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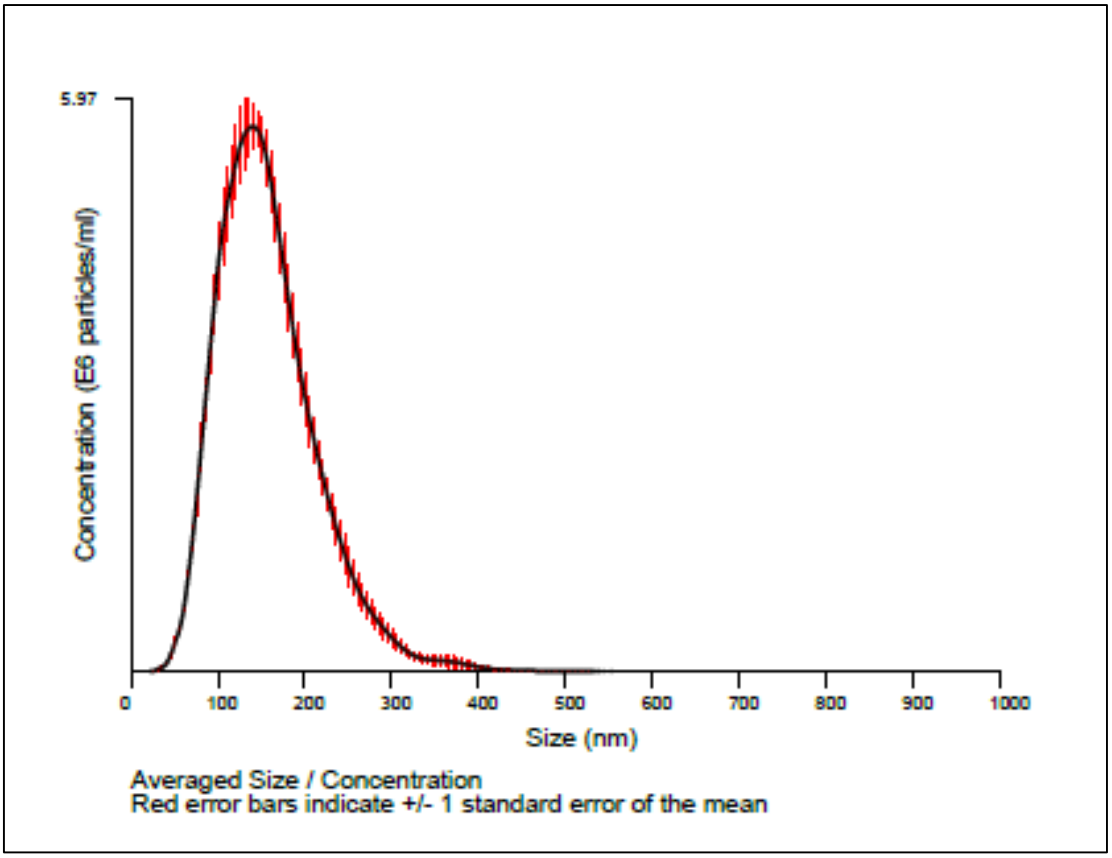
Appendix Figure S1. CDC-EVs and NHDF-EVs size/concentration.

