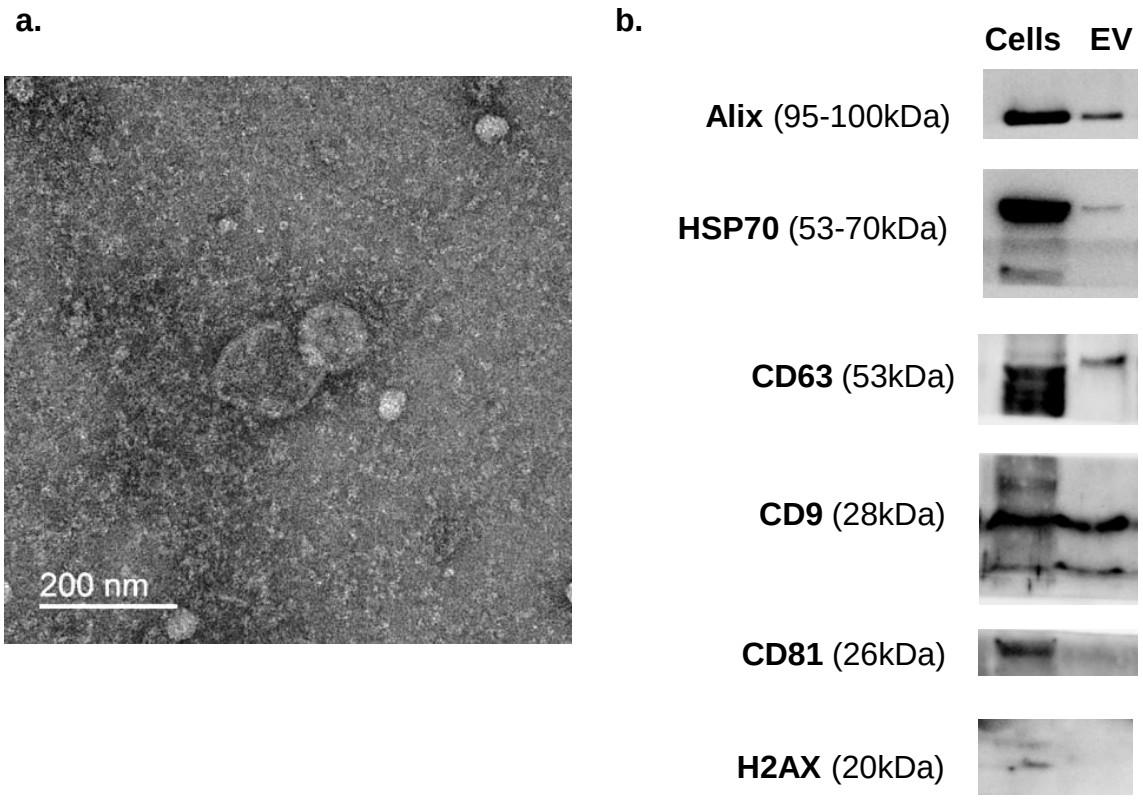
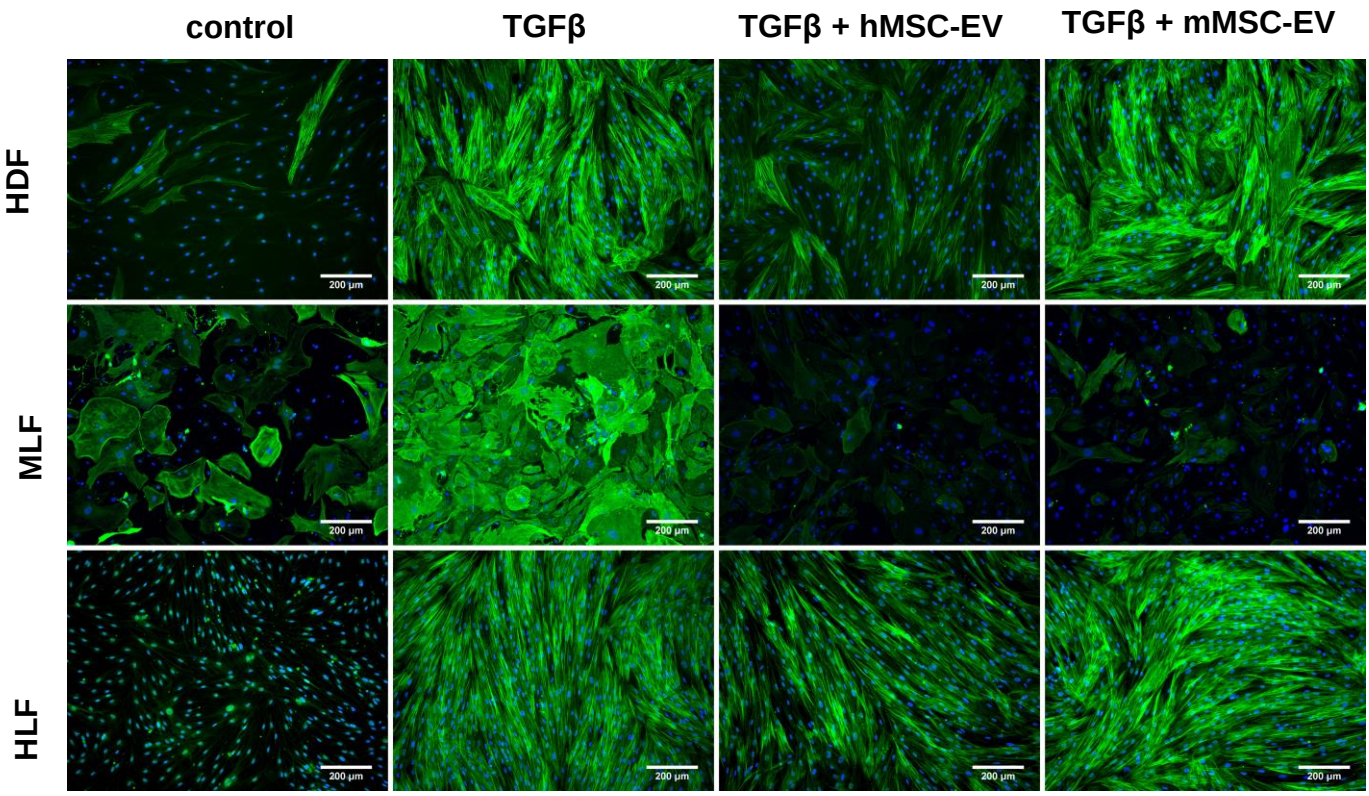
