A11/00

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INEB
Instituto de Engenharia Biomédica

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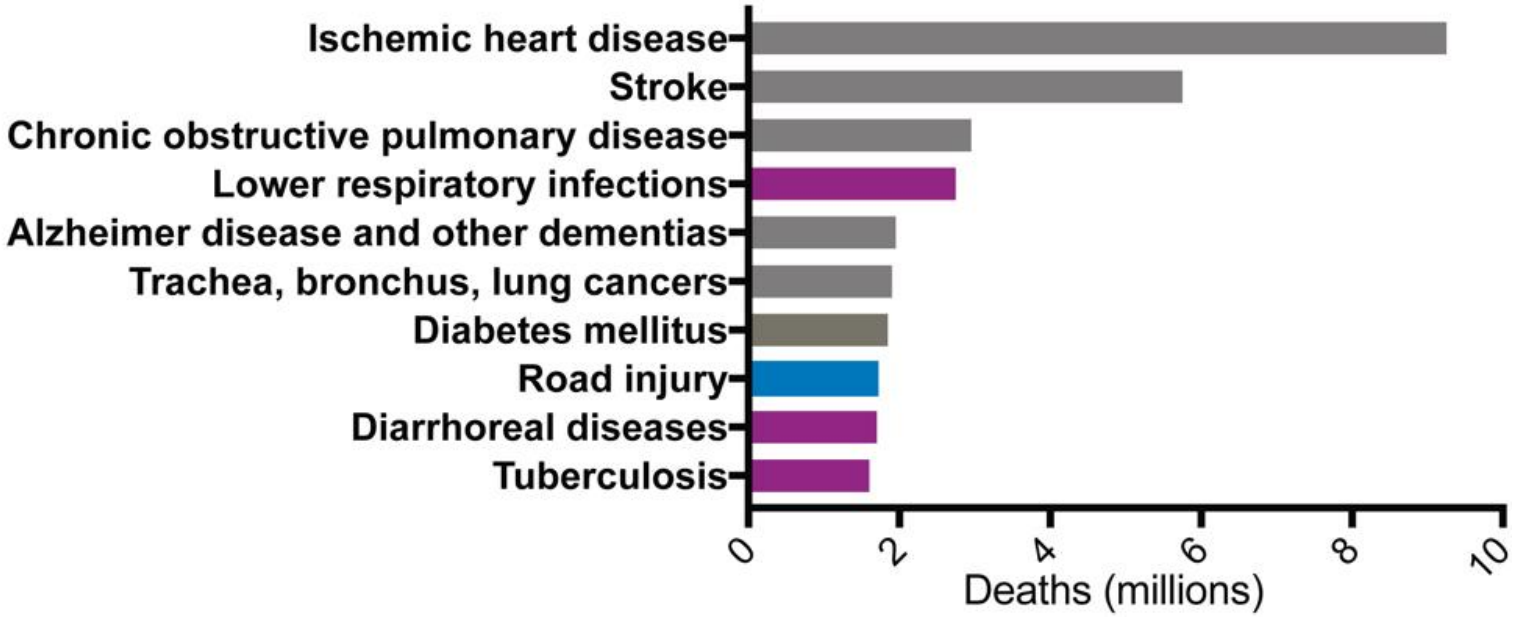
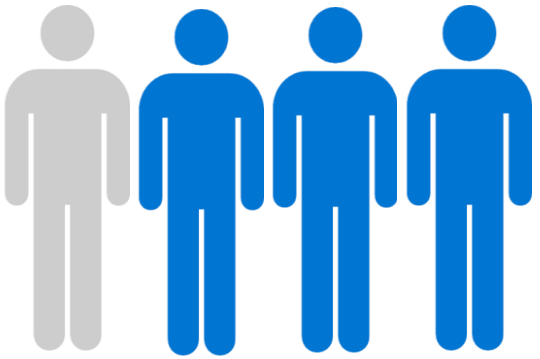
Cardiac aging and injury: alterations in the cellular and extracellular compartments

Diana S Nascimento
(dsn@ineb.up.pt)