A



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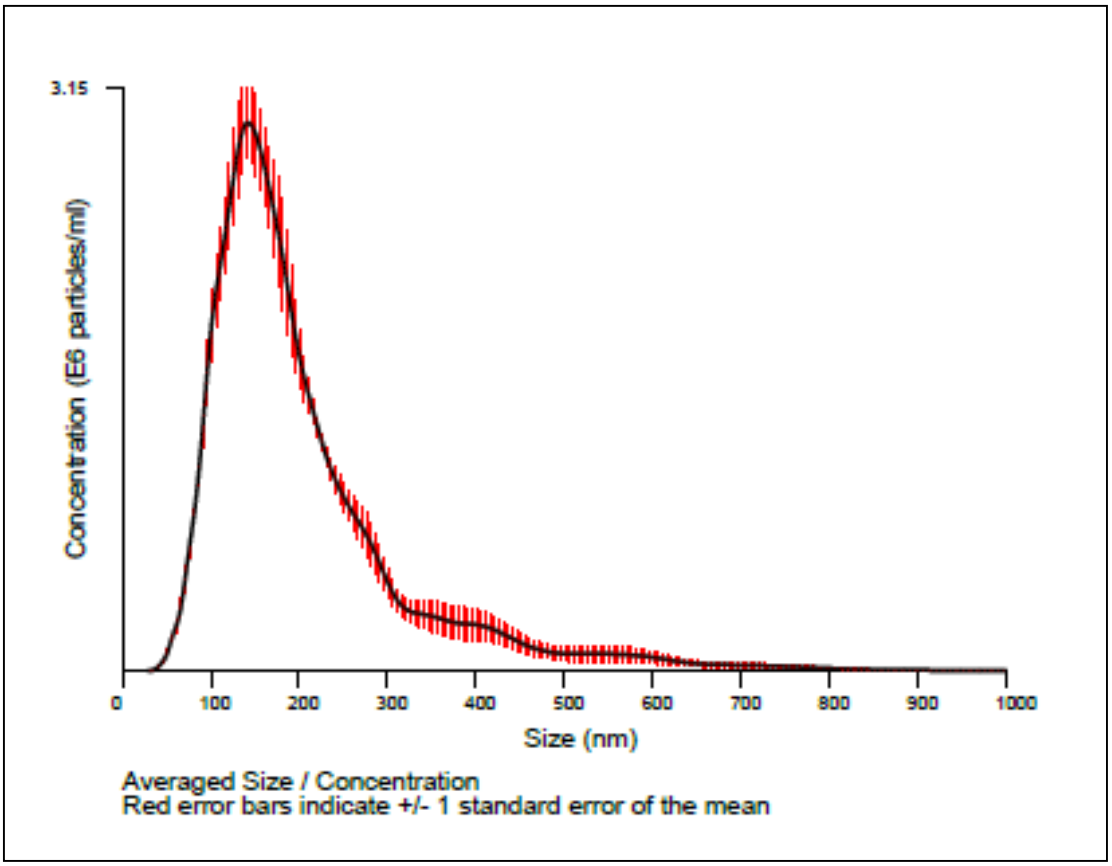
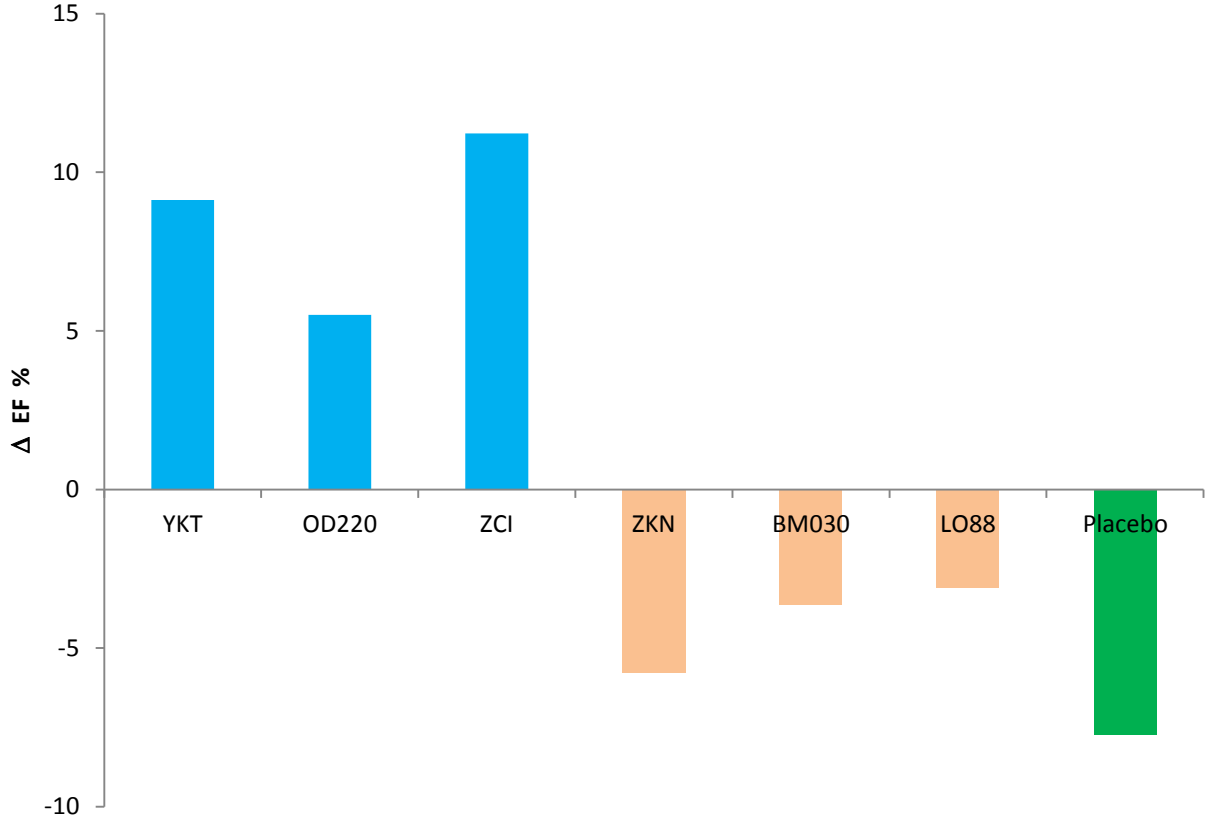
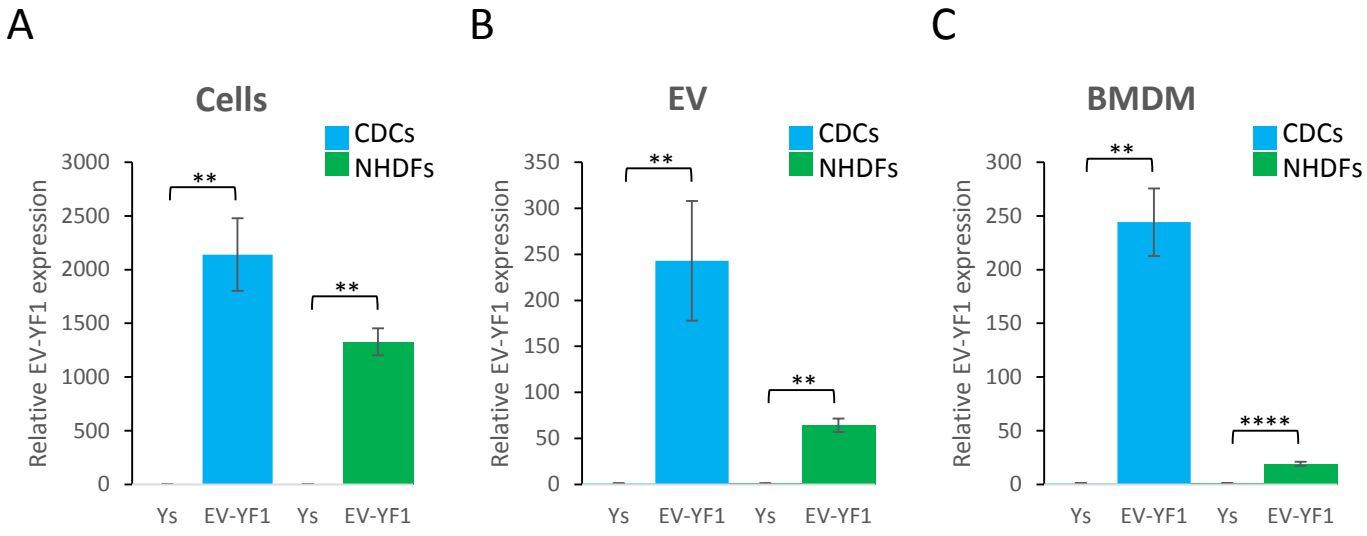