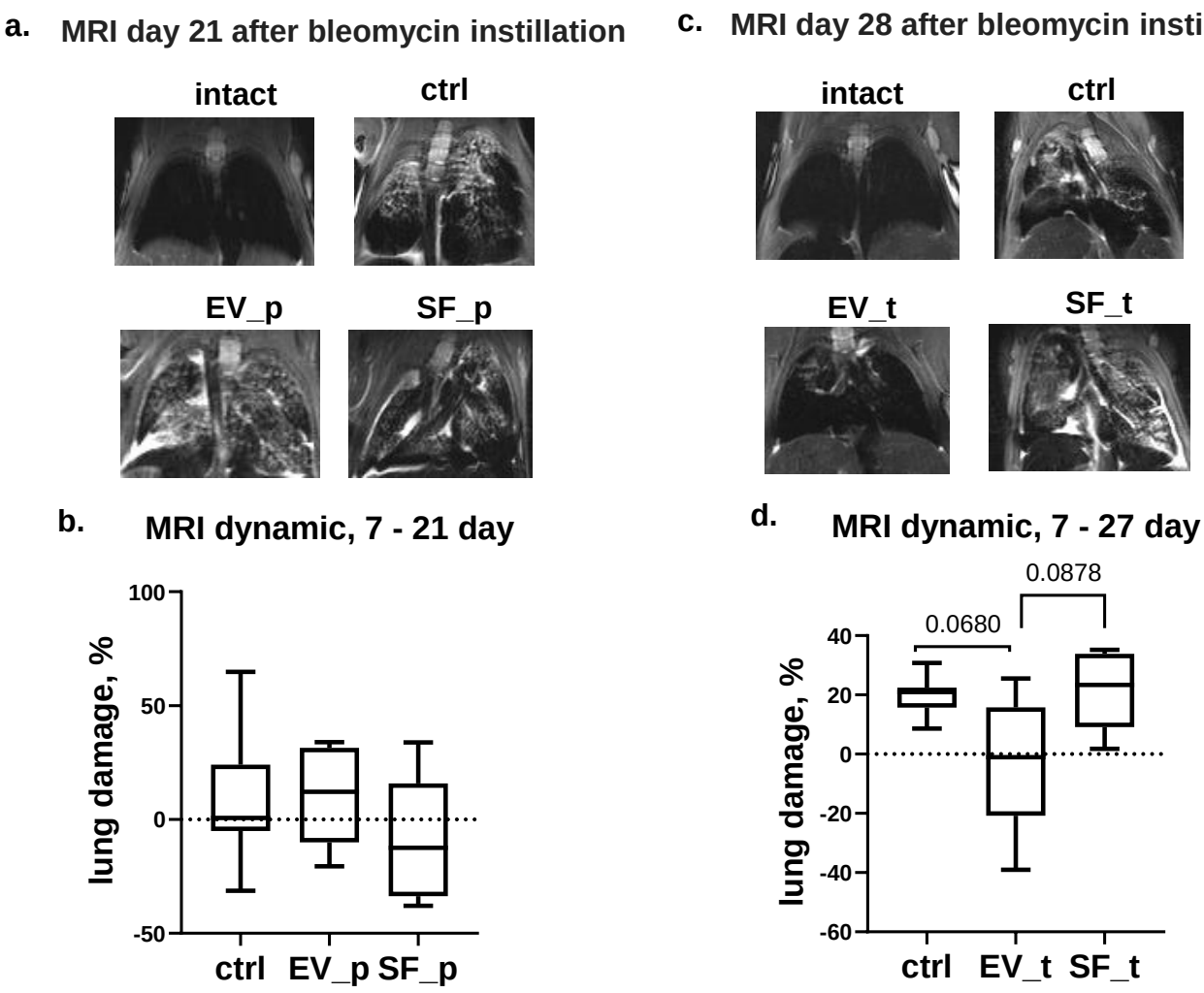