Cardiovascular Diseases Are the Leading Cause of Death Worldwide



Adapted from Global Health Estimates 2016 | World Health Organization 2018



1 in every 4 deaths

are from Heart Diseases

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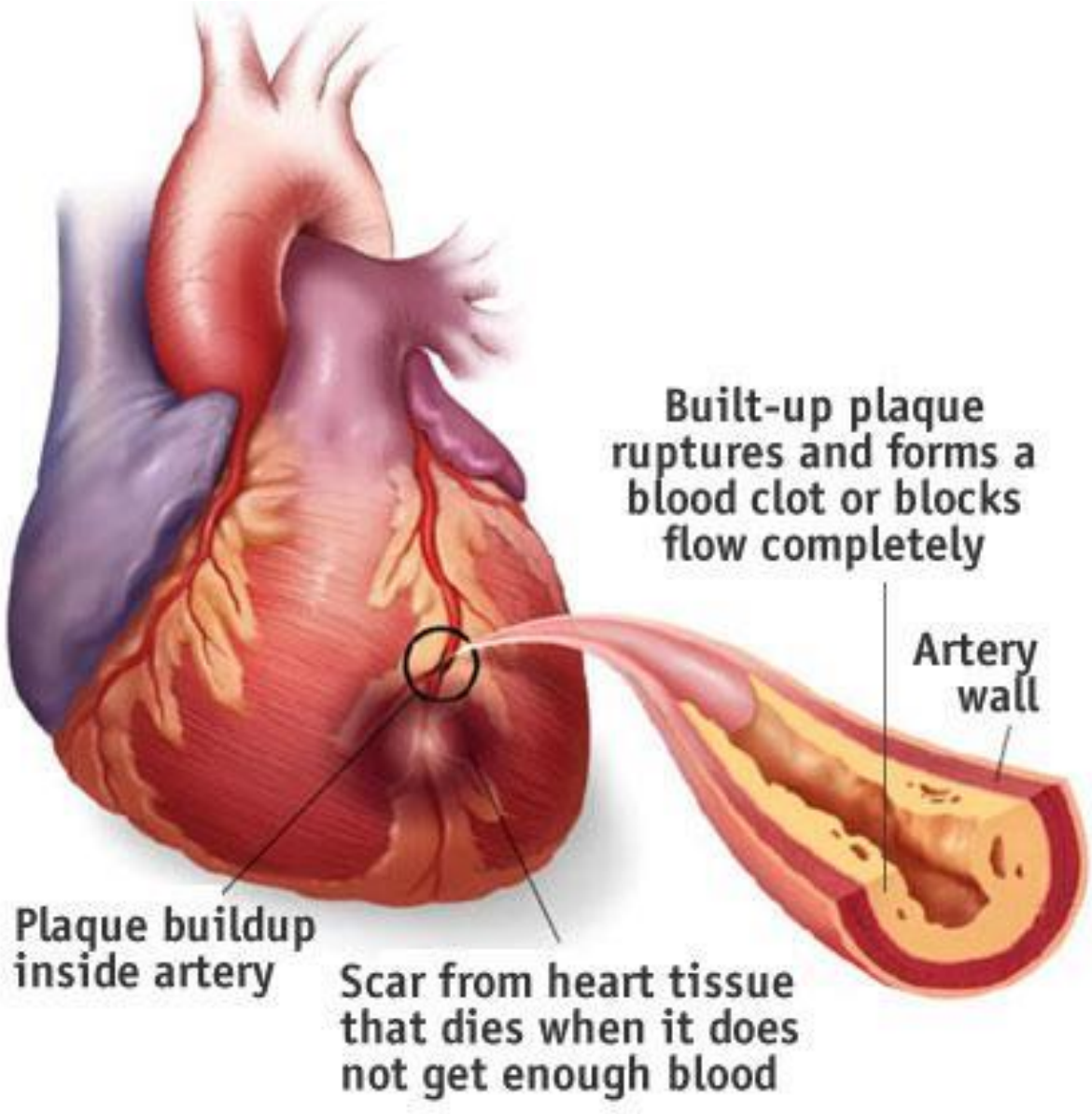
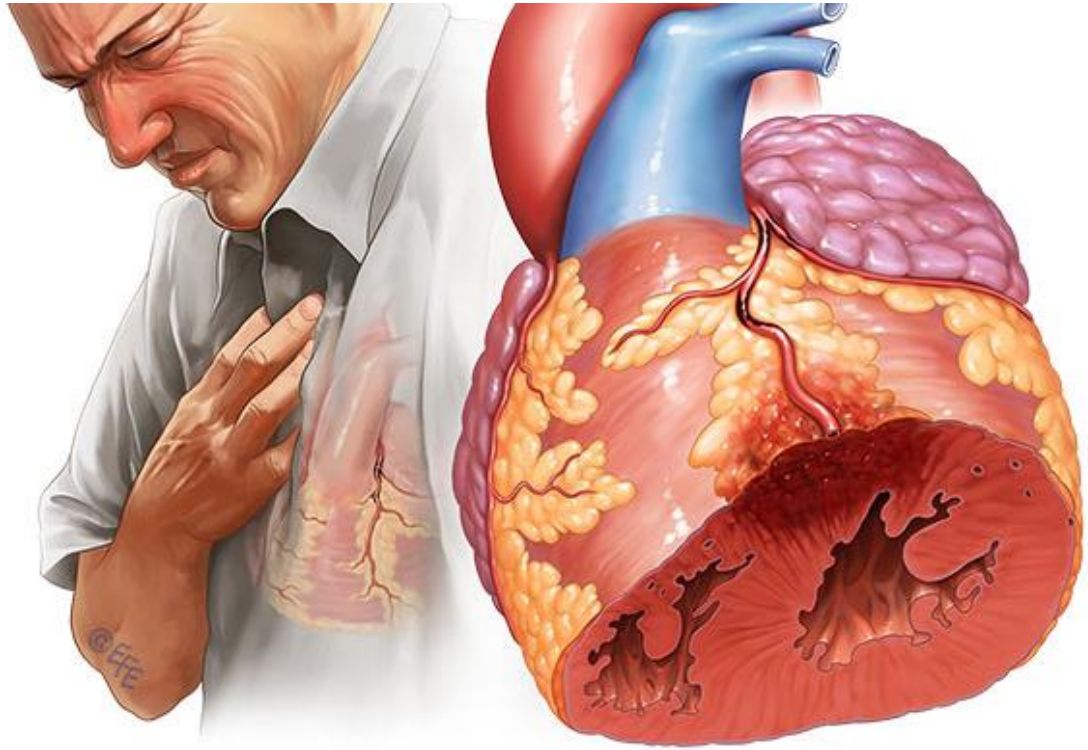
Myocardial infarction





