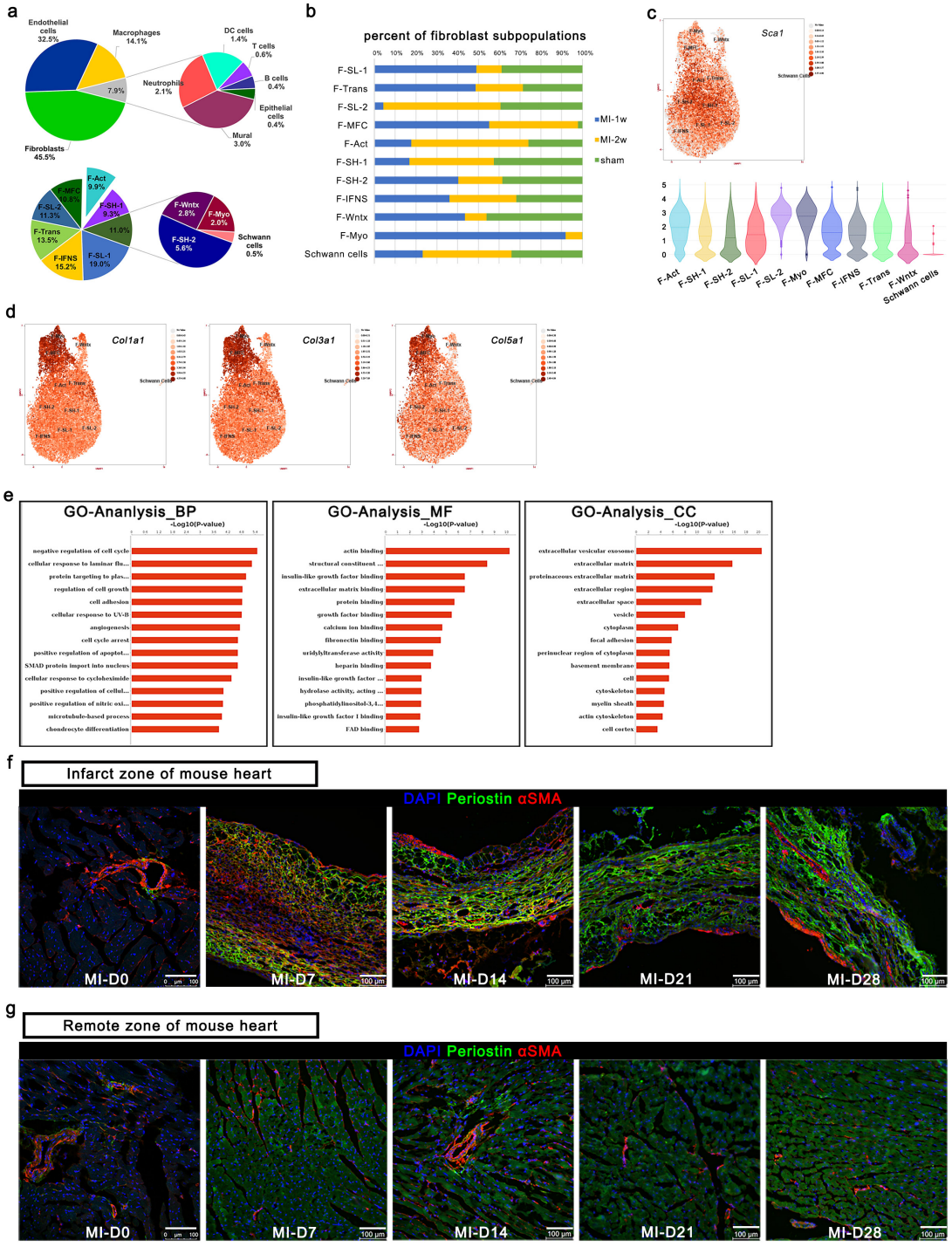
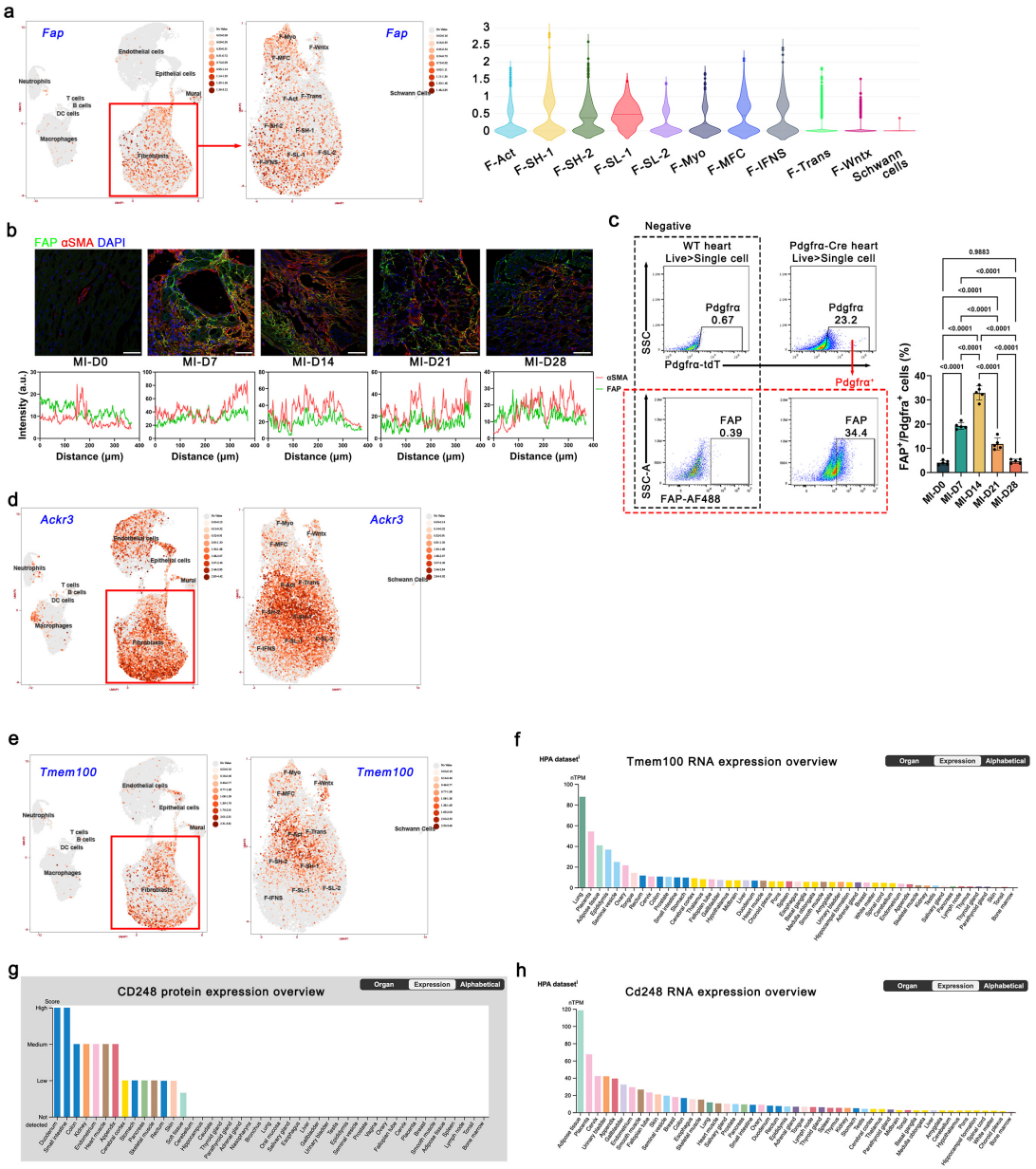
Supplementary Fig. 1-9