Supplementary Fig. 1. MSC-EV characteristics.

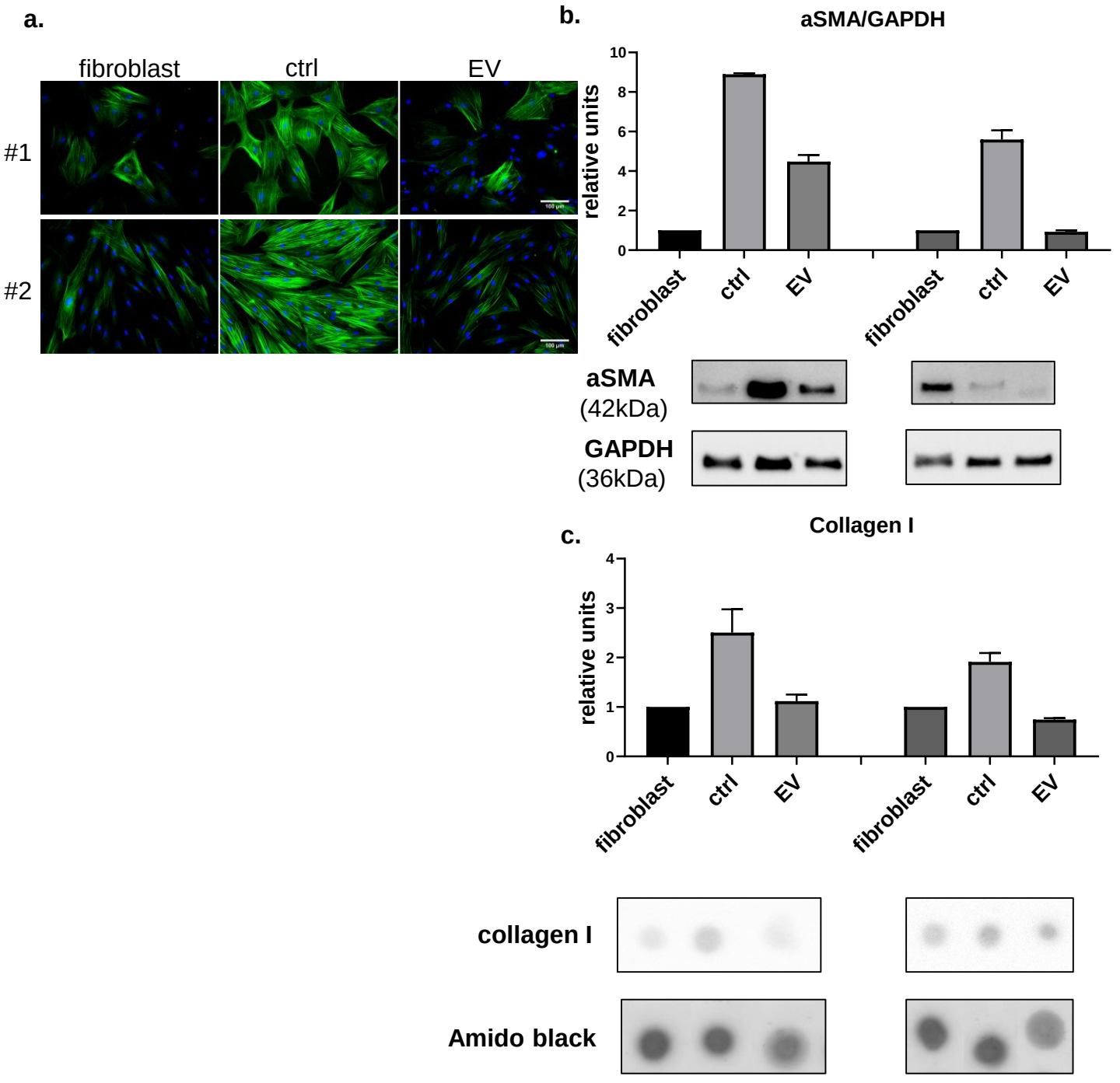
a. Representative image of hMSC-EV visualized *via* transmission electron microscopy (TEM). Scale bar = 200 nm. **b.** Immunoblotting for Alix, HSP70, CD63, CD9, CD81, and H2AX in hMSC-EV and MSC lysates. **c.** Size and concentration analysis of non-concentrated hMSC-EV after 2 days of conditioning (green) and control aliquots of MSC-CM after 30 min of conditioning (blue) by NTA using ZetaView.