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Animal models of disease

The adult mammalian heart does not regenerate

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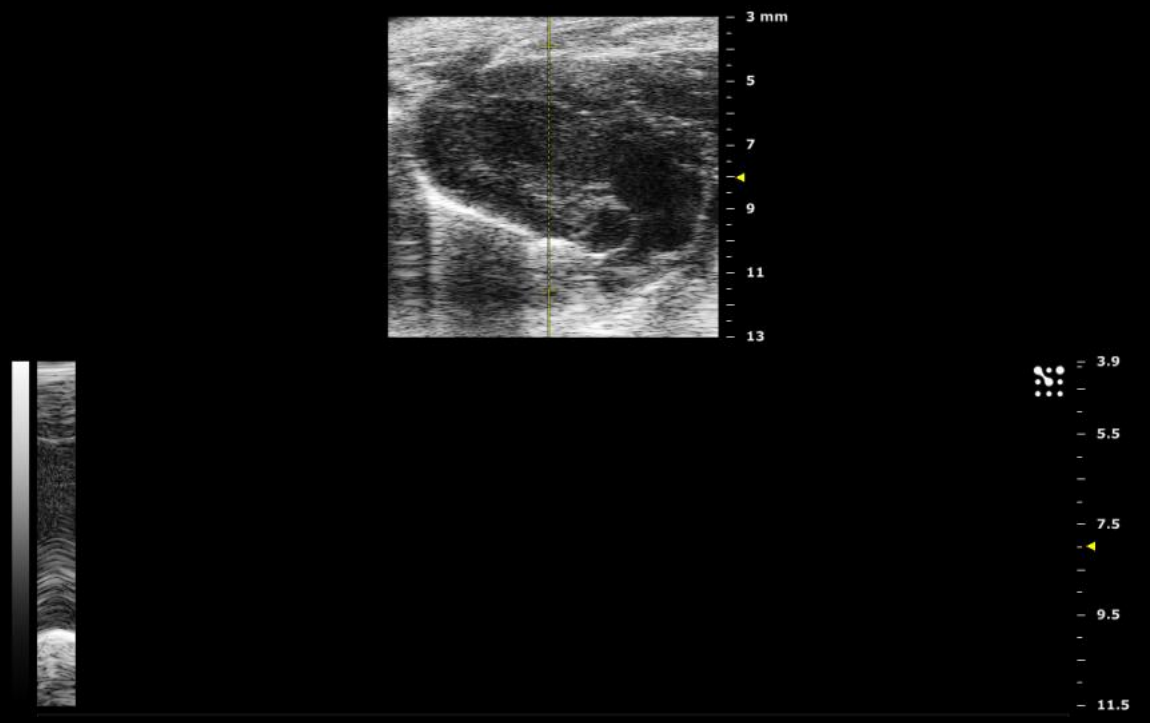
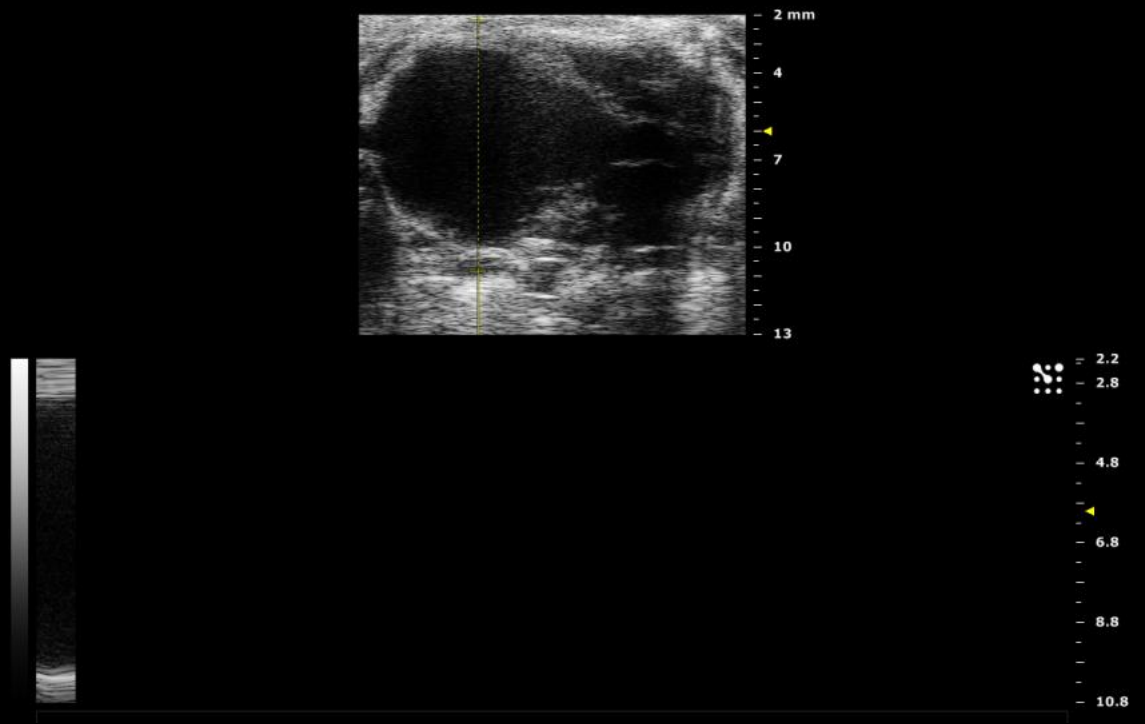
The adult mammalian heart does not regenerate





