**Figure Legends**

**Figure 1. Bioinformatic analysis for gene prioritization.** Workflow diagram depicting the computational analyses leading to the identification of regulatory genes predicted to be involved in both senescence and heart failure. As demonstrated, we constructed a table of human and mouse genes with features of log2(FC) and p-adjusted value for a multitude of genomic datasets where, based on the regulatory role and significance of each gene from the genomic data analyses, one score per gene was derived and named regulation score. The prioritized ranked genes were used as a test set in the Endeavour algorithm where mouse genes and their human homologs related both with senescence and heart failure phenotypes were used as training sets. Data were obtained from the MGI database (http://www.informatics.jax.org/phenotypes.shtml).

**Figure 2. Human genes predicted to associate with senescence and heart failure.** A. Gene set enrichment analysis of key regulatory genes (top 75% of genes based on their regulation score) associated with both senescence and heart failure, in the left atrium. B. Same as in A, in the left ventricle. C. Enriched pathways for upregulated genes in heart failure versus control and D. Same as in C, for downregulated genes. E. Prediction based on bulk RNA-seq differential expression analysis upon atrial fibrillation versus control, in the right atrium. Red indicates differentially expressed genes, of which those associated with senescence are marked with their names. F. Pathway enrichment analysis in atrial fibrillation, based on E. Senescence-related pathways predicted to relate with heart dysfunction are implicated, among others, in inflammation, protein folding, protein metabolism and mitochondrial function. See also Table 1.

**Figure 3. Genes predicted to associate with human heart failure and senescence per cardiac cell type.** A. Uniform manifold approximation and projection (UMAP) clustering of genes per cardiac cell type in the left atrium. B. Differentially expressed senescence-associated genes compared to normal tissue in the left atrium. C. Same as in A, in left ventricle. D. Same as in B, in left ventricle. The training set for the gene prioritization analysis using the Endeavour algorithm consists of genes that are chosen based on specific phenotypes for senescence and heart diseases like cardiomyopathy, myocarditis and ischemic infarction, as these are registered in the Mouse Genome Informatics (MGI) portal (<http://www.informatics.jax.org/phenotypes.shtml>). See also Figure 1 and Table 1.

**Figure 4. Identifying specific senescence-associated markers in neonatal heart injury in regenerative mice (P1) versus non-regenerative mice (P8).** A. UMAP clustering for predicted genes in P1 mice. B. UMAP clustering for predicted genes in P8 mice. C. Heatmap displaying predicted genes corresponding to A. D. Heatmap displaying predicted genes corresponding to B. See color coding for relevant cardiac cell types. See also Table 1.

**Figure 5. Comparative expression of predicted senescence-associated markers in neonatal P1 and P8 mice upon heart injury.** Several predicted senescence-associated genes alter their expression levels in P1 versus P8 mice upon heart injury, implying that senescence-related genes may be differentially regulated upon heart regeneration. \*P<0.05, \*\*P≤0.01 and \*\*\*P<<0.01, based on Bonferroni adjustment. See also Table 1.

**Table 1. Raw data for analyses presented in Figures 1-5.**

**Spreadsheets:**

**concencus\_mosthighly\_enriched\_g =** prioritized ranked gene sets associated with senescence and heart diseases.

**Translation\_efficiency\_relation=** Translation efficiency changes regarding the analysis of https://pubmed.ncbi.nlm.nih.gov/31155234/

**mice\_heart\_infraction=** Differential expression analysis of healthy versus cardio disease regarding the study in GSE132144 (analysis performed with Seurat )

**markers \_mice\_heart\_infraction=** cell type markers associated with study GSE132144 (analysis performed with Seurat for more information of the code used to extract diff in expression and different cell types please see the provided notebook).

**diff\_LA\_LVheart\_disease=**Differential expression analysis of healthy versus cardio disease regarding the study in GSE121893 (analysis performed with Seurat). The various different cell types can be seen in Figure 3.

**LA\_LV\_markers=**cell type markers associated with study GSE121893 (analysis performed with Seurat ) The various different cell types can be seen in Figure 3.

t**opmarkers\_monocle\_LA**=cell type markers of the Left atrium associated with study GSE121893 (analysis performed with Monocle).

**topmarkers\_monocle\_LV**=cell type markers of the Left ventricular associated with study GSE121893 (analysis performed with Monocle ).

**P8vsP1** = Differential expression analysis of P8 versus P1 mice after heart injury regarding the study in GSE153480.

**P8vsP1\_markers=Cell type markers** of P8 versus P1 mice after heart injury regarding the study in GSE153480. These results are associated with Figures 4 and 5.

**P1\_M1\_Monocole**=Trajectories as extracted with Monocole for GSE153480 study for P1 mice.

**P8\_M1\_Monocole=**Trajectories as extracted with Monocole for GSE153480 study for P8 mice.

**P1\_M3\_Monocole=**Trajectories as extracted with Monocole for GSE153480 study for P1 mice at day 3.

**P8\_M3\_Monocole=**Trajectories as extracted with Monocole for GSE153480 study for P8 mice at day 3.

**Trans-membrane \_domains=** Highly prioritized genes associated with senescence and heart failure potentially secreted.