**Supplemental Figure 1** Immuno-neutralization of heart-derived DDT attenuates cardiac function recovery following ischemia-reperfusion. Isolated mouse hearts were treated with anti-DDT or non-immune control IgG prior to 15 min ischemia and 30 min reperfusion. Left ventricular (LV) developed pressure (LVDP) (A), heart rate (HR) (B), LV dp/dt (C) and LV –dp/dt (D) were recorded at baseline for 10 min prior to ischemia and during the last 10 min of reperfusion. Data are means ± SEM, n = 4-6 per group. * P < 0.05 comparing ischemic conditions with IgG vs. anti-DDT treatment.
Supplemental Figure 2  Immuno-neutralization of endogenous secreted DDT inhibits hypoxia-induced AMPK activation in cardiomyocytes. Adult rat ventricular cardiomyocytes were treated with DDT or non-immune IgG antibody (100 µg/ml) for 30 min and then incubated under aerobic or hypoxic conditions for an additional 30 min. Cell lysates underwent immunoblotting for phospho and total AMPK and ACC. Values are means ± SEM, n=5 per group. * P < 0.05 vs. control. # P < 0.05 vs. non-immune IgG with hypoxia.
Supplemental Figure 3 The morphology and histology of DDT cardiac specific knockout hearts. Ex vivo photographs (left panel) and H&E staining of left ventricular sections (right panel) from control Ddt floxed (Ddt^{fl/fl}) and MHC-Cre (Myh6-Cre Ddt^{+/-}) mice and cardiomyocyte-specific DDT knockout (Myh6-Cre Ddt^{fl/fl}) mice at 8 weeks of age.
Supplemental Figure 4 Impaired cardiac contractile function in mouse hearts from DDT cardiomyocyte specific knockout mice following ischemia-reperfusion. Hearts from control Ddt floxed (Ddt^{fl/fl}) and MHC-Cre (Myh6-Cre Ddt^{+/+}) mice, and DDT knockout (Myh6-Cre Ddt^{fl/fl}) mice were subjected to ex vivo ischemia (15 min) and reperfusion (30 min). In a separate group, cardiomyocyte-specific DDT knockout hearts were also perfused with buffer containing rDDT (50 ng/ml). Left ventricular developed pressure (LVDP) (A), heart rate (HR) (B), LV dp/dt (C) and LV –dp/dt (D) were recorded. Data are means ± SEM, n = 4-6 per group. * P < 0.05 vs. DDT knockout.
Supplemental Figure 5  

**rDDT stimulates AMPK activation and glucose uptake.**  
(A) Excised rat left ventricular papillary muscles were incubated with rDDT (50 to 400 ng/ml) for 15 min. (B) Muscles were treated with 400 ng/ml rDDT for 5 to 60 min. Muscle homogenates were then immunoblotted for phospho and total AMPK and ACC. (C) Glucose uptake was measured with $^3$H-2-deoxyglucose in the presence of 5 mM glucose. Values are means ± SEM, n=4 per group, *P < 0.05 vs. control.
Supplemental Figure 6 rDDT treatment transiently increases intracellular calcium in unpaced isolated adult rat cardiomyocytes. Intracellular calcium imaging was performed in rat adult ventricular cardiomyocytes pre-incubated with fura-2-acetoxymethyl ester (2 µM), before (upper left panel) or after (upper right panel) the addition of rDDT (400 ng/ml). The ratio of 340 to 380 nm fluorescence intensity \( R_{340/380} \) was quantified as a relative measure of intracellular calcium concentration ([Ca\(^{2+}\)]\_i) (lower panel graph).
Supplemental Figure 7 Differential cardiac function recovery after ischemia in Mif<sup>−/−</sup> and Cd74<sup>−/−</sup> hearts. Hearts from wild type (WT), MIF knockout (Mif<sup>−/−</sup>) and CD74 knockout (Cd74<sup>−/−</sup>) mice were perfused <em>ex vivo</em> at normal flow for 30 min and then subjected to ischemia (15 min) with or without subsequent reperfusion (30 min). Left ventricular developed pressure (LVDP) (A), heart rate (HR) (B), LV dp/dt (C) and LV –dp/dt (D) were recorded at baseline for 10 min prior to ischemia and during the last 10 min of reperfusion. Data are means ± SEM, n = 4-6 per group. * P < 0.05 vs. WT; # P < 0.05 vs. Mif<sup>−/−</sup>. 

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**Legend:**
- **LVDP (mm Hg):** Pre-ischemia: WT, Mif<sup>−/−</sup>, Cd74<sup>−/−</sup>
  - WT: 100 ± 10
  - Mif<sup>−/−</sup>: 90 ± 10
  - Cd74<sup>−/−</sup>: 80 ± 10

- **Heart rate (times/s):** Pre-ischemia: WT, Mif<sup>−/−</sup>, Cd74<sup>−/−</sup>
  - WT: 500 ± 50
  - Mif<sup>−/−</sup>: 450 ± 50
  - Cd74<sup>−/−</sup>: 400 ± 50

- **LV dp/dt (mm Hg/s):** Pre-ischemia: WT, Mif<sup>−/−</sup>, Cd74<sup>−/−</sup>
  - WT: 6000 ± 600
  - Mif<sup>−/−</sup>: 5000 ± 600
  - Cd74<sup>−/−</sup>: 4000 ± 600

- **LV –dp/dt (mm Hg/s):** Pre-ischemia: WT, Mif<sup>−/−</sup>, Cd74<sup>−/−</sup>
  - WT: -500 ± 50
  - Mif<sup>−/−</sup>: -400 ± 50
  - Cd74<sup>−/−</sup>: -300 ± 50
Supplemental Figure 8 The effects of DDT and MIF on cardiac function in WT and Cd74−/− hearts. Mouse hearts were perfused with or without 50 ng/ml of rDDT (A) or rMIF for 15 min (B). Data are means ± SEM, n = 4-6 per group. * P < 0.05 vs. WT.
Supplemental Figure 9  *DDT pretreatment prior to ischemia improves post-ischemic cardiac function.* Hearts isolated from WT mice were treated with saline (CON) or rDDT (50 ng/ml) for 15 min and then subjected to 20 min global ischemia followed by 30 min reperfusion. Left ventricular developed pressure (LVDP) (A), heart rate (HR) (B), LV dp/dt (C) and LV –dp/dt (D) were recorded at baseline for 10 min prior to ischemia and during the last 10 min of reperfusion. Data are means ± SEM, n = 4-6 per group. * P < 0.05 vs. WT.
Supplemental Figure 10 DDT requires AMPK activation to reduce injury during ischemia-reperfusion. Hearts isolated from AMPK kinase-inactivated “kinase-dead” (KD) mice Tg(Ckmm-AmpkαK45R) were treated with saline (CON) or rDDT (50 ng/ml) for 15 min and then subjected to 20 min global ischemia followed by 30 min reperfusion. (A) Cardiac contractile function was evaluated as the product of LV developed pressure (LVDP) and heart rate (HR). (B) Triphenyl tetrazolium chloride vital staining was used to quantify the extent of necrosis (infarct area calculated as a percentage of ventricular area). Data are means ± SEM, n=4-6 per group.