Supplementary Fig. 2. Comparison of murine and human MSC-EV antifibrotic effects *in vitro*. Representative images of HDF, MLF, and HLF immunocytochemical analysis for the αSMA expression. The cells were incubated with TGFb for 4 days (TGFb) in the presence of human MSC-EV (TGFb + hMSC-EV) or murine MSC-EV (TGFb + mMSC-EV) and compared with the cells cultured without TGFb (control). Scale bar = 200 μm.

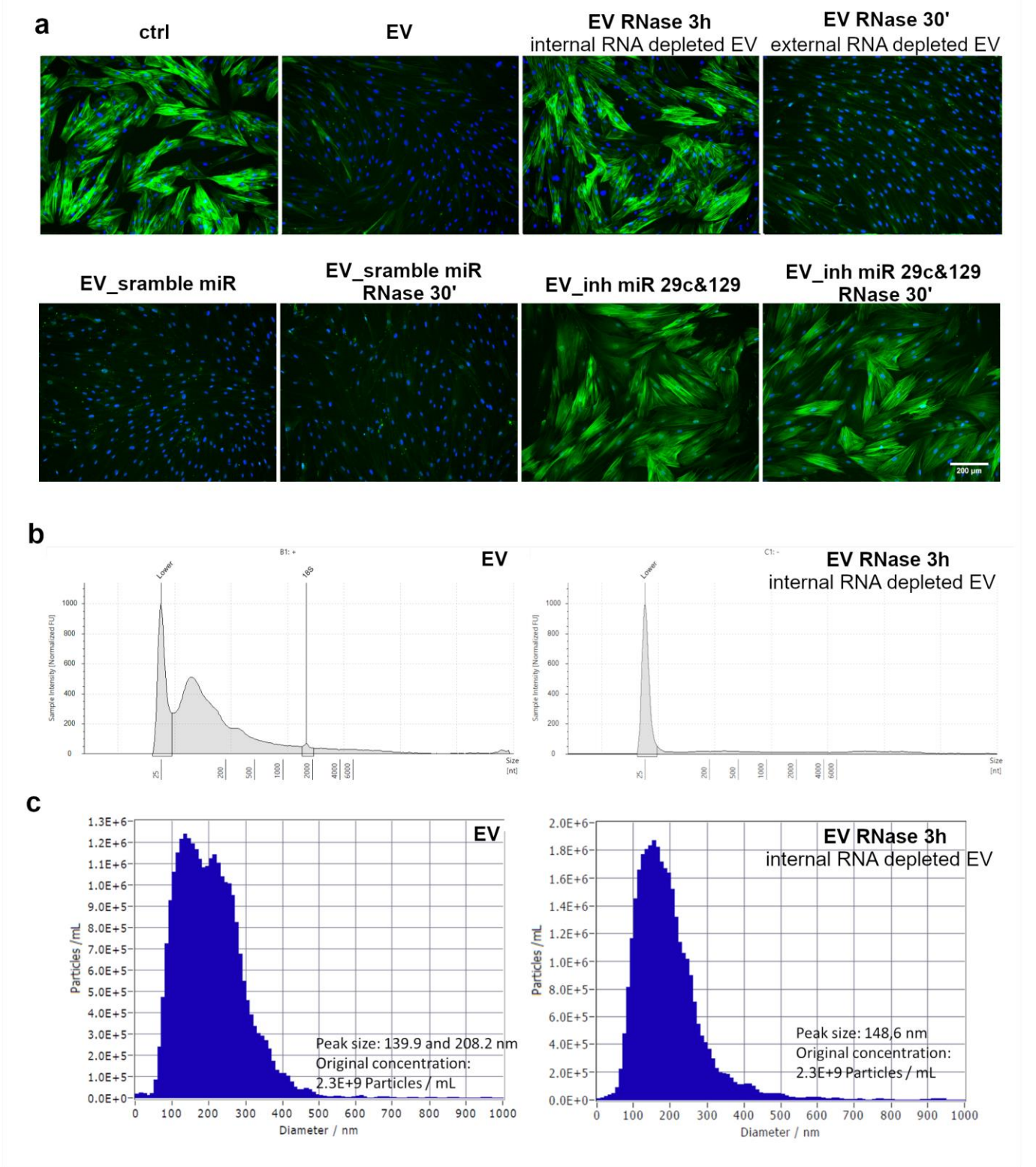


Supplementary Fig. 3. Dynamic changes in the lung tissue density in mice with bleomycin-induced pulmonary fibrosis treated with MSC-EV measured *via* MRI. a. Representative MR images for the fibrosis prevention groups. **b.** Quantification of dynamic changes in the lung tissue density measured *via* MRI in **the** fibrosis prevention groups. **a–b Ctrl** (DMEM 1 day after bleomycin administration), n = 11; **EV_p** (MSC extracellular vesicles 1 day after bleomycin administration), n = 9; **SF_p** (MSC soluble factors 1 day after bleomycin administration), n = 6, n = biological independent animals per group. Number of analyzed fields of view per sample = 3–10 for each animal. **c.** Representative MR image for the fibrosis treatment groups. **d.** Quantification of dynamic changes in the lung tissue density measured *via* MRI in the fibrosis treatment groups. **c–d**; **Ctrl** (DMEM 14 days after bleomycin administration), n = 11; **EV_t** (MSC extracellular vesicles 14 days after bleomycin administration), n = 9; **SF_t** (MSC soluble factors 14 days after bleomycin administration), n = 6; n = biological independent animals per group. Number of analyzed fields of view per sample = 3–10 for each animal.