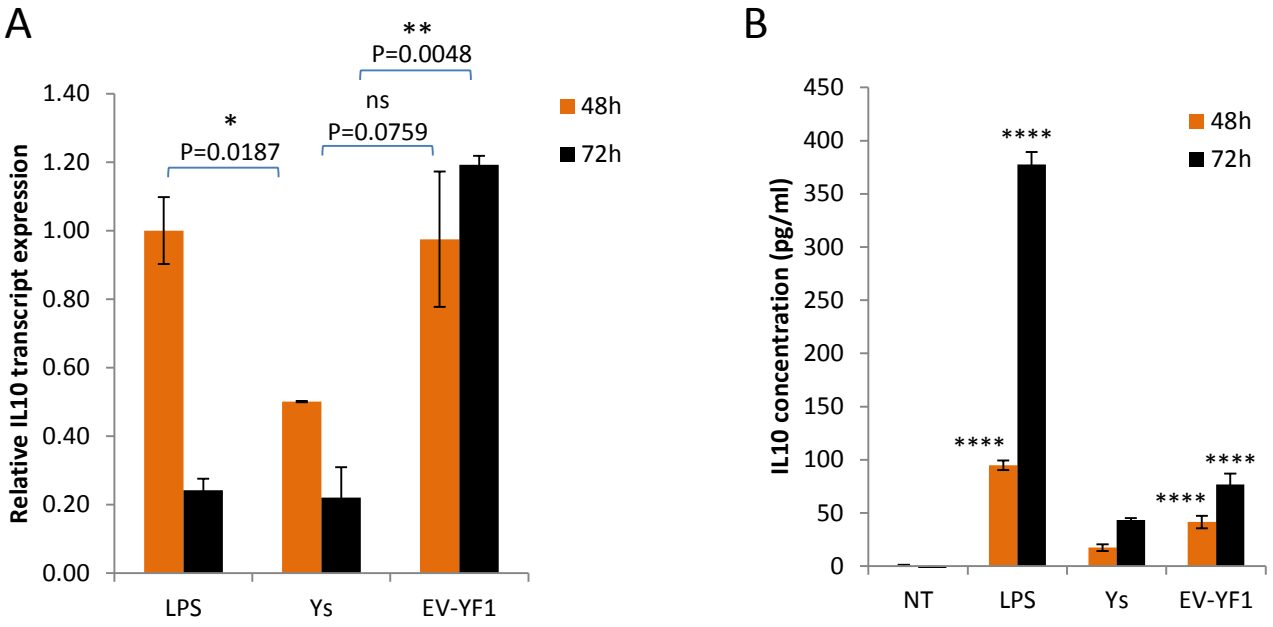
Appendix Figure S2. CDCs potency from different donors *in vivo*.