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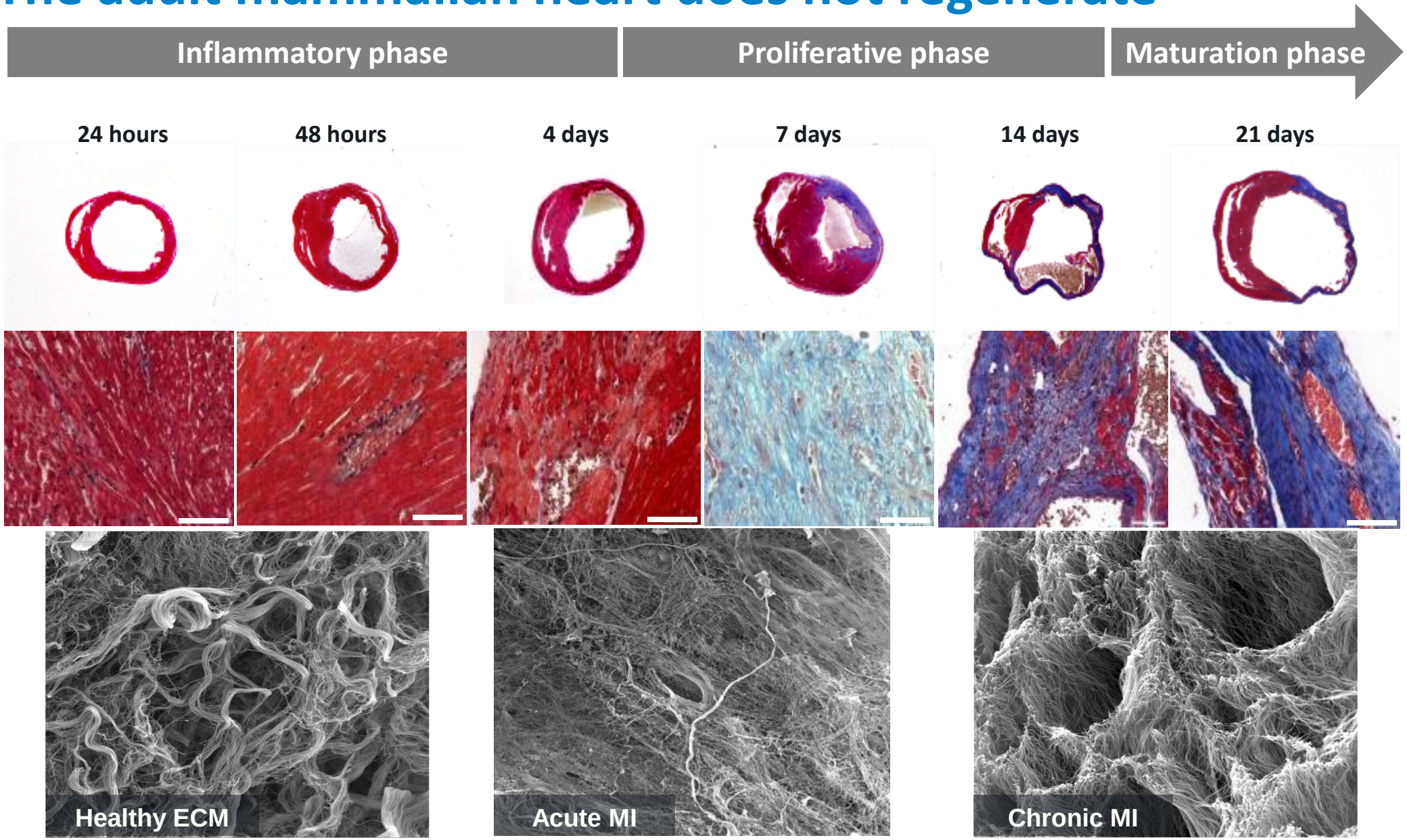
The adult mammalian heart does not regenerate



Perestrelo et al. (manuscript in revision)

