

Table S3. ARNi administration in animal models of anthracycline-induced cardiotoxicity.

Paper by	Animal model	Group size	Dox protocol	Gavage protocol	Drugs + Dosage (mg/kg/d)	Other findings (in comparison to DOX + Vehicle groups)
Boutagy [1]	11-12-wk-old ♂ Wistar rats	<i>n</i> = 25 each	2.15 mg/kg ip every 3 rd day for 3 wks (up to 15 mg/kg)	Started on the day of Dox, cont. for 6 wks	Sham - no Dox Dox + Vehicle Dox + ARB 31 Dox + ARNi 68	↑ LVEF in ARNi ↓ Myocyte vacuolation in ARNi and ARB ↓ Myocardial fibrosis in ARNi and ARB at 4 wks (no longer seen at 6 wks) ↓ Capillary density in ARNi at 6 wks ↓ MMP activity in ARNi at 4 wks ↓ Myocyte CSA and heart weight in all Dox-receiving groups No differences in cellular apoptosis between groups
Dindas [2]	7–8-wk-old ♂ Balb-c mice	<i>n</i> = 6 each	20 mg/kg ip. – 1 dose on 5th day of gavage	Started 4 days before Dox, cont. for 9 days	Vehicle ARNi 80 Dox + Vehicle Dox + ARNi 80	↓ Degenerative changes and streaking in cardiomyocytes in Dox + ARNi ↓ QRS duration, ST interval and QT/PQ index in Dox + ARNi ↓ NT-proBNP, TNF- α , IL-1 β , IL-6, caspase 3 immunoreactivity in DOX + ARNi ↓ Total oxidant status and ↑ total antioxidant status in DOX + ARNi
Kim [3]	♂ Sprague-Dawley rats	<i>n</i> = 8 each	5 mg/kg ip. q1w for 3 wks (up to 15 mg/kg)	Started 1 day before Dox, cont. for 6 wks	Vehicle Dox + Vehicle Dox + ARNi 60	↓ Cardiomyocyte apoptosis in ARNi group ↓ Endoplasmic reticulum stress levels in ARNi group ↓ Serum troponin I and NT-proBNP levels in ARNi group
Miyoshi [4]	♂ Sprague-Dawley rats	<i>n</i> = 15 each	1.5 mg/kg ip. for 10 days (up to 15 mg/kg) followed by 8 days of no treatment	Started on the day of Dox, cont. for 18 days	Sham - no Dox Dox + Vehicle Dox + Val 31 Dox + Sac/Val 68	No differences in LVEF and FS ↑ Cardiomyocyte cross-sectional area in ARNi ↓ Cardiac fibrosis in ARNi ↓ Cardiac TNF α and ANP mRNA expression in ARB and ARNi ↓ Collagen I mRNA expression in ARNi ↓ Cardiac troponin T and NT-proBNP levels in ARNi ↓ Cardiac reactive oxygen species levels in ARNi ↑ Phosphorylation of AMPK and ↓ Bax/Bcl-2 ratio in ARNi
Maurea [5]	♀ C57Bl/6 mice	<i>n</i> = 6 each	2.17 mg/kg ip. daily for 10 days	Cont. for 10 days	Sham Sac/Val 60 Dox Dox + Sac/Val 60	ARNi improved EF and prevented the reduction of radial and longitudinal strain ↓ Cardiac expression of NLRP3, MyD88, DAMPs, and NF- κ B in ARNi ↑ Expression of phosphorylated AMPK in ARNi ↓ Levels of Calgranulin S100 and galectine-3 in ARNi
Xia [6]	8-wk-old ♂ Balb-c mice	<i>n</i> = 7 each	15 mg/kg ip. 3x/wk for 2 wks	Started the day after Dox, cont. for 4	Vehicle Dox + Vehicle	↓ Cardiac hypertrophy, myocardial fibrosis and cellular apoptosis in ARNi ↓ Heart weight/body weight ratio and ↑ heart weight/tibial length ratio in

				wks,	Dox + ARNi 80	ARNi
						↑ Single cardiomyocyte contractile function in ARNi ↓ Pathologic morphologic changes to mitochondria and ↓ myocardial Drp1 expression in ARNi ↓ Cleaved caspase 3 level in ARNi
Ye [7]	8-wk-old ♂ C57BL/6 mice	<i>n</i> = 7 each	5 mg/kg ip. q1w for 3 wks (up to 15 mg/kg)	Started the day after Dox, cont. 6 wks,	Vehicle Dox + Vehicle Dox + ARNi 60 TLR2 KO + Vehicle TLR2 KO + Dox	↑ LVEF in ARNi, TLR2 KO, and TLR2 KO + Dox ↓ Thinning of the ventricular wall and enlargement of the heart cavity in ARNi and TLR2 KO ↓ Myocardial fibrosis in ARNi and TLR2 KO ↓ Myocardial collagen I and TGF- β protein levels in ARNi and TLR2 KO ↓ Myocardial TNF α and NF- κ B levels in ARNi and TLR2 KO
Yu [8]	12-wk-old ♂ New Zealand white rabbits	<i>n</i> = 5 each	1.5 mg/kg iv. q1w for 5 wks (up to 7.5 mg/kg)	Started one wk after Dox, cont. for 4 wks	Vehicle Dox + Vehicle Dox + ARNi 5 Dox + ARNi 10	↓ PR segment, QRC segment prolongation, QT interARB and QT/PQ index in ARNi groups ↓ Serum BNP level in ARNi groups ↑ Activity of superoxide dismutase and catalase and ↓ lipid peroxidation in ARNi groups

Abbreviations: AMPK – adenosine monophosphate-activated protein kinase; ANP – atrial natriuretic peptide; ARB – valsartan; ARNi – sacubitril/valsartan; BNP – brain natriuretic peptide; CSA – cross-sectional area; Dox – doxorubicin; Drp1 – dynamin-related protein 1; KO – knock-out; IL – interleukin; LVEF – left ventricle ejection fraction; NF- κ B - nuclear factor kappa-light-chain-enhancer of activated B cells; NT-proBNP – N-terminal prohormone of brain natriuretic peptide; TGF β – transforming growth factor β ; TNF α – tumor necrosis factor α ; q1w – every week; wk – week. Symbols: ↑ / ↓ – significantly increased/decreased, ♂ – male, ♀ – female.

References

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