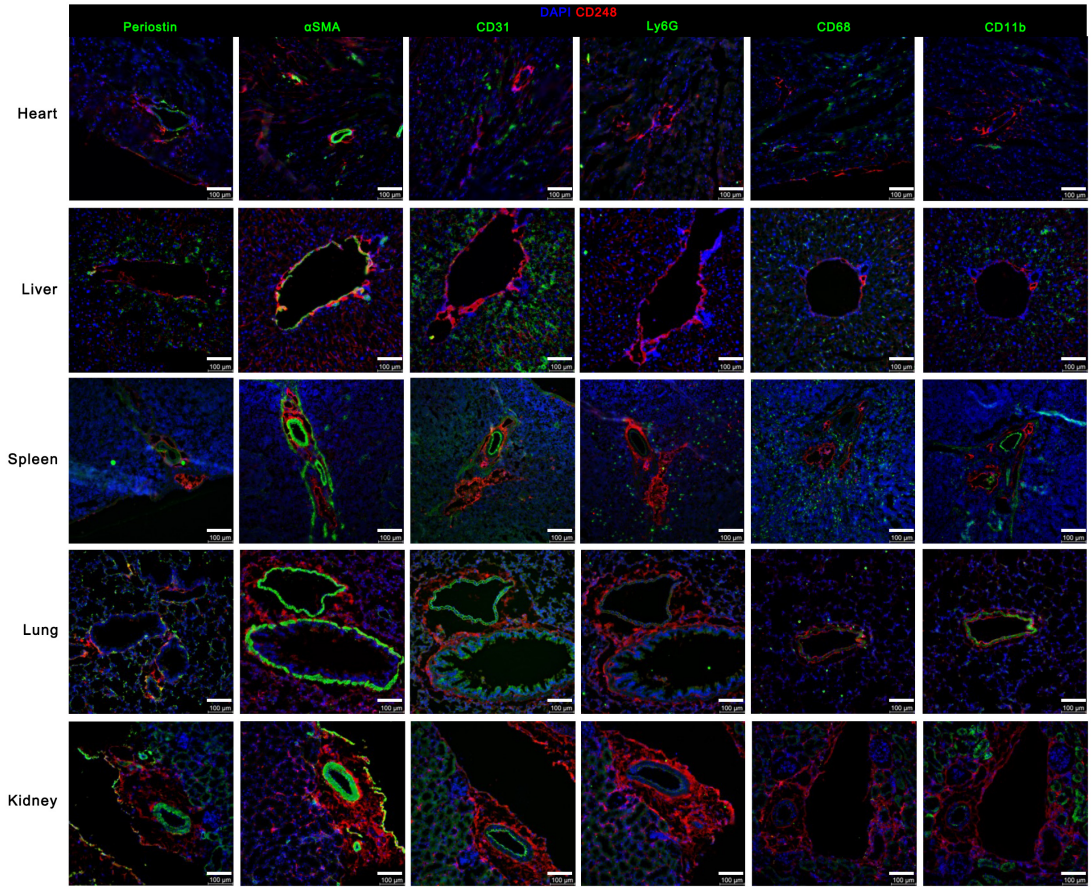
Supplementary Fig. 1| Identification of cardiac fibroblast subpopulation F-Act. a The pie chart illustrates the proportions of different cell types and different fibroblast subpopulations. **b** The bar chart shows the proportions of different fibroblast subpopulations in the sham group, 7 days post-MI, and 14 days post-MI. **c** The UMAP and violin plots demonstrate the expression of *Sca1* in different fibroblast subpopulations. **d** The UMAP plot reveals the high expression of collagen-