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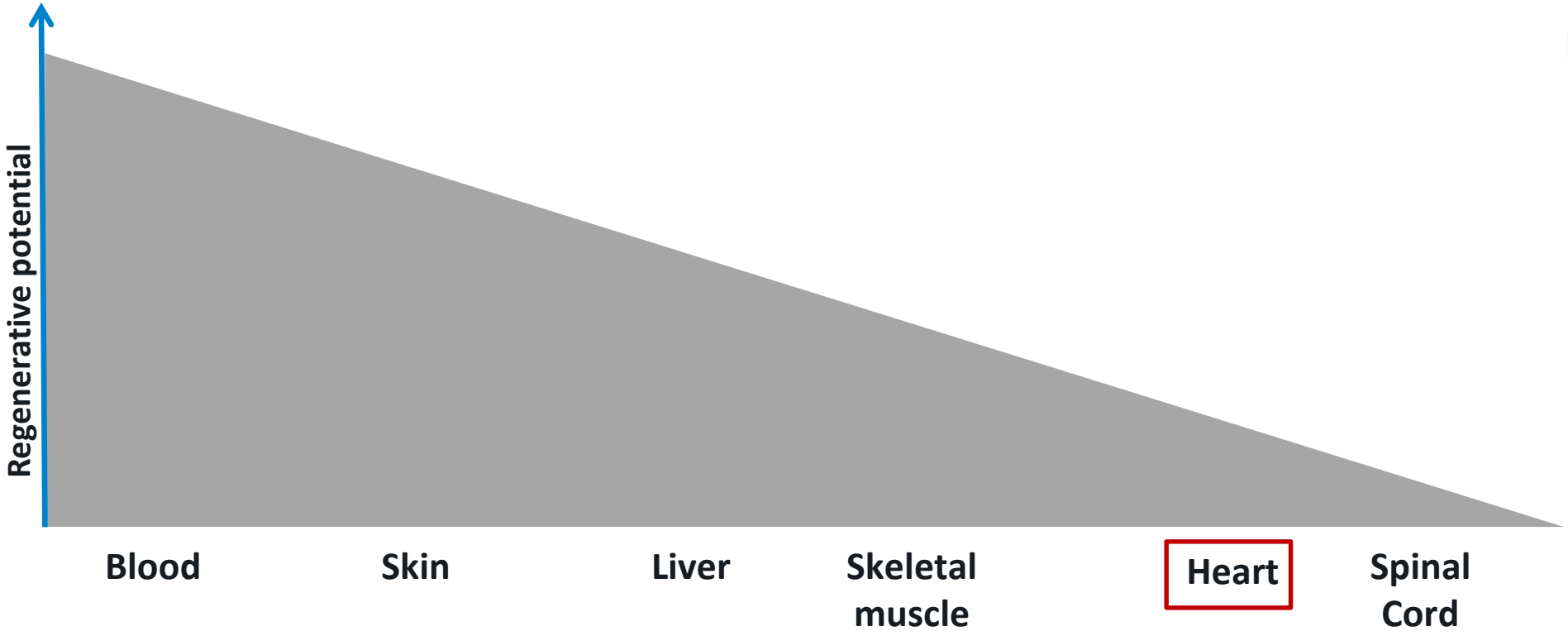
Why does the heart fails to regenerate?

The adult mammalian heart does not regenerate



Adapted from Rando TA. Nature (2005) and Poss KD. Seminars in Cell & Developmental Biology (2007)