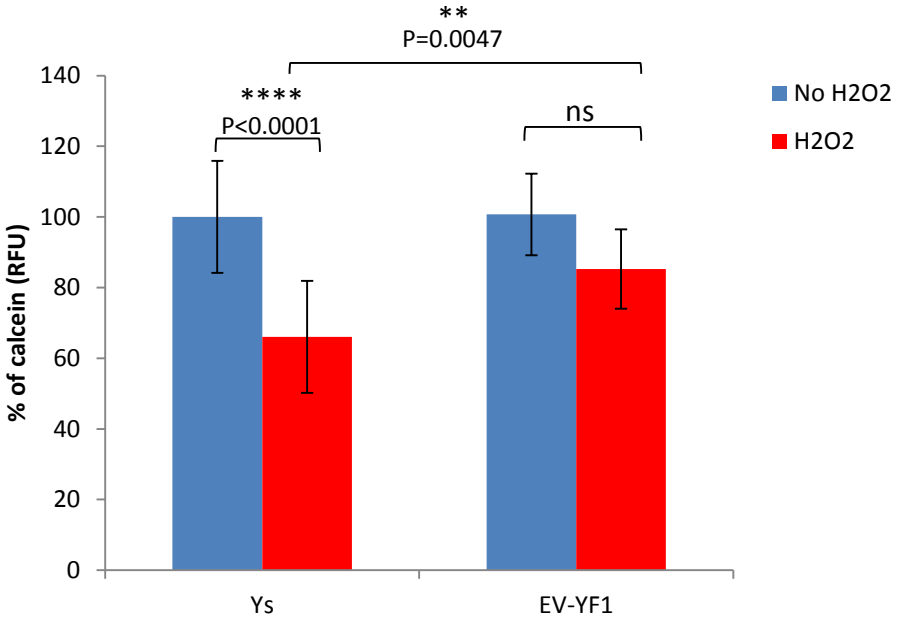
Appendix Figure S3. EV-YF1 transfer in control NHDFs compared to CDCs.



Appendix Figure S4. EV-YF1 modulates IL-10 expression.