related genes (*Col1a1, Col3a1, Col5a1*) in the F-Myo subpopulation. **e** Gene Ontology (GO) enrichment analysis of the biological process (BP), molecular function (MF), and cellular component (CC) genes upregulated in fibroblast population F-Act. P-adjusted value<0.05. **f-g** Triple immunofluorescence (IF) staining for periostin (green) and the αSMA (red) in the infarct zone (**f**) and remote zone (**g**) of the hearts of C57BL/6J WT mice 0, 7, 14, 21, and 28 days after MI surgery. Nuclei were stained blue. Scale bar = 100μm. Each experiment was repeated 5 times independently with similar results.

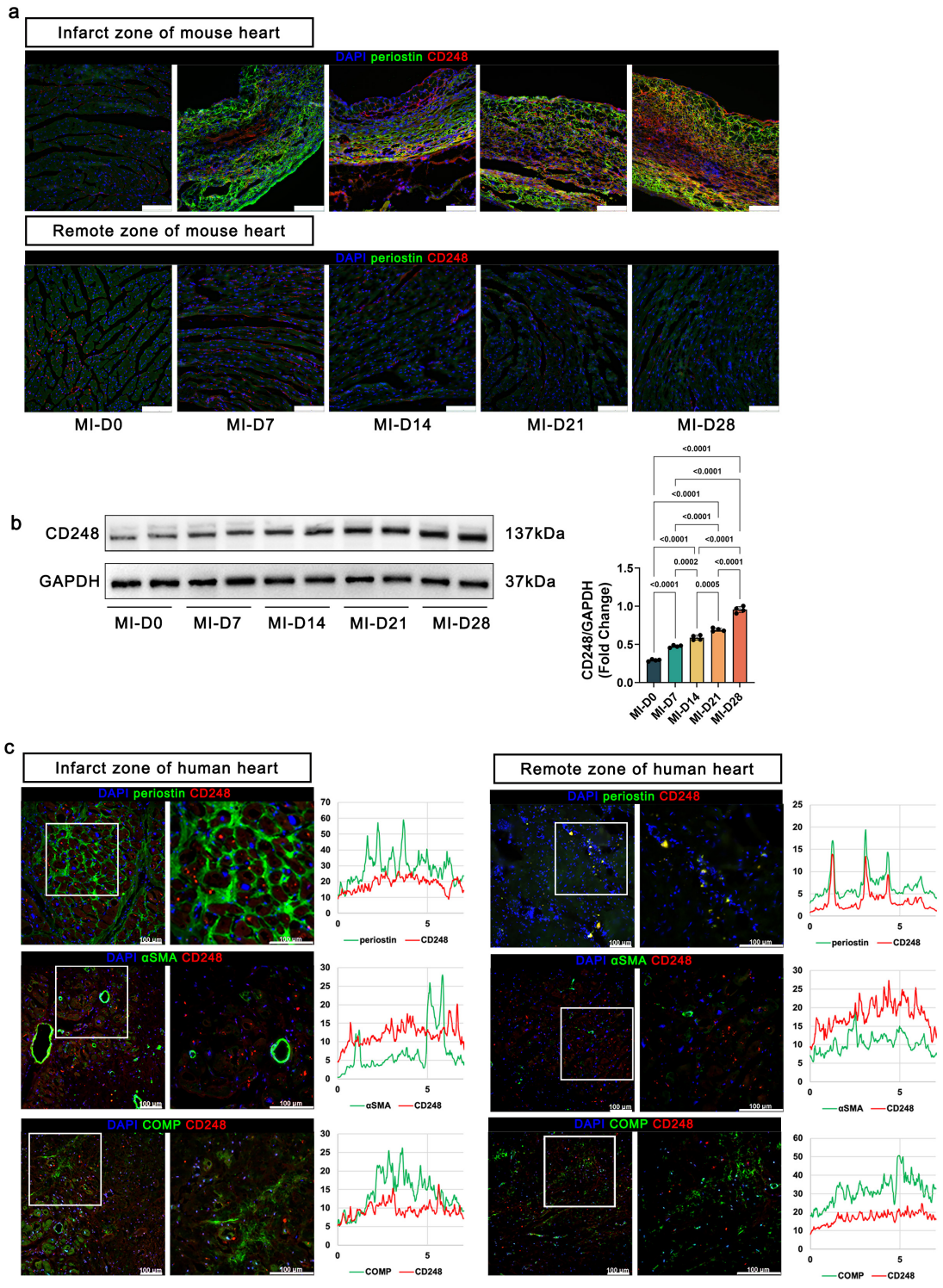


Supplementary Fig. 2| Screening for the characteristic surface antigen of F-Act. a UMAP and violin plot shows *Fap* expression in different fibroblast subpopulations. **b** Triple