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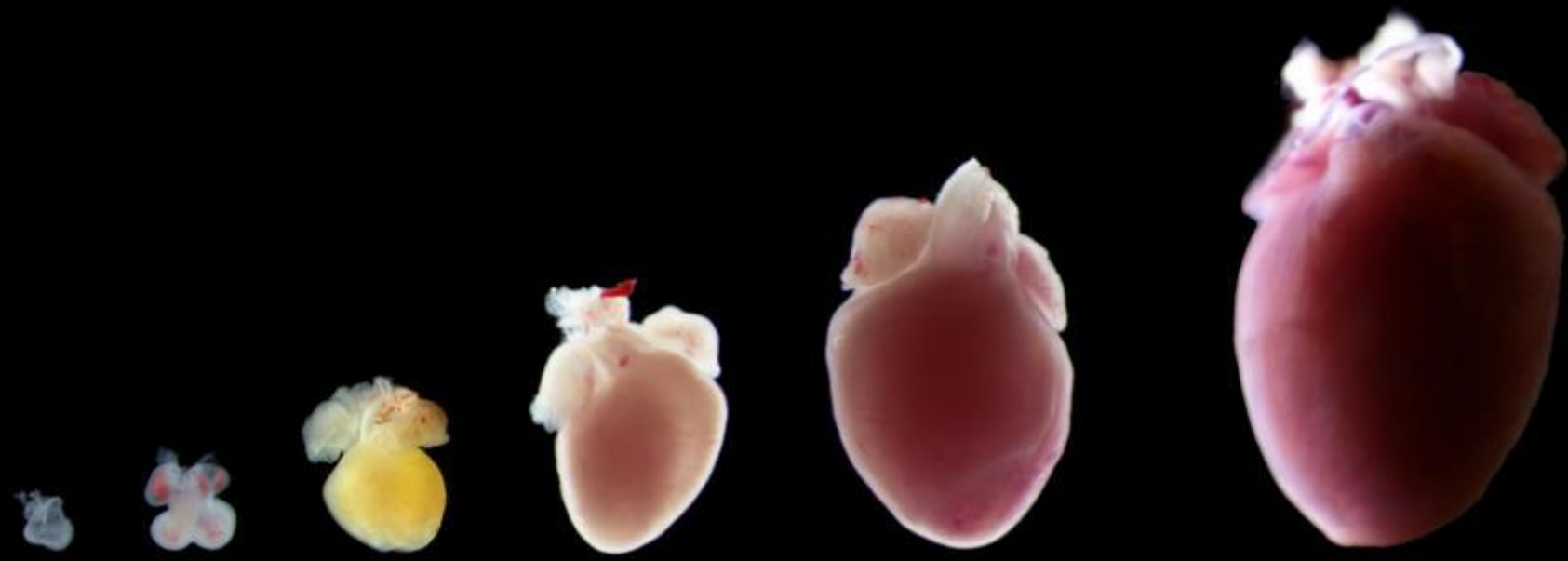