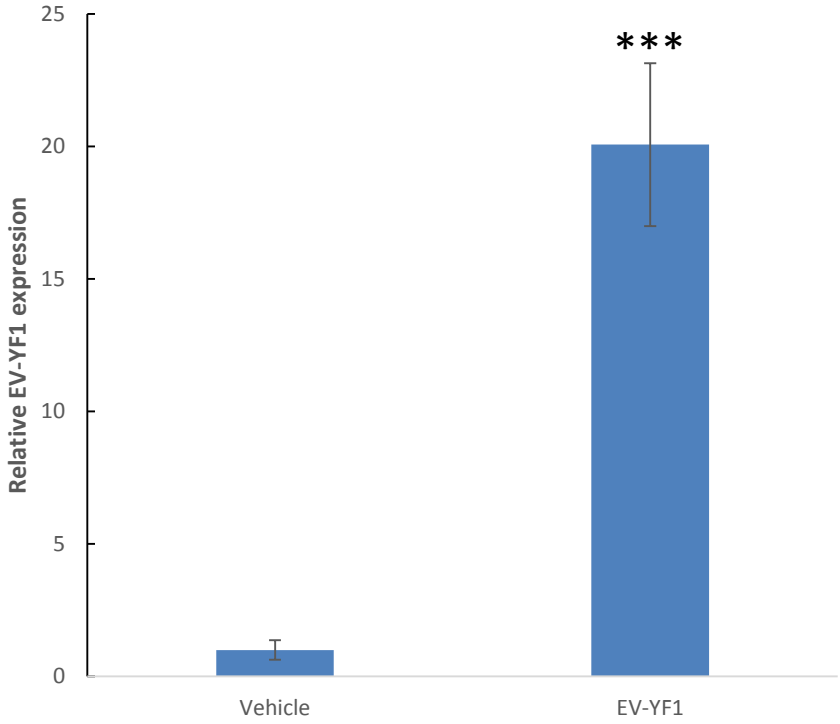


Appendix Figure S5. EV-YF1 induced direct protection of cardiomyocytes from oxidative stress.

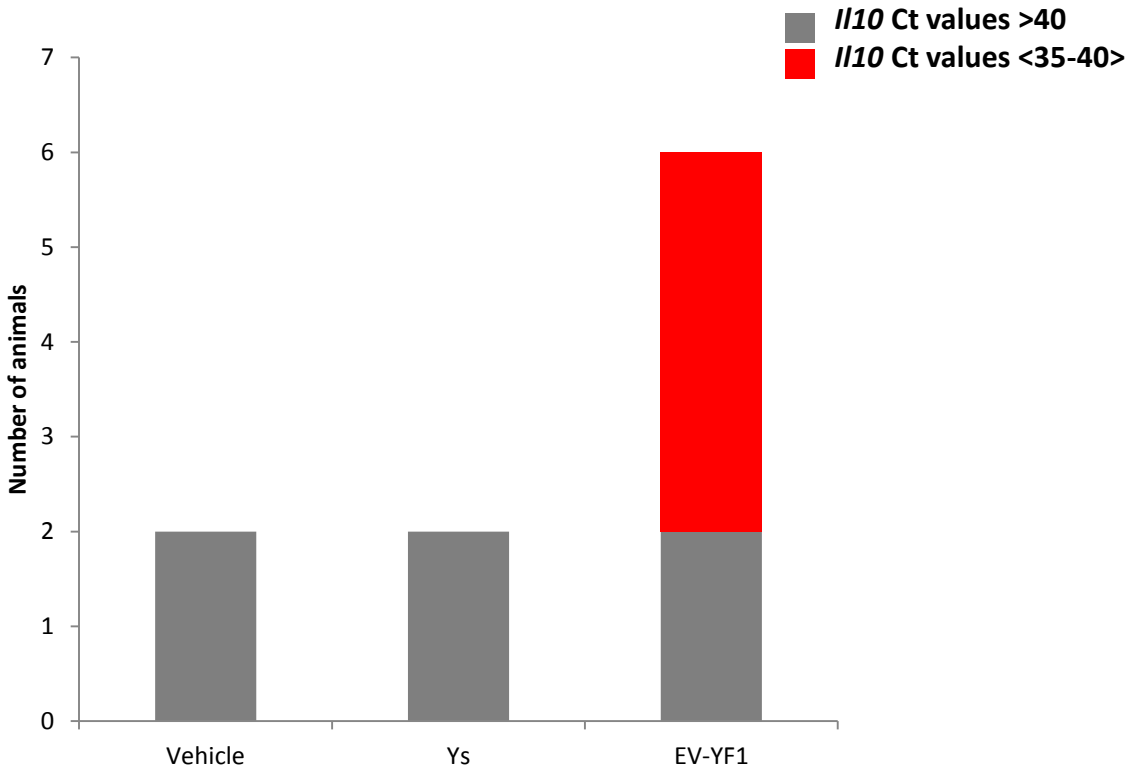


Appendix Figure S6. Cardiac *Il10* and EV-YF1 expression after I/R.