immunofluorescence staining for FAP (green) and αSMA (red) in the peri-infarct zone of the hearts of C57BL/6J WT mice 0, 7, 14, 21, 28 days after MI surgery. Nuclei were stained blue. Scale bar = 20µm. Each experiment was repeated 5 times independently with similar results. **c** Flow cytometry of fibroblasts isolated from C57BL/6J WT mouse and Pdgfra-CRE:tdTomato mouse hearts. Total cardiac fibroblasts were lineage traced by pdgfrα. Quantification of the FAP^+ fibroblasts ratio in $pdgfra^+$ fibroblasts. n=5 mice at each time point after MI. Data are mean±SEM and p-values are displayed in the bar charts, one-way ANOVA followed by Tukey's multiple comparison test. **d-e** UMAP depicts *Ackr3* and *Tmem100* expression in cardiac interstitial cells and fibroblasts. **f** Tmem100 RNA expression in all organs according to the Human Protein Atlas (HPA). **g,h** CD248 protein and RNA expression in all organs according to the HPA.

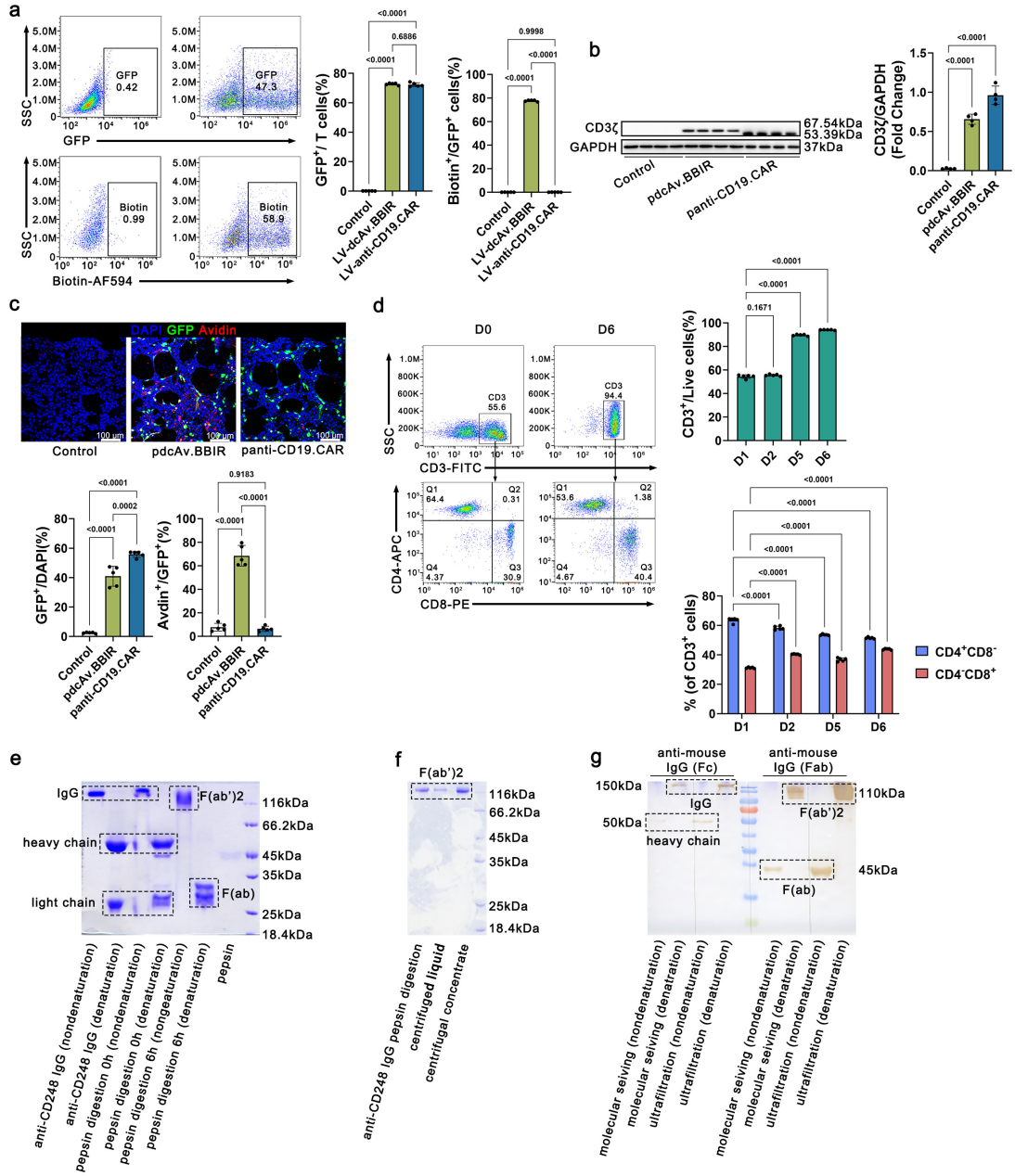


Supplementary Fig. 3| CD248 protein expression in healthy mouse tissues. Triple IF staining for periostin, αSMA, CD31, Ly6G, CD68, CD11b (green), and CD248 (red) in the hearts of C57BL/6J WT healthy mice. Nuclei were stained blue. Scale bar = 100µm. Each experiment was repeated 5 times independently with similar results.