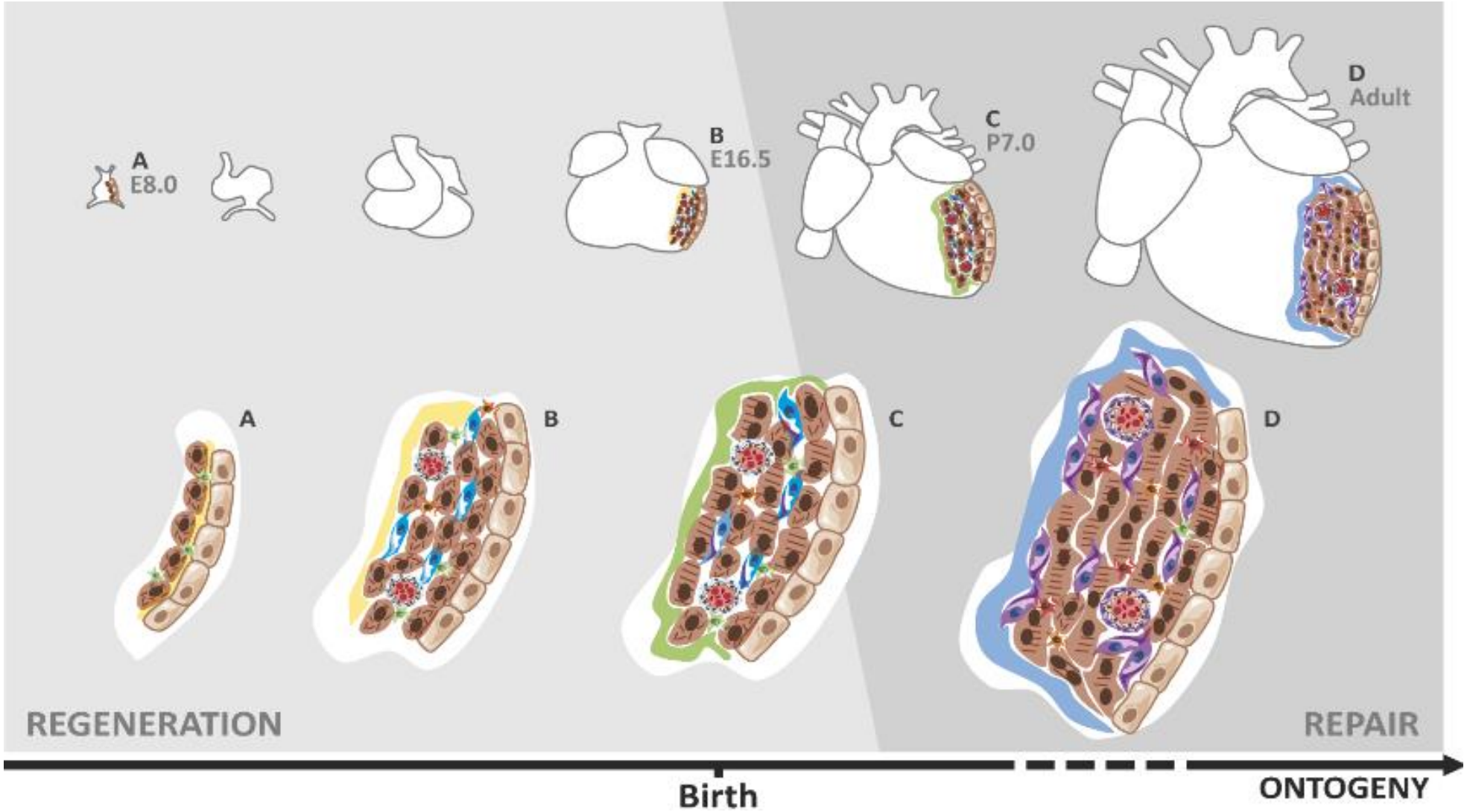
Cell turnover of cardiomyocytes through ontogeny



