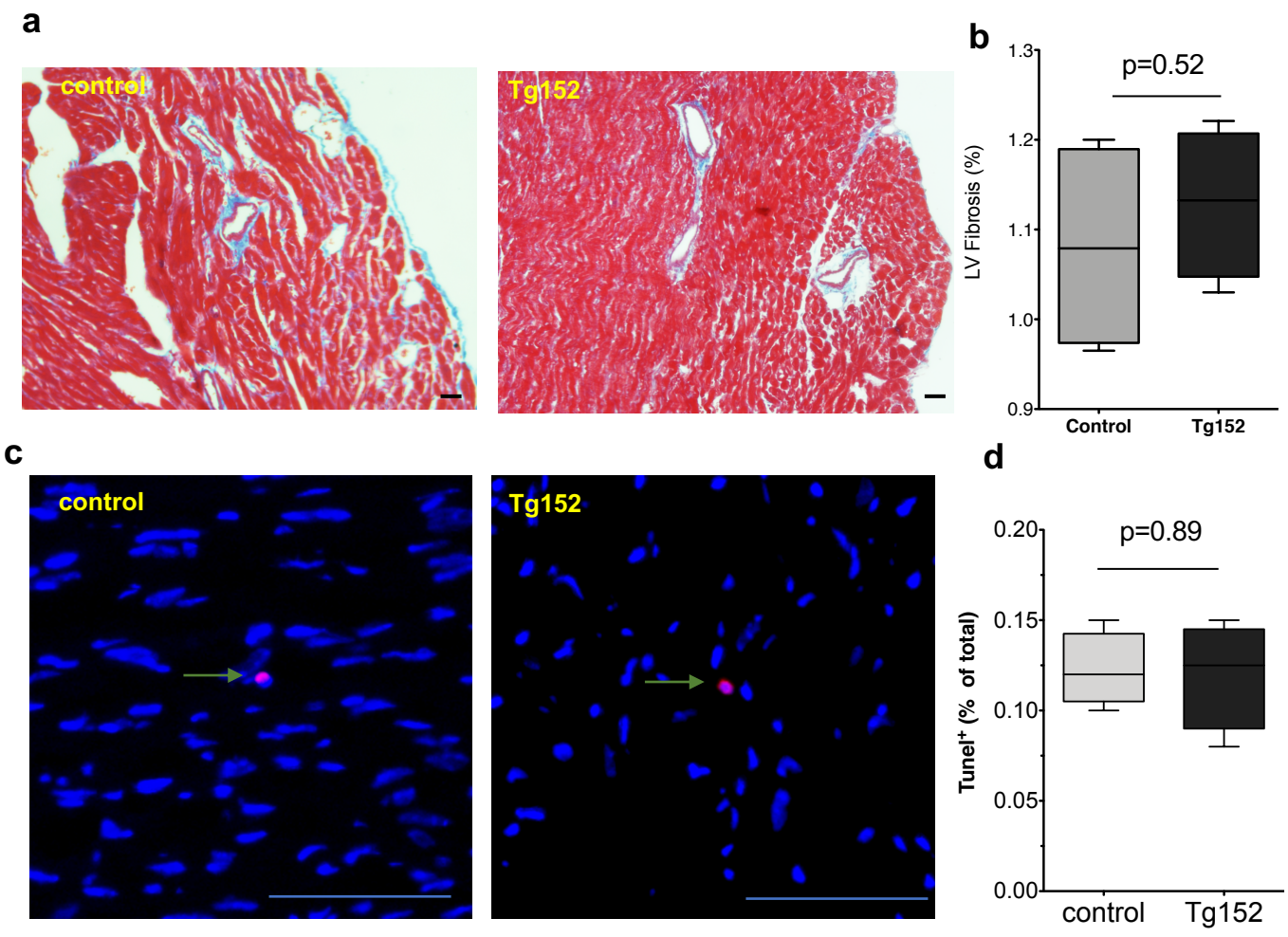
Supplementary Figure 2





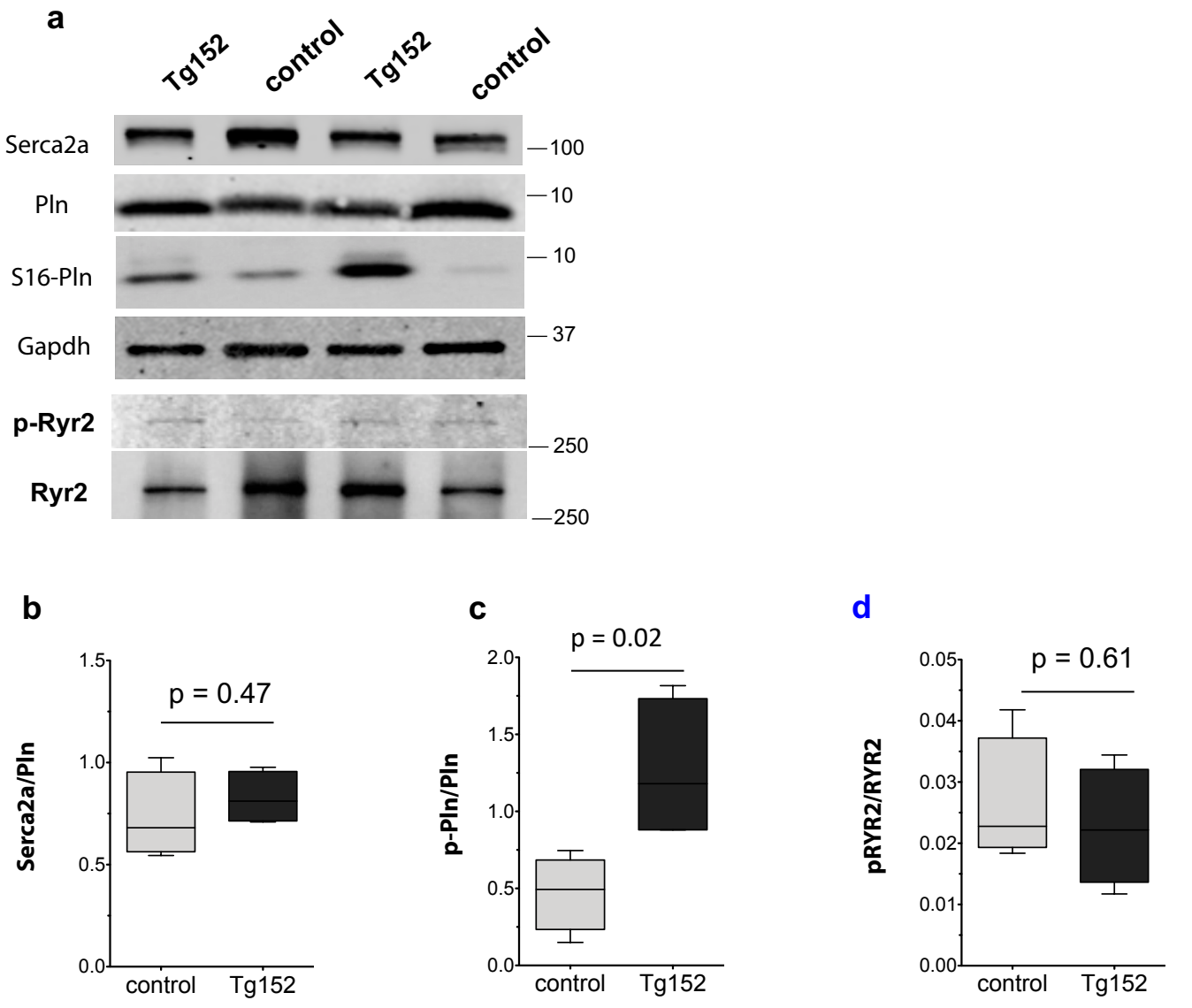
Supplementary Figure 2. Invasive hemodynamics analysis. **a-b**) Representative pressure-volume (P-V) loops at baseline and after inferior vena cava (IVC) occlusion in control and Tg152 animals at 1-week and 4-weeks following tamoxifen administration. Slope indicates ESPVR. **c**) Assessment of the load-independent index PRSW. Box-and-whisker plots show the minimum, the 25th percentile, the median, the 75th percentile, and the maximum. Comparison by 2-way ANOVA, n=6 animals per group. Comparison by 2-way ANOVA. ESPVR: end-systolic pressure volume relationship; PRSW, preload-recruitable stroke work.