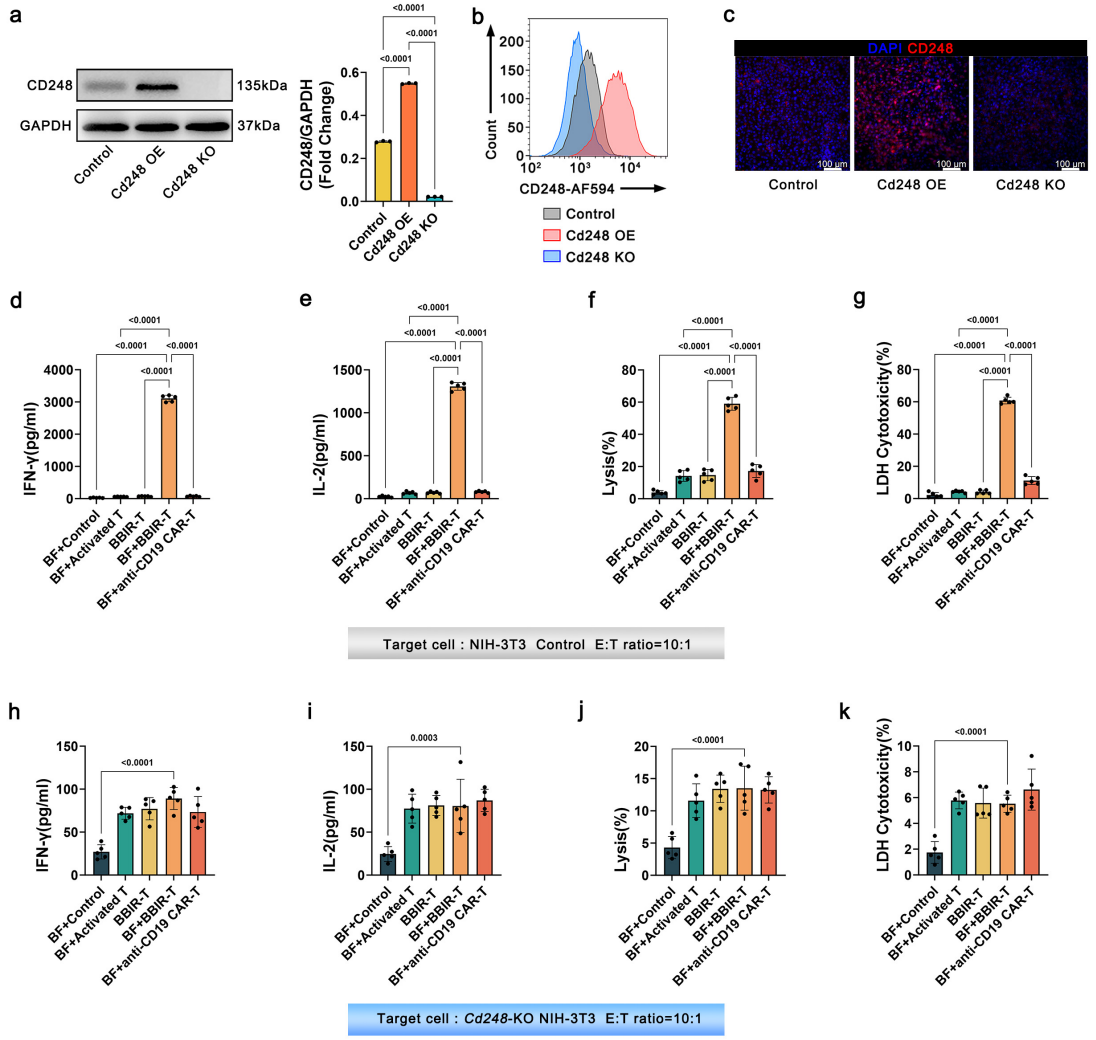
Supplementary Fig. 4| Identification of CD248 as the target antigen for CAR-T cells against F-Act. a Triple IF staining for periostin (green) and CD248 (red) in the infarct zone and remote zone of the hearts of C57BL/6J WT mice 0, 7, 14, 21, and 28 days after MI surgery. Nuclei were stained blue. Scale bar = 100μm. Each experiment was repeated 5 times independently with similar results. **b** Western blot shows CD248 protein expression in the left ventricle and ventricular septum

0, 7, 14, 21, and 28 days after MI surgery. Quantifying the relative protein expression of CD248 to GAPDH, n=4 mice at each time point. The samples derive from the same experiment and that gels/blots were processed in parallel. Data are mean±SEM and p-values are displayed in the bar charts, one-way ANOVA followed by Tukey's multiple comparison test. **c** Triple IF staining of periostin, αSMA, COMP (stained green), and CD248 (stained red) in the infarct zone and remote zone of the heart from a MI patient donor. Nuclei were stained blue. Scale bar = 100μm. Each experiment was repeated 5 times independently with similar results.



