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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.

Sample size was chosen by the available resources, the ability to culture 12 hiPSC lines in parallel, and cost (adding another line would double the cost of the study). The cost and time to generate each iPSC line as well as to sequence each clone by RNA-seq and ChIP-seq: stemgent kit $2000; generating 12 hiPSC clones from 6 reprogramming methods: 1.5 years; sequencing: 2 weeks for library prep and 2 months to return the data from one lane of sequencing, and each lane costs $3800 for 2x100 on the Hiseq.; data analysis: 16 months.
Given that each set of cardiac differentiation takes 2 weeks to perform, 9 differentiation sets could only be allocated. Using a power test to reach significance (ANOVA p value for 12 groups) would have taken months of differentiations.
In addition, handling 12 lines simultaneous with equal passaging was technically challenging. Addition of one more clone per reprogramming method would not have been possible.

2. Data exclusions

Describe any data exclusions.

ChIP-seq data with no enriched peaks (ES02 and LentiVirus_CL1 of H3K27me3) were excluded. Therefore, these samples had Spearman correlation values near zero and were excluded.

3. Replication

Describe whether the experimental findings were reliably reproduced.

Comparisons made between hiPSCs and hESCs were performed using a large sample size. Statistics performed on RNA-seq data showed little variance, which indicated reliable reproduction of the findings. Independent lines were also assessed by real-time PCR to ensure that findings were also reproduced in an independent dataset.

4. Randomization

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

No randomization was used.

5. Blinding

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

For the FACS, the researchers were blinded to which lines were made from which reprogramming method.

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.	All software is open source (Tophat, Bowtie, AltAnalyze, Homer, bedtools).

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.	No restrictions on data use or material are given. Raw fastq files are stored under the Gene Expression Omnibus accession number GSE69626.

9. Antibodies

Describe the antibodies used and how they were validated for use in the system under study (i.e. assay and species).	OCT4 (AF1759, R&D Systems) SOX2 (AB5603, Millipore) Tra-1-81 (mab4381, Millipore) tra-1-60 (SC-33759, Santa Cruz) POU5F1 (OCT4) (SC-9081, Santa Cruz) Cardiac Troponin-T antibody (MS-295-P, Thermo-Scientific) H3K4me3 (39159, Active Motif) H3K27me3 (39155, Active Motif) HDAC2 (2545S, Cell Signaling) H3 (61475, Active Motif) ChIP-seq antibodies were validated in previous studies and by ChIP-PCR. Antibodies for cardiomyocytes and hiPSCs were also validated by each company and in previous studies.

10. Eukaryotic cell lines

a. State the source of each eukaryotic cell line used.

hESCs were obtained from the following sources: HUES9 (HSCI iPS Core facility), H7 (WA07) (WiCell Research Institute, Inc.), H9 (WA09) (WiCell Research Institute, Inc), ES02(HES-2) (WiCell Research Institute, Inc.), LSJ1 and LSJ2 (Human Pluripotent Stem Cells Core Facility Stanford Institute for SCBRM).

b. Describe the method of cell line authentication used.

Cell lines were authenticated by sequencing.

c. Report whether the cell lines were tested for mycoplasma contamination.

All hiPSCs were tested to be mycoplasma-negative using the Mycoalert Mycoplasma testing kits (LT07-318, Lonza).

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.

No

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.

No animals were included in this study.

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.

Human protocols were approved by the following committees: IRB, Stem Cell Research Oversight (SCRO) at Stanford University. The skin punch biopsy (2 x 2 mm) was performed on a patient following IRB approval and informed consent.