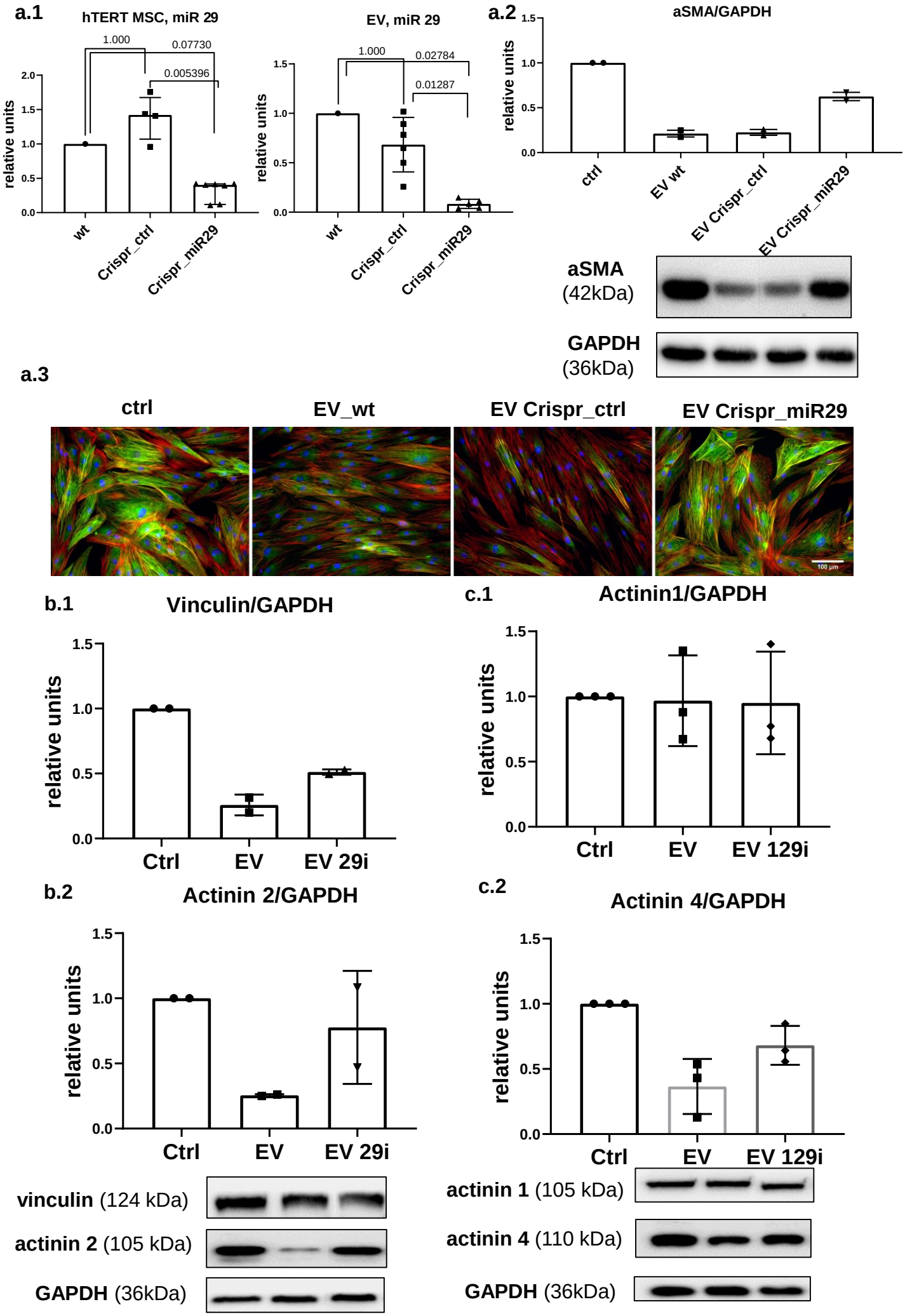


Supplementary Fig. 4. Isolation of MSC-EV by gradient ultracentrifugation does not change their antifibrotic effect.