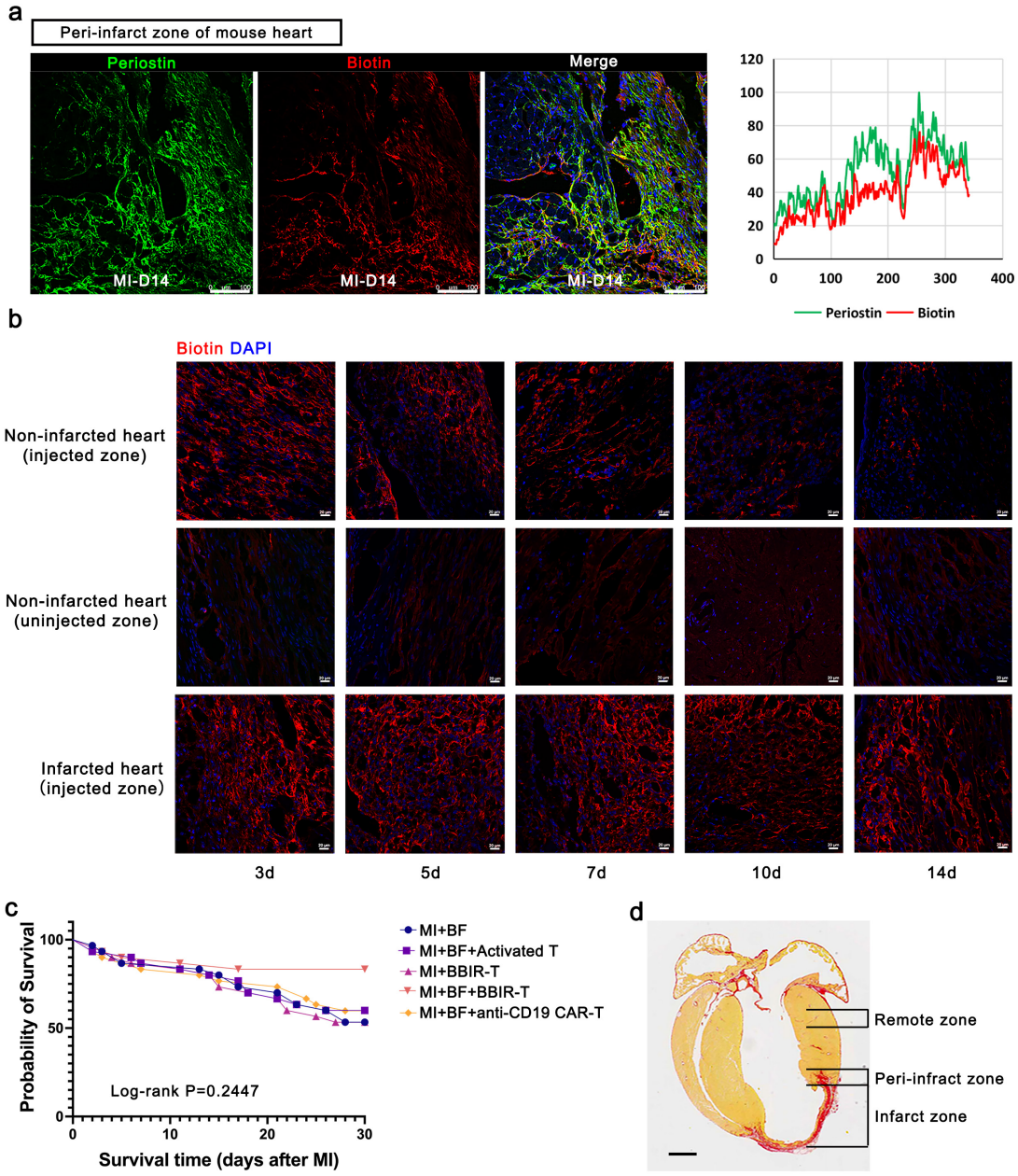
Supplementary Fig. 5| Construction and Functional Verification of the BBIR-T Cell System Target CD248. a Flow cytometry of 293T cells transfected with dcAv. BBIR-28-137ζ and CD19.

CAR-137ζ plasmids. The plasmids express GFP. Quantifying GFP^+ cells ratio to total T cells and $biotin^+$ cells ratio to GFP+ cells. n=5 cell culture wells of each group. **b** Western blot shows exogenous CD3ζ expression in 293T cells transfected with dcAv. BBIR-28-137ζ and CD19. CAR-137ζ plasmids. Quantifying the relative protein expression of CD3ζ to GAPDH. n=4 cell culture wells of each group. The samples derive from the same experiment and that gels/blots were processed in parallel. **c** Triple immunofluorescence staining of avidin (red). The plasmids express GFP. Nuclei are stained blue. Scale bar = 100μm. Quantifying the GFP^+ cells ratio to DAPI and $avidin^+$ cells ratio to GFP^+ cells. n=5 cell culture wells of each group. **d** Flow cytometry of human peripheral blood mononuclear cells (PBMCs) 1, 2, 5, and 6 days after stimulating culture. Quantifying the $CD3^+$ T-cell ratio to total live cells and the $CD4^+CD8^-$ or $CD4^-CD8^+$ T-cell ratio to $CD3^+$ T cells. n=5 cell culture wells of each time point. **e** SDS–PAGE of anti-CD248 antibody digested by pepsin. **f** SDS–PAGE of anti-CD248 F(ab')2 recovered by ultrafiltration. **g** Western blot shows the expression of anti-CD248 F(ab')2. The samples derive from the same experiment and that gels/blots were processed in parallel. **a-d** Data are mean±SEM and p-values are displayed in the bar charts, one-way ANOVA followed by Tukey's comparison test, 2-way ANOVA followed by Bonferroni's multiple comparisons tests.



