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☐ Initial submission ☐ Revised version ☒ Final submission

Life Sciences Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form is intended for publication with all accepted life science papers and provides structure for consistency and transparency in reporting. Every life science submission will use this form; some list items might not apply to an individual manuscript, but all fields must be completed for clarity.

For further information on the points included in this form, see Reporting Life Sciences Research. For further information on Nature Research policies, including our data availability policy, see Authors & Referees and the Editorial Policy Checklist.

Experimental design

1. Sample size

Describe how sample size was determined.

The number of mice for gel/miR-302 treatment group was at least 11 males to give 80% power to detect an effect size of 1.3 SDs using a two-group t test with a 0.05 two-sided significance level.

2. Data exclusions

Describe any data exclusions.

Outliers were removed using the robust regression and outlier removal method (ROUT) in Prism (1 animal in Gel/miR-NC group for Fig. 7a-d).

3. Replication

Describe whether the experimental findings were reliably reproduced.

In vitro studies were performed in triplicate or more (>3 gels per group) where noted. In vivo studies were performed in at least 3 animals per group where noted. Results were reliably reproduced between biological replicates.

4. Randomization

Describe how samples/organisms/participants were allocated into experimental groups.

This study was not randomized.

5. Blinding

Describe whether the investigators were blinded to group allocation during data collection and/or analysis.

For the histology studies, all IHC were quantified by two-blinded, independent observers (LLW, YL). For Confetti studies, images were quantified by a single-blinded observer (YL). For all in vivo injections, the surgeons (JJC, ACG, TW) were blinded to the treatment groups; however, it is clear immediately upon injection whether the treatment group contained gel or not, as there is added pressure required for product extrusion for the treatment groups with gel. Subsequently, the technician performing the echocardiography (S. Schultz, Penn Small Animal Imaging Facility) was blinded to all treatment groups. The analyzer of echocardiography (LLW) was blinded to the results for an initial subset of animals containing at minimum 5 animals per group but was subsequently not blinded, as additional animals were done in each group on separate days.

Note: all studies involving animals and/or human research participants must disclose whether blinding and randomization were used.

6. Statistical parameters

For all figures and tables that use statistical methods, confirm that the following items are present in relevant figure legends (or in the Methods section if additional space is needed).

n/a	Confirmed
☐	☒ The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement (animals, litters, cultures, etc.)
☐	☒ A description of how samples were collected, noting whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☐	☒ A statement indicating how many times each experiment was replicated
☐	☒ The statistical test(s) used and whether they are one- or two-sided (note: only common tests should be described solely by name; more complex techniques should be described in the Methods section)
☐	☒ A description of any assumptions or corrections, such as an adjustment for multiple comparisons
☐	☒ The test results (e.g. *P* values) given as exact values whenever possible and with confidence intervals noted
☐	☒ A clear description of statistics including central tendency (e.g. median, mean) and variation (e.g. standard deviation, interquartile range)
☐	☒ Clearly defined error bars

See the web collection on statistics for biologists for further resources and guidance.

Software

Policy information about availability of computer code

7. Software

Describe the software used to analyze the data in this study.	Image analysis was performed with ImageJ. Statistical analyssi was performed with Graphpad Prism 7.

For manuscripts utilizing custom algorithms or software that are central to the paper but not yet described in the published literature, software must be made available to editors and reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). *Nature Methods* guidance for providing algorithms and software for publication provides further information on this topic.

Materials and reagents

Policy information about availability of materials

8. Materials availability

Indicate whether there are restrictions on availability of unique materials or if these materials are only available for distribution by a for-profit company.	All unique materials can be readily synthesized according to our protocols, and we can make them available. A detailed protocol was recently published (Loebel et al, Nature Protocols, 2017). We would be happy to assist others in this.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	The following antibodies were used: Cardiac Troponin T (ThermoScientific, MS295), Ki-67 (Abcam, ab16667), Histone H3 phosphorylated at serine10 (Cell Signaling, 9701), Aurora B kinase (LSBio, LSB6592), Yap (Cell Signaling, 4912S), von Willebrand Factor (Abcam, ab8822), Troponin I (Abcam, ab10231), ACTC1 (Abcam, ab46805). Each of these antibodies has been previously validated for IHC, and frequently used by the Penn Histology Core. They were used in accordance with the manufacturer's dilution recommendations.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.	N/A
b. Describe the method of cell line authentication used.	N/A
c. Report whether the cell lines were tested for mycoplasma contamination.	N/A
d. If any of the cell lines used are listed in the database of commonly misidentified cell lines maintained by ICLAC, provide a scientific rationale for their use.	N/A

Animals and human research participants

Policy information about studies involving animals; when reporting animal research, follow the ARRIVE guidelines

11. Description of research animals

Provide details on animals and/or animal-derived materials used in the study.	Male C57BL/6 mice (7-9 weeks) were used in our studies. Confetti mice were obtained by breeding Myh6-MerCreMer and R26R-Confetti reporter mice.

Policy information about studies involving human research participants

12. Description of human research participants

Describe the covariate-relevant population characteristics of the human research participants.	N/A