Supplementary Figure 3



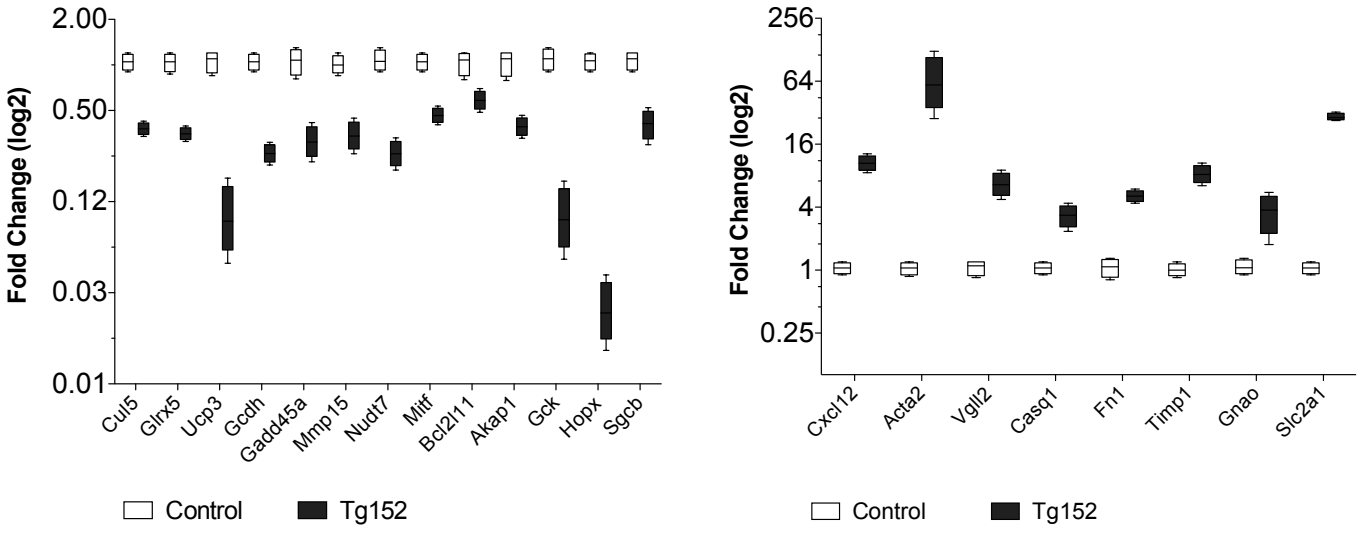
Supplementary Figure 3. Histopathological assessment of cardiac fibrosis and apoptosis in Tg152 hearts at 1-week post TAM treatment. a) Representative micrographs of Masson Trichrome-stained cryosections of LV myocardium from control and Tg152 hearts at 1-week post tamoxifen treatment. Scale bar = 100 μm. **b)** Quantification of the myocardial collagen fraction showed similar levers of fibrotic areas in compared control to Tg152 hearts. Data represent mean ± se (n=3 hearts per group). **c**) Representative epifluorescence images of TUNEL staining of control and Tg152 hearts at 1-week after tamoxifen treatment. DAPI was used for nuclear staining. Arrows indicate TUNEL positive nuclei. (n=4 animals; 500 cells heart) Scale bar = 100 μm. **d**) Quantification of TUNEL-positive cells in control and Tg152 hearts (n=3 per group). Box-and-whisker plots show the minimum, the 25th percentile, the median, the 75th percentile, and the maximum. All comparison by unpaired Student's t-test.