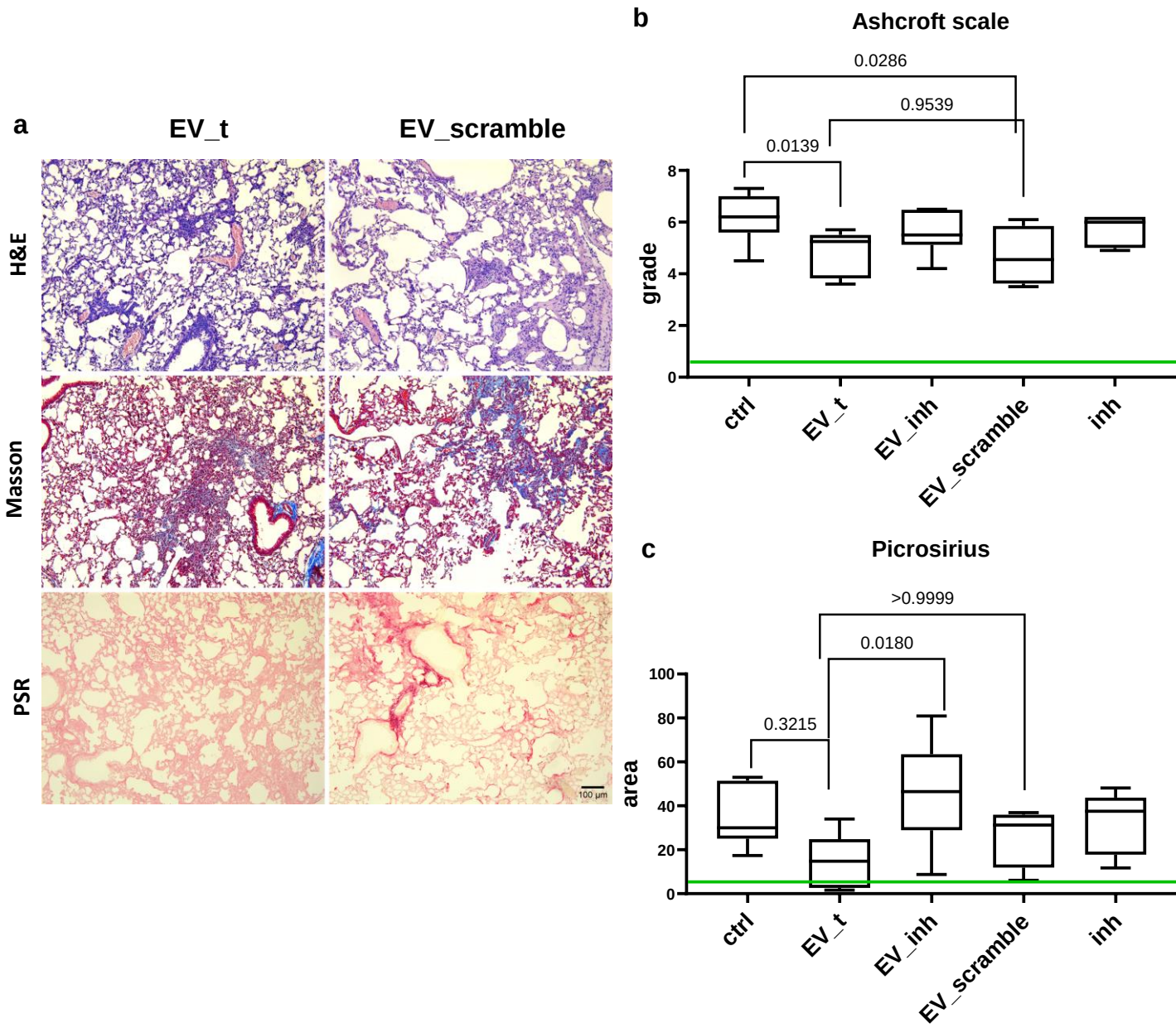
a. Representative image of myofibroblast immunocytochemical analysis for the αSMA expression. Scale bar = 100 μm. **b**. Western-blot analysis of aSMA. *n* = 2 biological independent experiments. **c.** Dot blot analysis of collagen type I. *n* = 2 biological independent experiments for all methods. #1 and #2 – independent data for two different HDF donors. **Fibroblast** – undifferentiated fibroblasts, **ctrl** – myofibroblasts treated with DMEM during 4 days, **EV** - myofibroblasts treated with EV during 4 days.