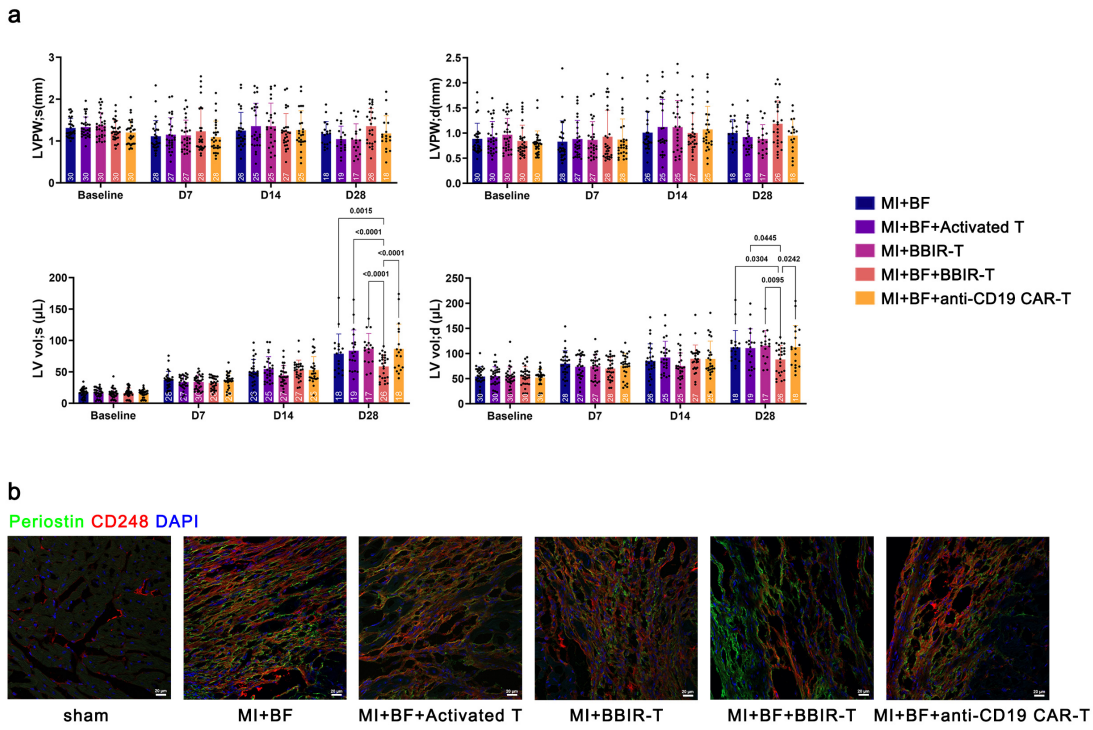
Supplementary Fig. 6| The BBIR-T therapy targets CD248-positive fibroblasts in vitro. a-c Overexpression or knockout of *Cd248* in NIH-3T3 cells by using lentivirus. **a** Western blotting showed the expression of CD248. Quantifying the relative protein expression of CD248 to GAPDH, n=4 cell culture wells at each time point. The samples derive from the same experiment and that gels/blots were processed in parallel. **b** Flow cytometry of NIH-3T3 cells to detect the expression of CD248. **c** Double IF staining for CD248 (stained red) in NIH-3T3 cells. Nuclei were stained blue. Scale bar = 100μm. **d-k** Different effector cells cocultured with NIH-3T3 cells with or without *Cd248* knockout. E: T=10:1. ELISA determined the secretion of IFN-γ (**f, h**) and IL-2 (**g, i**) in the supernatant 24h after coculture. n=5 cell culture wells of each group. **f, j** Cell lysates were analyzed at 24h after coculture by CCK-8 cell viability assay. n=5 cell culture wells of each group. **g, k** Cytotoxicity was measured by LDH activity in the supernatant 24h after coculture.

n=5 cell culture wells of each group. **a, d-k** Data are the mean±SEM and p-values are displayed in the bar charts, one-way ANOVA followed by Tukey's comparison test.