Supplementary Figure 4



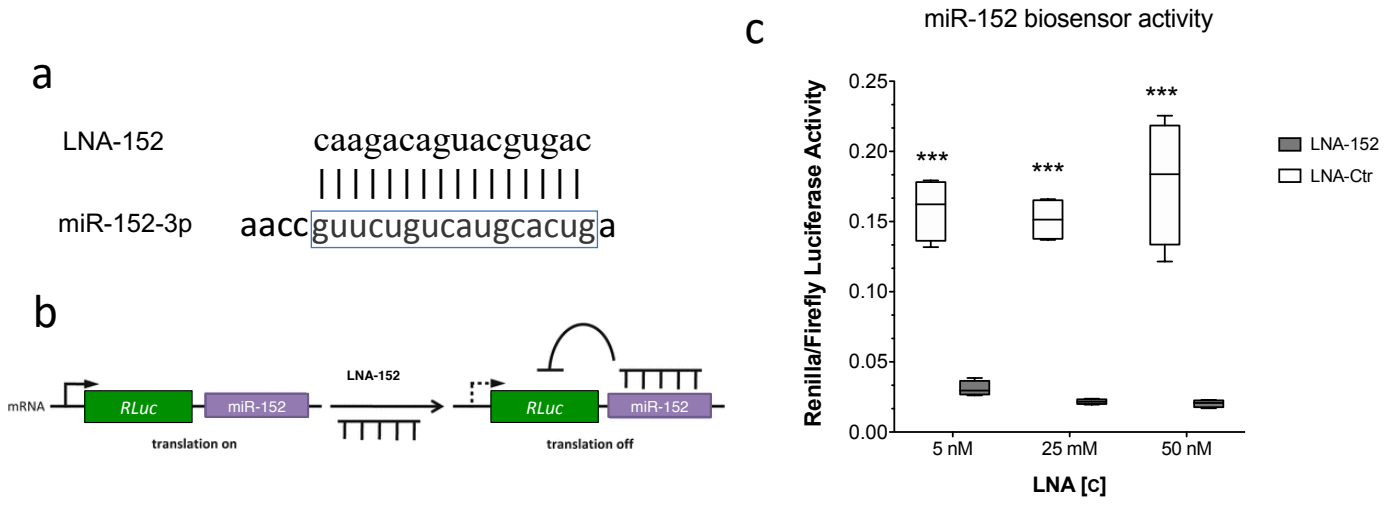
Supplementary Figure 4. Expression analysis of key calcium handling proteins in Tg152 hearts. a) Representative Western blot analysis of *Serca2a, Pln*, and phospho-*Pln*. **b-d)** Densitometric analysis of phospho-Pln (serine 16), Pln, Serca2a, RyR2 and phospho-RyR2 (Serine 2808) protein expression levels expressed as phospho-Pln/Pln, Pln/Serca2a phosphoRyR2/RyR2 ratio. Gapdh protein expression is shown as loading control. Box-and-whisker plots show the minimum, the 25th percentile, the median, the 75th percentile, and the maximum. Comparison by unpaired Student's t-test, n=4 per group. *Pln*: phospholamban; *Serca2a*: sarcoplasmic reticulum Ca^{2+}-ATPase 2a, RyR2: ryanodine receptor 2. Numbers indicate the molecular weight marker size (kDa).

Supplementary Figure 5



Supplementary Figure 5. Validation of microarray gene expression data. Quantitative real-time PCR (qRT-PCR) was used to validate the microarray data. The expression of transcript levels of selected down (**a**) and upregulated (**b**) genes as indicated. The qRT-PCR results corroborate the microarray results. (n=6 per group). *P < 0.001 compared to control. Box-and-whisker plots show the minimum, the 25th percentile, the median, the 75th percentile, and the maximum

Supplementary Figure 6



Supplementary Figure 6. Validation of locked-nucleic acid (LNA)-modified anti-miR152. a) An anti-miR oligonucleotide was designed as complementary to the 5' region of the mature miR-152 sequence (nucleotides 2-16). **b**) Schematic view of the biosensor construct used to monitor the activity of miR-152. The biosensor was generated by cloning three copies of the mature miR-152 sequence downstream of the *Renilla* Luciferase reporter gene. **c**) Luciferase activity in HEK293T cells co-transfected with the miR-152 biosensor construct and either the control antagomir (LNA-control) or anti-miR-152 (LNA-152) at the indicated concentration. Luciferase activity was averaged from 8 replicates from n = 3 independent experiments. Comparison by 2-way ANOVA. ***P<0.001.

Supplementary Table 1. M-mode echocardiographic data of the control and Tg152 mice

	Control	**Tg152**	**Control**	**Tg152**	**Control**	**Tg152**
Time, weeks	0	0	1	1	4	4
n	6	6	6	6	6	6
LVID;d, mm	2.99 ± 0.90	3.05 ± 0.80	2.98 ± 0.80	3.40 ± 1.40*	3.18 ± 0.12	5.18 ± 0.12*
LVPW;d, mm	1.00 ± 0.04	1.03 ± 0.04	1.04 ± 0.04	0.97 ± 0.06	0.95 ± 0.04	0.82 ± 0.03*
LVID;s, mm	1.39 ± 0.10	1.31 ± 0.06	1.28 ± 0.05	2.22 ± 0.14*	1.55 ± 0.06	4.32 ± 0.30*
LVAW;d, mm	0.98 ± 0.03	0.98 ± 0.04	0.98 ± 0.03	0.89 ± 0.05	1.00 ± 0.04	0.77 ± 0.02*
FS, %	56.7 ± 2.7	54.7 ± 2.2	57.2 ± 2.4	35.9 ± 3.5*	56.7 ± 1.2	17.3 ± 2.3*
Heart rate, beats/min	480 ± 20	470 ± 20	470 ± 20	470 ± 20	460 ± 20	480 ± 20