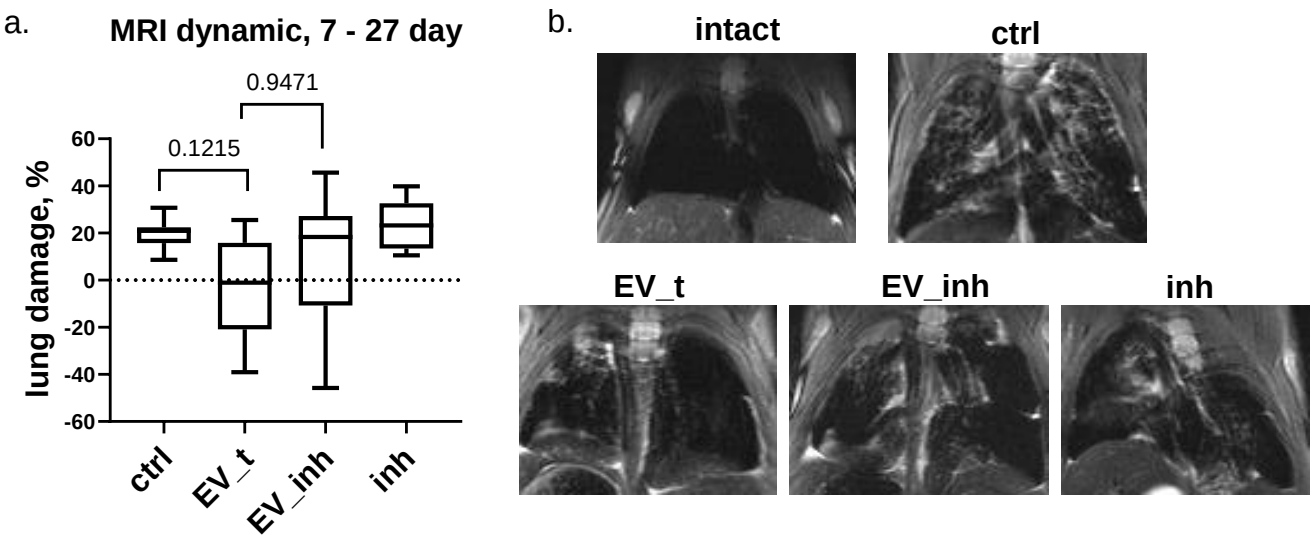
Supplementary Fig. 5. Critical contribution of RNAs to the MSC-EV antifibrotic effects, part 1. a. Representative image of the myofibroblast immunocytochemical analysis for the αSMA expression in the presence of MSC-EV treated with RNase. MSC-EV treated with RNAse for 3 h (EV RNase 3h, internal RNA-depleted EV) or for 30 min (EV RNase 30', external RNA-depleted EV), MSC-EV transfected by scramble miR ± RNase 30-min treatment, MSC-EV transfected by the miR-29c and miR129 inhibitor ± RNase 30-min treatment. n = 3 biological independent experiments. b. Analysis of the length distribution of nucleic acid fragments within native MSC-EV or MSC-EV treated by RNAse for 3 h. c NTA for MSC-EV or MSC-EV treated by RNAse for 3 h.



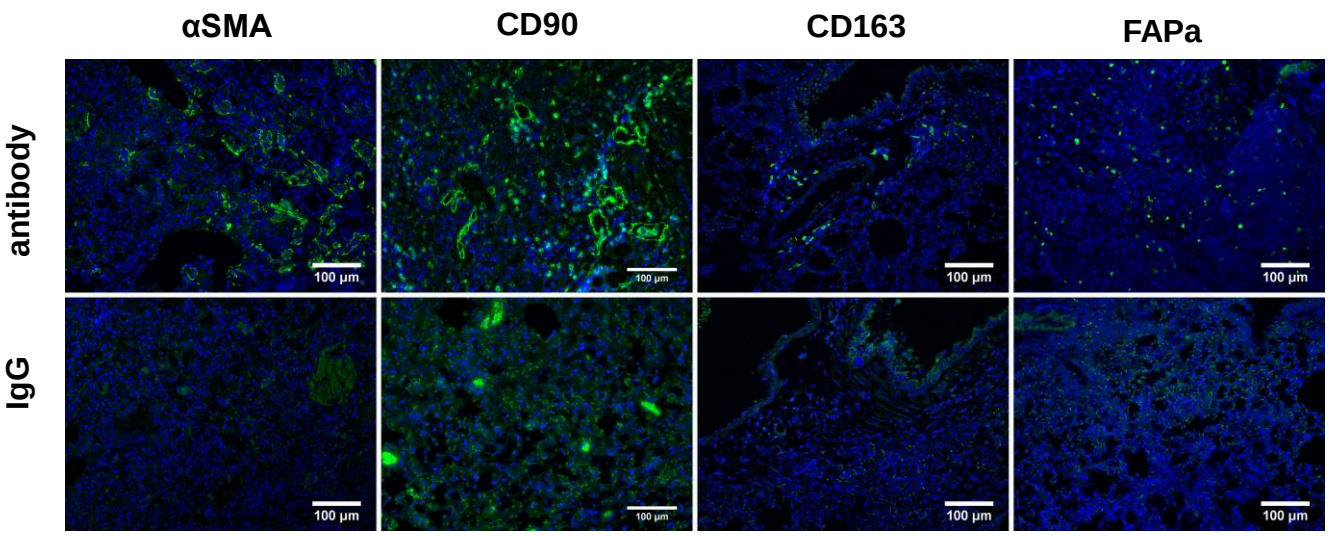
Supplementary Fig. 6. Critical contribution of RNAs to the MSC-EV antifibrotic effects, part 2. a. Representative image of the myofibroblast immunocytochemical analysis for the αSMA expression in the presence of EV from MSC with Crispr-Cas9 miR-29 knockdown. Wt, EV from hTERT-MSC ; Crispr_ctrl, EV from hTERT-MSC with Crispr-Cas9 nonsense knockdown; and Crispr_miR29, EV from hTERT-MSC with Crispr-Cas9 miR-29 knockdown. b.1 miR29 expression within hTERT-MSC (left graph) or appropriate EV (right graph), RT-PCR. b.2,3. Analysis of the aSMA expression within the myofibroblasts after exposure to serum-free cultured control (ctrl) or hTERT-MSC EV (EV wt), hTERT-MSC Crispr_ctrl EV (EV Crispr_ctrl), or hTERT-MSC Crispr_miR29 EV (EV Crispr_miR29). b.2 Western blotting, b.3 immunocytochemical analysis, n = 2. b,c Western blot analysis specific targets for miR-29c (b1, b2. n = 2 biological independent experiments) and miR-129 (c1, c2. n = 3 biological independent experiments)



