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Corresponding author(s): Jason R. Spence NP-P180080C

Reporting Summary

Nature Research wishes to improve the reproducibility of the work that we publish. This form provides structure for consistency and transparency in reporting. For further information on Nature Research policies, see Authors & Referees and the Editorial Policy Checklist.

Statistical parameters

When statistical analyses are reported, confirm that the following items are present in the relevant location (e.g. figure legend, table legend, main text, or Methods section).

n/a	Confirmed	
☒	☐	The exact sample size (*n*) for each experimental group/condition, given as a discrete number and unit of measurement
☒	☐	An indication of whether measurements were taken from distinct samples or whether the same sample was measured repeatedly
☒	☐	The statistical test(s) used AND whether they are one- or two-sided *Only common tests should be described solely by name; describe more complex techniques in the Methods section.*
☒	☐	A description of all covariates tested
☒	☐	A description of any assumptions or corrections, such as tests of normality and adjustment for multiple comparisons
☒	☐	A full description of the statistics including central tendency (e.g. means) or other basic estimates (e.g. regression coefficient) AND variation (e.g. standard deviation) or associated estimates of uncertainty (e.g. confidence intervals)
☒	☐	For null hypothesis testing, the test statistic (e.g. *F*, *t*, *r*) with confidence intervals, effect sizes, degrees of freedom and *P* value noted *Give P values as exact values whenever suitable.*
☒	☐	For Bayesian analysis, information on the choice of priors and Markov chain Monte Carlo settings
☒	☐	For hierarchical and complex designs, identification of the appropriate level for tests and full reporting of outcomes
☒	☐	Estimates of effect sizes (e.g. Cohen's *d*, Pearson's *r*), indicating how they were calculated
☒	☐	Clearly defined error bars *State explicitly what error bars represent (e.g. SD, SE, CI)*

Our web collection on statistics for biologists may be useful.

Software and code

Policy information about availability of computer code

Data collection	N/A
Data analysis	N/A

For manuscripts utilizing custom algorithms or software that are central to the research but not yet described in published literature, software must be made available to editors/reviewers upon request. We strongly encourage code deposition in a community repository (e.g. GitHub). See the Nature Research guidelines for submitting code & software for further information.

Data

Policy information about availability of data

All manuscripts must include a data availability statement. This statement should provide the following information, where applicable:

- Accession codes, unique identifiers, or web links for publicly available datasets
- A list of figures that have associated raw data
- A description of any restrictions on data availability

Some of the data presented in the current study was generated for and shown in previously published reports. Figure 2 B-D was reproduced with permission from Dye et al. 2016 and licensed under CC BY-NC-ND 4.0. The original data can be viewed at https://doi.10.7554/eLife.05098 . Figure 2 E and Figure 5 B-C, G-J were reproduced with permission from Dye et al. 2015 and licensed under CC BY-NC-ND 4.0. The original data can be viewed at https://doi.10.7554/eLife.05098 . Figure 2

Field-specific reporting

Please select the best fit for your research. If you are not sure, read the appropriate sections before making your selection.

☒ Life sciences ☐ Behavioural & social sciences ☐ Ecological, evolutionary & environmental sciences

For a reference copy of the document with all sections, see nature.com/authors/policies/ReportingSummary-flat.pdf

Life sciences study design

All studies must disclose on these points even when the disclosure is negative.

Sample size	Three independent directed differentiation experiments were performed; one using H1 stem cells and two using H9 stem cells. Each directed differentiation experiment was performed in a 24 well plate, corresponding to 24 technical replicates per experiment. The purpose of these experiments was to document normal experimental progression and cell morphology to aid recapitulation of the protocol. No statistical analyses were performed.
Data exclusions	No data were excluded from these analyses.
Replication	The experiment was performed in two separate cell lines. The protocol was reproducible in all measured outcomes. Results here were consistent with our previously published work.
Randomization	Randomization of subjects is not relevant to this study.
Blinding	Blinding of researchers to data from this study was not relevant to this work. Three separate experiments were performed for the purpose of documenting protocol progression. Results were consistent between these three experiments and with our previously published work.