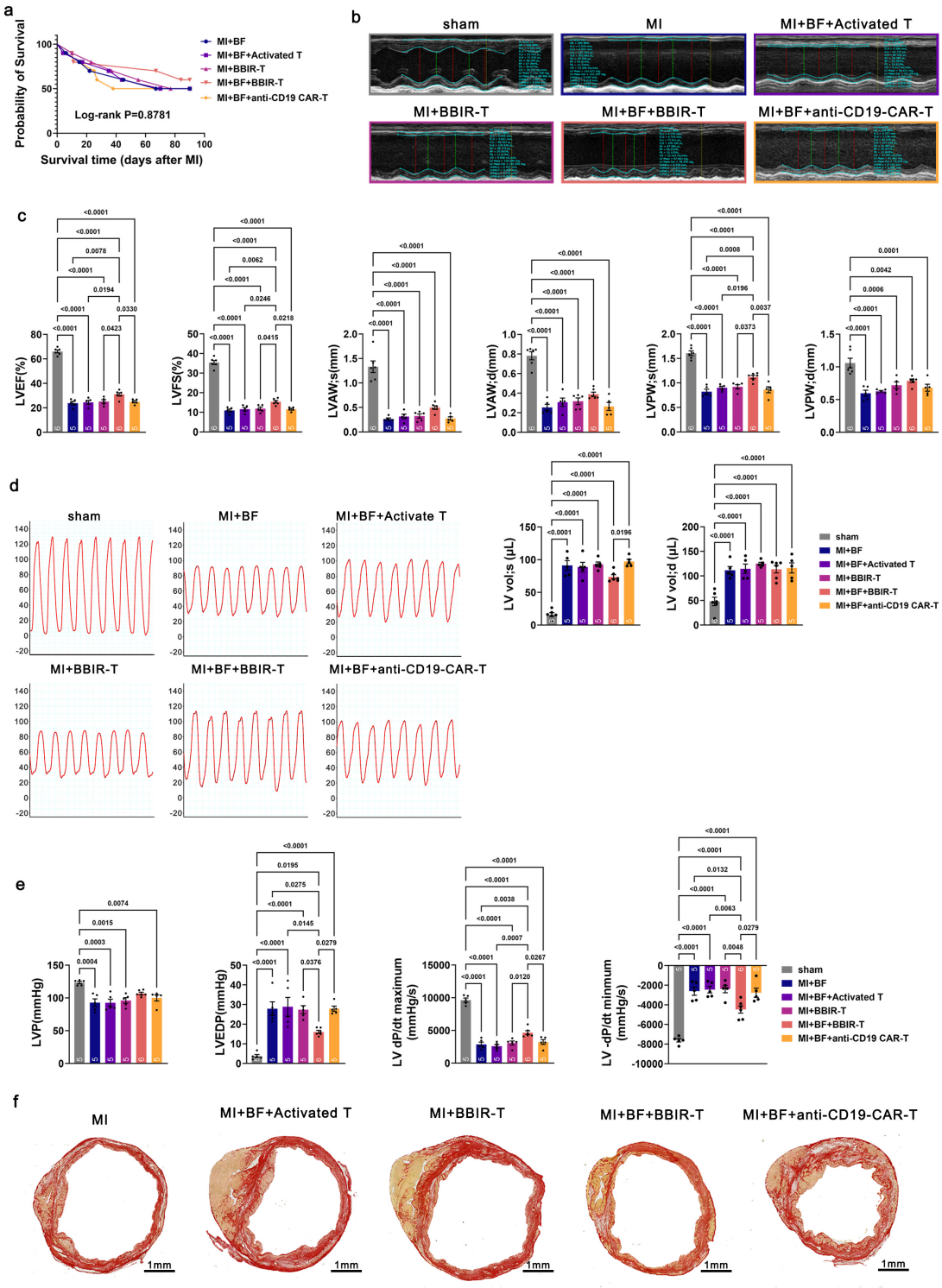


Supplementary Fig. 7| Three-times Injection of BBIR-T Cells Improved the Cardiac Function of MI Mice. a Triple IF staining for periostin (green) and biotin (red) in the peri-infarct zone of the hearts of C57BL/6J WT mice 14 days after MI surgery. Nuclei are stained blue. Scale bar = 100μm. Each experiment was repeated 5 times independently with similar results. **b** Immunofluorescence staining for biotin (red) in the infarcted and non-infarcted hearts of C57BL/6J WT mice 3, 5, 7, 10, 14 days after intramyocardial injection of biotinylated anti-CD248 F(ab')2. Nuclei were stained blue. Scale bar = 20μm. From top to bottom, they are the injected zone of the non-infarcted heart,

the uninjected zone of the non-infarcted heart, and the injected zone of the infarcted heart. Each experiment was repeated 5 times independently with similar results. **c** Kaplan–Meier survival curve of all mice one month after MI, n(d0) =30 of per group. **d** A diagram illustrating the delineation of the infarct zone, peri-infarct zone, and remote zone in the Sirius Red-stained images of coronary heart section slices. Scale bar = 1mm.



Supplementary Fig. 8| Three-times Injection of BBIR-T Cells Improved the Cardiac Function of MI Mice. a Quantifying the LVPW thickness and LV volume during the systolic and diastolic periods (LVPW; s, LVPW; d, LV vol; s, and LV vol; d) at different time points. The number of surviving mice (n) for each treatment group at each time point was displayed at the bottom of the bar chart. Data are mean±SEM, and p-values are displayed in the bar charts, 2-way ANOVA followed by Bonferroni's multiple comparisons tests. **b** Triple immunofluorescence staining for periostin (green) and CD248 (red) in the peri-infarct zone of the hearts of different groups. Nuclei were stained blue. Scale bar = 20μm. Each experiment was repeated 5 times independently with similar results.



Supplementary Fig. 9| Long term outcome of BBIR-T cell strategy. a Kaplan–Meier survival curve of all mice 3 months after MI, n(d0)=10 of per group. **b-c** typical short-axis M-type echocardiographic images in each group of mice 3 months after MI. The LVEF, LVFS, LVPW, LVAW and LV vol were quantified at different time points. The number of mice (n) for each treatment group was displayed at the bottom of the bar chart. **d-e** Typical LVP image of each group

of mice detected by LV catheterization. The LVP, LVEDP, LV dP/dt maximum, and LV -dP/dt minimum were quantified. The number of mice (n) for each treatment group was displayed at the bottom of the bar chart. **c,e** Data are mean±SEM and p-values are displayed in the bar charts, one-way ANOVA followed by Tukey's comparison test. **f** Representative full-view images of heart Picro-Sirius Red staining. Scale bar = 1mm.