Supplementary Fig. 7. MSC-EV transfection with scramble oligos as controls for specific miR inhibitors does not affect MSC-EV antifibrotic effects *in vivo*. a. Representative images of hematoxylin–eosin (H&E), Masson trichrome and Picrosirius Red (PSR) staining. Scale bar = 100 µm. **b.** Quantification of the pulmonary fibrosis severity using the Ashcroft scale; **Ctrl** (DMEM 14 days after bleomycin administration), n = 11; **EV_t** (MSC extracellular vesicles 14 days after bleomycin administration), n = 9; **EV_inh** (MSC extracellular vesicle, transfected by the miRNA-29 & miRNA-129 inhibitors 14s day after bleomycin administration), n = 8; **inh** (miRNA-29 and miRNA-129 inhibitors 14 days after bleomycin administration), n = 5; **EV_scramble** (MSC extracellular vesicle, transfected by the miRNA Inhibitor Control 14s day after bleomycin administration), n= 4, n = biological independent animals per group. Assessment was conducted by two independent blinded experts. **c.** Quantification of the ECM deposition on the PSR staining image. The green line indicates the median for the intact group.



Supplementary Fig. 8. **Dynamic changes in the lung tissue density in mice with bleomycin-induced pulmonary fibrosis treated with MSC-EV transfected by miR inhibitors measured *via* MRI.** a. Quantification of dynamic changes in the lung tissue density measured *via* MRI. b. Representative MR images. **Ctrl** (DMEM 14 days after bleomycin administration), n = 11; **EV_t** (MSC extracellular vesicles 14 days after bleomycin administration), n = 9; **EV_inh** (MSC extracellular vesicle, transfected by the miRNA-29 & miRNA-129 inhibitors 14s day after bleomycin administration), n = 9; **inh** (miRNA-29 and miRNA-129 inhibitors 14 days after bleomycin administration), n = 5; n = biological independent animals per group. Number of analyzed fields of view per sample = 3–10 for each animal.



Supplementary Fig. 9. Immunohistochemical analysis for the aSMA, CD90, CD163, and FAPa expressions in pulmonary tissue (antibody) compared with staining with the corresponding isotype control antibodies (IgG). Scale bar = 100 μm.

MicroRNA and Target Gene Description:

miRNA Name	hsa-miR-129-5p	**miRNA Sequence**	CUUUUUGCGGUCUGGGCUUGC
Previous Name	hsa-miR-129		
Target Score	90	**Seed Location**	96, 225
NCBI Gene ID	1277	**GenBank Accession**	NM_000088
Gene Symbol	COL1A1	**3' UTR Length**	1406
Gene Description	collagen type I alpha 1 chain		

3' UTR Sequence

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miRNA Name	mmu-miR-129-5p	**miRNA Sequence**	CUUUUUGCGGUCUGGGCUUGC
Previous Name	mmu-miR-129		
Target Score	60	**Seed Location**	228, 1421
NCBI Gene ID	12842	**GenBank Accession**	NM_007742
Gene Symbol	Col1a1	**3' UTR Length**	1439
Gene Description	collagen, type I, alpha 1		

3' UTR Sequence

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Supplementary Table 1. hsa-microRNA-129-5p and mmu-microRNA-129-5p have binding sites on collagen type I alpha 1

MicroRNA and Target Gene Description:

miRNA Name	hsa-miR-29c-3p	**miRNA Sequence**	UAGCACCAUUUGAAAUCGGUUA
Previous Name	hsa-miR-29c		
Target Score	98	**Seed Location**	881, 923, 1056
NCBI Gene ID	1277	**GenBank Accession**	NM_000088
Gene Symbol	COL1A1	**3' UTR Length**	1406
Gene Description	collagen type I alpha 1 chain		

3' UTR Sequence

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MicroRNA and Target Gene Description:

miRNA Name	mmu-miR-29c-3p	**miRNA Sequence**	UAGCACCAUUUGAAAUCGGUUA
Previous Name	mmu-miR-29c		
Target Score	95	**Seed Location**	877, 919, 1097
NCBI Gene ID	12842	**GenBank Accession**	NM_007742
Gene Symbol	Col1a1	**3' UTR Length**	1439
Gene Description	collagen, type I, alpha 1		

3' UTR Sequence

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Supplementary Table 2. hsa-microRNA-29c-3p and mmu-microRNA-29c-3p have binding sites on collagen type I alpha 1