A

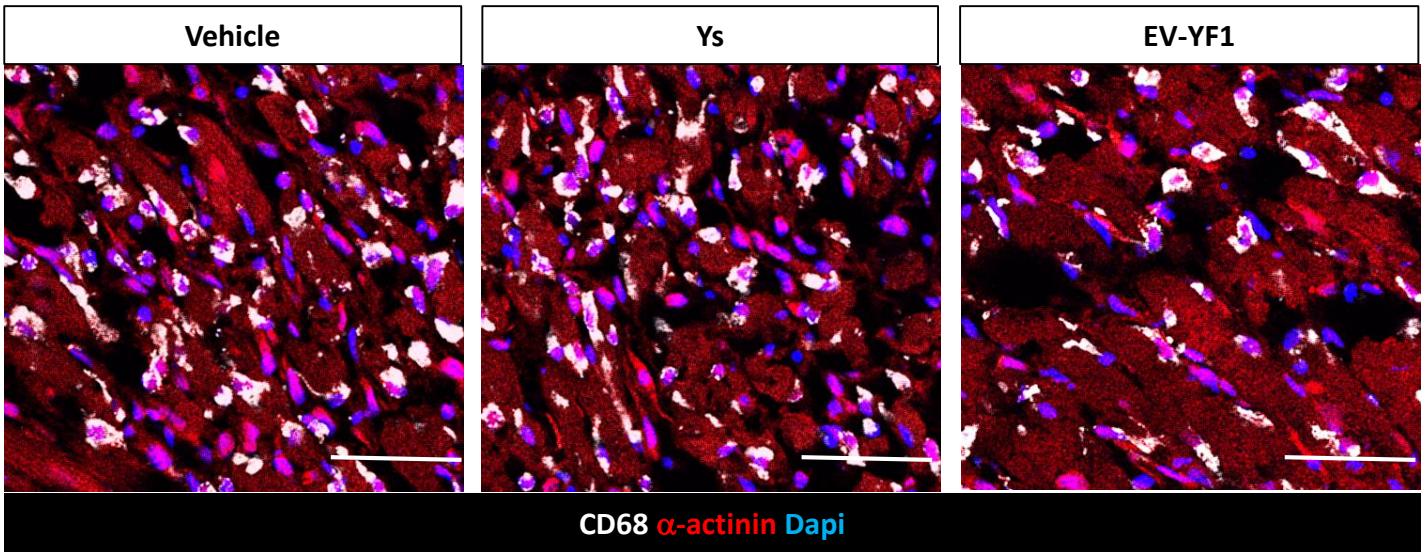


B



Appendix Figure S7. EV-YF1 reduced the number of inflammatory macrophages CD68+ and apoptotic cardiomyocytes in scar area.