Values are mean ± se. LVID, left ventricular internal diameter; LVPW, left ventricular posterior wall thickness; LVAW, left ventricular anterior wall thickness; d, diastole; s, systole; FS, fractional shortening. Time, the time point after tamoxifen administration *$P < 0.001$ compared with control.

Supplementary Table 2. Hemodynamics data

	Control	**Tg152**	**Control**	**Tg152**
Time, weeks	1	1	4	4
n	5	5	6	6
HR, beats/min	500 ± 20	510 ± 20	450 ± 20	490 ± 20
ESV, µl	12 ± 2	42 ± 6*	12 ± 2	66 ± 4*
EDV, µl	37 ± 3	69 ± 6*	36 ± 4	79 ± 4*
Systolic function				
EF, %	76 ± 2.8	47.1 ± 3.7*	75.9 ± 3.3	31.1 ± 1.3*
dP/d*t*max, mmHg/s	5,842 ± 375	4,454 ± 676	5,560 ± 218	3,900 ± 566
PRSW, mmHg	102 ± 12	62 ± 5*	96 ± 6	53 ± 10*
ESPVR, mmHg/µl	5.59 ± 0.8	2.17 ± 0.4	6.62 ± 0.7	2.26 ± 0.6
Diastolic function				
−dP/d*t*min, mmHg/s	4,228 ± 328	3,726 ± 483	4,047 ± 267	3,422 ± 485
Tau, ms	9.2 ± 0.6	9.6 ± 1.3	9.5 ± 0.6	11.6 ± 0.9
EDPVR, mmHg/µl	0.10 ± 0.02	0.07 ± 0.10	0.95 ± 0.02	0.67 ± 0.06

Values are mean ± se. HR, heart rate; ESV, end-systolic volume; EDV, end-diastolic volume; EF, ejection fraction; dP/dtmax, maximum value of the pressure derivative; PRSW, preload-recruitable stroke work; −dP/dtmin, opposite of minimum value of the pressure derivative; tau, time constant for isovolumetric relaxation (Weiss's method); ESPVR, slope of end-systolic pressure-volume relationship; EDPVR, slope of end-diastolic pressure-volume relationship. Time, time point after tamoxifen administration. *$P < 0.001$ compared with control.

Supplementary Table 3. M-mode echocardiographic data of LNA-control and LNA-152 treated mice

TAC + LNA-Control			
Time, weeks	2	4	5
n	9	9	9
EF, %	52.9 ± 1.7	43.1 ± 1.7	35.1 ± 2.3
LVPW;s, mm	1.03 ± 0.04	1.09 ± 0.03	1.09 ± 0.03
LVPW;d, mm	0.68 ± 0.03	0.70 ± 0.03	0.66 ± 0.02
LVAW;s, mm	1.03 ± 0.18	1.00 ± 0.08	1.00 ± 0.15
LVAW;d, mm	0.69 ± 0.04	0.66 ± 0.04	0.60 ± 0.01
LVID;d, mm	4.18 ± 0.10	4.58 ± 0.11	4.85 ± 0.13
LVID;s, mm	3.07 ± 0.10	3.61 ± 0.05	4.02 ± 0.06
Heart rate, beats/min	450 ± 10	460 ± 20	460 ± 20
TAC + LNA-152			
Time, weeks	2	4	5
n	10	10	10
EF, %	53.7 ± 1.6	51.1 ± 2.0*	53.4 ± 2.3***
LVPW;s, mm	1.04 ± 0.03	1.08 ± 0.03	1.09 ± 0.03
LVPW;d, mm	0.65 ± 0.02	0.67 ± 0.02	0.68 ± 0.02
LVAW;s, mm	0.96 ± 0.10	0.98 ± 0.13	0.77 ± 0.02
LVAW;d, mm	0.63 ± 0.02	0.64 ± 0.03	0.63 ± 0.02
LVID;d, mm	4.10 ± 0.07	4.39 ± 0.10	4.56 ± 0.12
LVID;s, mm	2.99 ± 0.06	3.26 ± 0.14	3.37 ± 0.29**
Heart rate, beats/min	450 ± 20	460 ± 20	460 ± 10
Sham			
Time, weeks	2	4	5
n	4	4	4
EF, %	60.1 ± 0.2	62.5 ± 2.1	63.2 ± 0.1
LVPW;s, mm	0.97 ± 0.13	1.11 ± 0.03	1.11 ± 0.04
LVPW;d, mm	0.58 ± 0.01	0.61 ± 0.03	0.58 ± 0.06
LVAW;s, mm	0.88 ± 0.04	0.88 ± 0.09	0.94 ± 0.06
LVAW;d, mm	0.54 ± 0.1	0.56 ± 0.05	0.53 ± 0.06
LVID;d, mm	3.92 ± 0.19	3.96 ± 0.11	4.11 ± 0.09
LVID;s, mm	2.68 ± 0.12	2.64 ± 0.09	2.72 ± 0.23
Heart rate, beats/min	440 ± 20	460 ± 20	460 ± 10