Reporting for specific materials, systems and methods

Materials & experimental systems

n/a	Involved in the study
☒	☐ Unique biological materials
☐	☒ Antibodies
☐	☒ Eukaryotic cell lines
☒	☐ Palaeontology
☒	☐ Animals and other organisms
☒	☐ Human research participants

Methods

n/a	Involved in the study
☒	☐ ChIP-seq
☒	☐ Flow cytometry
☒	☐ MRI-based neuroimaging

Antibodies

Antibodies used

Primary Antibody Source Catalog # Dilution
(Sections)
Chicken anti-GFP Abcam Ab13970 1:500
*Biotin-Goat anti-TP63 R&D systems BAF1916 1:500
*Biotin-Mouse anti MUC5AC Abcam ab79082 1:500
Goat anti-CC10 (SCGB1A1) Santa Cruz Biotechnology sc-9770 1:200
Goat anti-Chromogranin A (CHGA) Santa Cruz Biotechnology sc-1488 1:100
Goat anti-SOX2 Santa Cruz Biotechnology Sc-17320 1:200
Goat anti-VIMENTIN (VIM) Santa Cruz Biotechnology sc-7558 1:100
Mouse anti-Acetylated Tubulin (ACTUB) Sigma-Aldrich T7451 1:1000
Mouse anti-alpha smooth muscle actin (SMA)*Cy3 conjugated Sigma C6198 1:400
Mouse anti-E-Cadherin (ECAD) BD Transduction Laboratories 610181 1:500
Mouse anti-FOXJ1 eBioscience 14-9965-82 1:500
Mouse anti-Human Nuclear Antigen (HuNu) Abcam ab191181 1:250
Mouse anti-Surfactant Protein B (SFTPB) Seven Hills Bioreagents Wmab-1B9 1:250
Rabbit anti-HOPX Santa Cruz Biotechnology Sc-30216 1:250
Rabbit anti-NKX2.1 Abcam ab76013 1:200
Rabbit anti-Nuclear Mitotic Aparatus – Human (NuMa) Thermo Scientific PA5-22285 1:500

Rabbit anti-PDGFRalpha Santa Cruz Biotechnology sc-338 1:100
Rabbit anti-Pro-Surfactant protein C (Pro-SFTPC) Seven Hills Bioreagents Wrab-9337 1:500
Rabbit anti-SOX9 Millipore AB5535 1:500
Rabbit anti-Synaptophysin Abcam AB32127 1:500

Secondary Antibody Source Catalog # Dilution
Donkey anti-goat 488 Jackson Immuno 705-545-147 1:500
Donkey anti-goat 647 Jackson Immuno 705-605-147 1:500
Donkey anti-goat Cy3 Jackson Immuno 705-165-147 1:500
Donkey anti-mouse 488 Jackson Immuno 715-545-150 1:500
Donkey anti-mouse 647 Jackson Immuno 415-605-350 1:500
Donkey anti-mouse Cy3 Jackson Immuno 715-165-150 1:500
Donkey anti-rabbit 488 Jackson Immuno 711-545-152 1:500
Donkey anti-rabbit 647 Jackson Immuno 711-605-152 1:500
Donkey anti-rabbit Cy3 Jackson Immuno 711-165-102 1:500
Donkey anti-goat 488 Jackson Immuno 705-545-147 1:500
Donkey anti-goat 647 Jackson Immuno 705-605-147 1:500
Donkey anti-goat Cy3 Jackson Immuno 705-165-147 1:500
Donkey anti-mouse 488 Jackson Immuno 715-545-150 1:500
Donkey anti-mouse 647 Jackson Immuno 415-605-350 1:500
Donkey anti-mouse Cy3 Jackson Immuno 715-165-150 1:500
Donkey anti-rabbit 488 Jackson Immuno 711-545-152 1:500
Donkey anti-rabbit 647 Jackson Immuno 711-605-152 1:500
Donkey anti-rabbit Cy3 Jackson Immuno 711-165-102 1:500
Streptavidin 488 Jackson Immuno 016-540-084 1:500

Validation

Antibody validation was performed by the manufacturer.

Eukaryotic cell lines

Policy information about cell lines

Cell line source(s)	hESC lines H9 and H1 (NIH registry #0062 and #0043, respectively) were obtained from the WiCell Research Institute.
Authentication	Cell lines are routinely karotyped to ensure no genetic transformations have occurred.
Mycoplasma contamination	All cell lines tested negative for Mycoplasma contamination.
Commonly misidentified lines (See ICLAC register)	*Name any commonly misidentified cell lines used in the study and provide a rationale for their use.*