A



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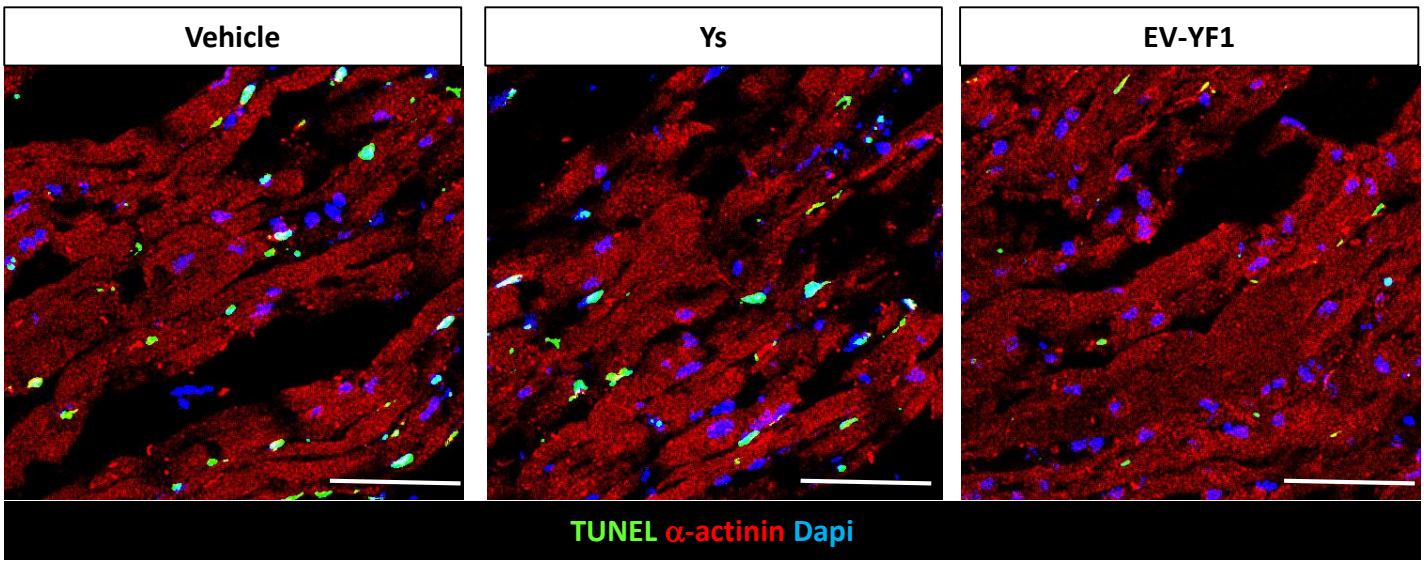
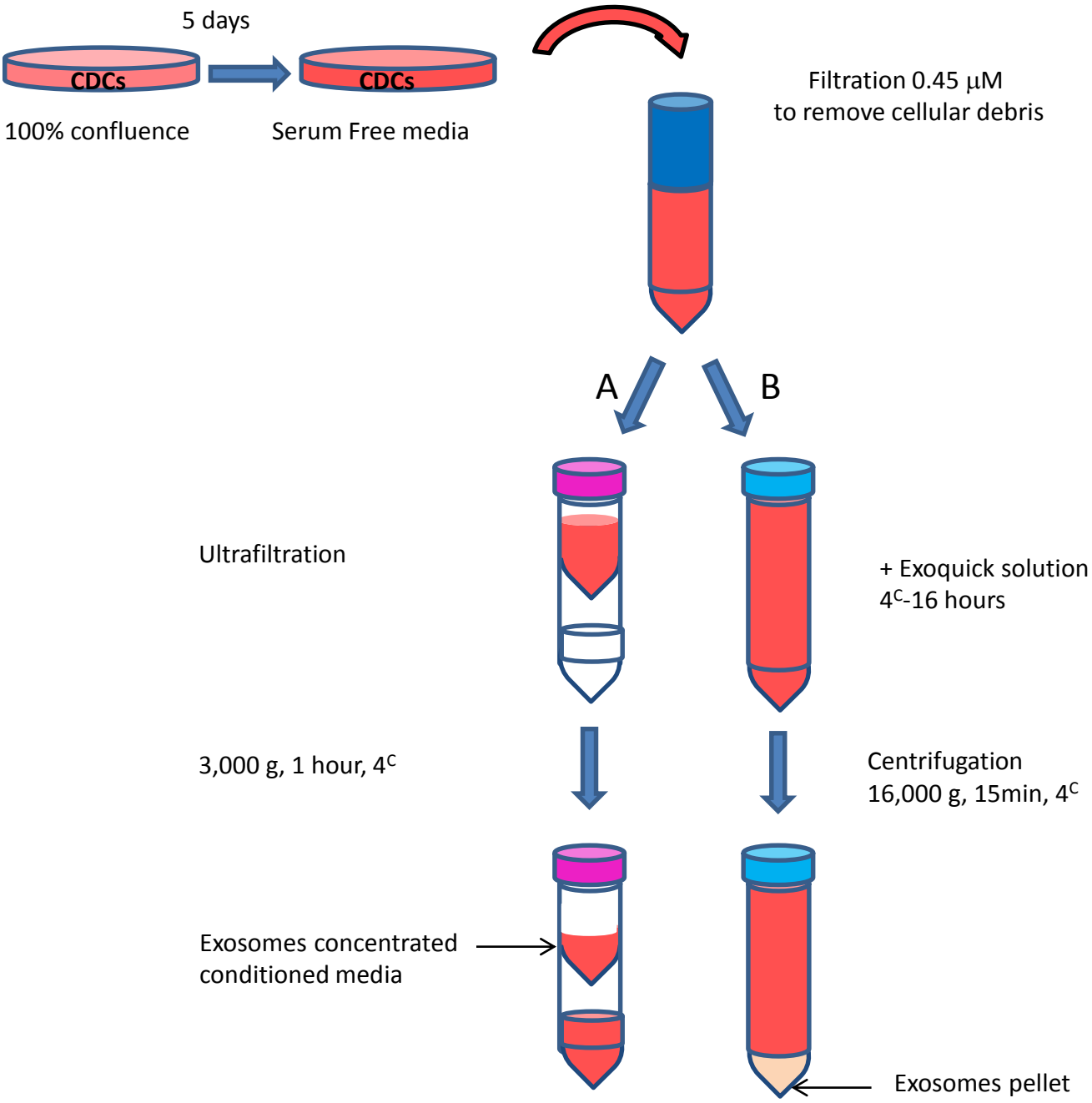


Appendix Figure S8. Exosome isolation protocol.