Values are mean ± se. LVID, left ventricular internal diameter; LVPW, left ventricular posterior wall thickness; LVAW, left ventricular anterior wall thickness; d, diastole; s, systole. Time, the time point after TAC operation. *$P < 0.05$ compared with LNA-control. **$P < 0.01$ compared with LNA-control. ***$P < 0.001$ compared with LNA-control.

Supplementary Table 4. Quantitative PCR Primer sequences

FORWARD	REVERSE	AMPLICON SIZE (bp)
GTGTAAATGCGCTGGTGACCTC	CTCCAAGTCCTTCAACATCGGC	152
CATCACTGCCACCCAGAAGACTG	ATGCCAGTGAGCTTCCCGTTCAG	153
AGCAACGCCGTGGTGCAGATTC	CGTTGAGGTACACTTGCGGGAT	139
CAACTGTGCTGAGATGGTGACC	TGGCACAGAAGCCAGCTCCAAA	119
GACAGTGGCTACAGGTCGATGA	GGCTCTGTAAGTCCAAAGCAGC	146
CCTGGAGGAAGTGCTCAGCAAG	GTCGTCTTCGTCAGCAGCCAG	130
CTGAGCAGCTATGGCACAGACA	TGCTGTGTCTCCTCGTTGAAGC	125
CGCCTGAGAAAGTCTGATGTCG	GGAAGCAGACTTCTCCAGGTTC	157
GATCGACCTCTACAGCAACCAG	GCTCTTGCTTCAGACTCTGTGG	132
GGAGATACGGATTGCACAGGAG	CTCCATACCAGACGGAAGATAAAG	156
GACCAATGAGGTGGAGATTCGC	GAGGAACCACACTGTCCAGAAG	140
GCATCTCTGACTTCCTGGACAAG	CTTGGTCCAGTTGAGCAGGATG	122
CTTCAACAAGGTCAACAAGCAC	AGGCGCTGCTTAAACCATT	105
GGCAACTTAGCCATCTGCGTGA	GTGGAACTCCATGCTATCACACC	126
GGAGGATAGATGTGCTCTGGAAC	AGTGAGGATGGAGACCGTGGTG	133
TGCTGACAGAGGCACCACTGAA	CAGTTGTACGTCCAGAGGCATAG	138
CCCTTAGCCACCCAAGCAGCT	TGGTACGCGCTGTTCCAGAAGG	136
TGGTGGACTCAGAGAAGGATGC	AACTCCACCAGAGTGTCTGCAG	133
CCCTATCTCTGATACCGTTGTCC	TGCCGCAACTACTGTGATTCGG	145
TCTTGGTTCCCTGGCGTACTCT	GTGAGTGTCACTCTCCAGTTTGC	131
CCACTCACCATCTGCTTTCCTG	GGCTGTAGACTTCCTTGTGAGC	118
GCTTCTCCAACTGGACCTCAAAC	ACGAGGAGCACCGTGAAGATGA	103
TACAGTGCGGTGTCCAACACAG	TGCTTCCTCAGTCTGCTCACTC	126