APPENDIX FIGURE LEGEND

Appendix Figure S1 - CDC-EVs and NHDF-EVs size/concentration.

A, B CDC-EVs (A) and NHDF-EVs (B) size distribution and particle number were analyzed by the LM10-HS system (NanoSight). Histogram of CDC-EVs diameter, representative of results from a total of 6 donors.

Appendix Figure S2 - CDCs potency from different donors *in vivo*.

Percent change in ejection fraction (baseline 2 hrs post-MI to 21 days, ΔEF%) post-MI with CDC treatment (6 different donors, n=8 animals/donor) or placebo (saline, n=14 animals). Potent CDCs (ZCI, YKT, OD220) were delineated from non-potent CDCs (LO88, BM030, ZKN) by positive ΔEF%.

Appendix Figure S3. EV-YF1 transfer in control NHDFs compare to CDCs.

A, B, C Expression of EV-YF1 by qPCR in cells (A), EVs (B) and BMDMs (C) according the same protocol described in Figure 4A for CDCs (blue) and NHDFs (green). Results depict the mean ± SEM of n=3. (Groups were compared using 2-tailed, unpaired, Student's t test; (A) (CDC: p=0.0013; NHDF: p=0.0088), (B) (CDC: p=0.0059; NHDF: p=0.0068) and (C) (CDC: p=0.0019; NHDF: p<0.0001).

Appendix Figure S4 – EV-YF1 modulates IL-10 expression.

A *Il10* gene expression in BMDMs at 48 and 72 hrs after treatment with LPS ([1μg/ml]; positive control) or transfection with EV-YF1 or Ys. Results depict the mean ± SEM of two independent experiments, n=6. (Groups were compared using 1-way ANOVA followed by Tukey's multiple comparisons test).

B IL-10 protein secretion from conditioned media in (A), as determined by ELISA. Results depict the mean ± SEM of an experiment representative of two independent experiments, n=6. (Groups were compared using 1-way ANOVA followed by Tukey's multiple comparisons test; ****p<0.0001).

Appendix Figure S5 - EV-YF1 induced direct protection of cardiomyocytes from oxidative stress. Graph depicts viability of NRVMs overexpressing EV-YF1 (or Ys) undergoing oxidative stress. NRVMs were transfected with EV-YF1 (or Ys) 48 hrs prior 15 min of H_2O_2 (75uM) treatment, then viability was assessed after 6 hrs by calcein staining. Results depict the mean ± SEM of three independent experiments in triplicate, n=9. (Groups were compared using 1-way ANOVA followed by Tukey's multiple comparisons test).

Appendix Figure S6 - Cardiac *Il10* and EV-YF1 expression after I/R.

A EV-YF1 expression was assessed in ischemic/reperfused heart by qPCR one hour after injection. Results depict the mean ± SEM of two animals per group. (Groups were compared using 2-tailed, unpaired, Student's t test; ***p=0.0007).

B *Il10* gene expression in hearts of animals treated with EV-YF1, Ys or vehicle 24h after I/R. Only animals treated with EV-YF1 revealed *Il10* expression (Ct values between 35 and 40); no *Il10* expression was detected in heart treated with Ys or vehicle (Ct values >40).

Appendix Figure S7. EV-YF1 reduced the number of inflammatory macrophages CD68+ in scar area.

Representative immunohistochemical images of the infarct tissue from animals treated with vehicle, Ys, or EV-YF1.

A Macrophage infiltration (Fig 7D). CD68 (white), α-actinin (green), and DAPI (blue). Scale bar: 10μm.

B TUNEL analysis (Fig 7E). TUNEL (green), α-actinin (red), and DAPI (blue). Scale bar: 10μm.

Appendix Figure S8 - Exosome isolation protocol.

A Exosomes-enriched EVs fraction concentrated from conditioned media are used to treat cells directly or after transfection of exosomes.

B Exosomes-enriched EVs fraction pellet submitted to RNA-seq.