Cell turnover of cardiomyocytes through ontogeny



Sampaio-Pinto V et al. Cardiac Regeneration and Repair: From Mechanisms to Therapeutic Strategies, *Springer Book*, 2020

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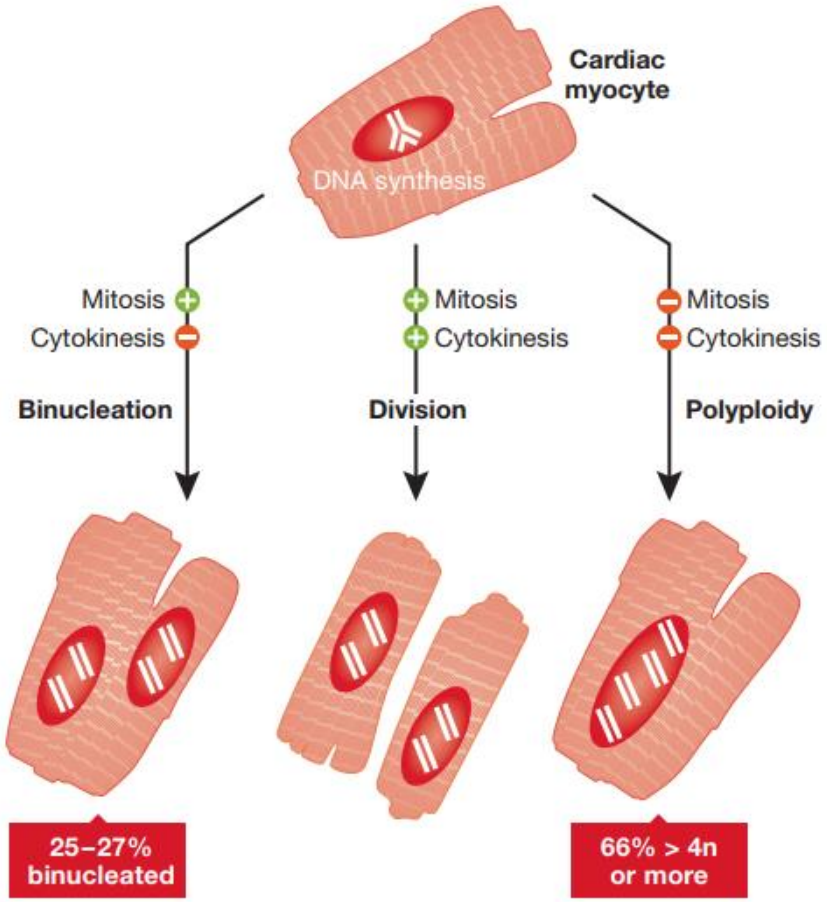
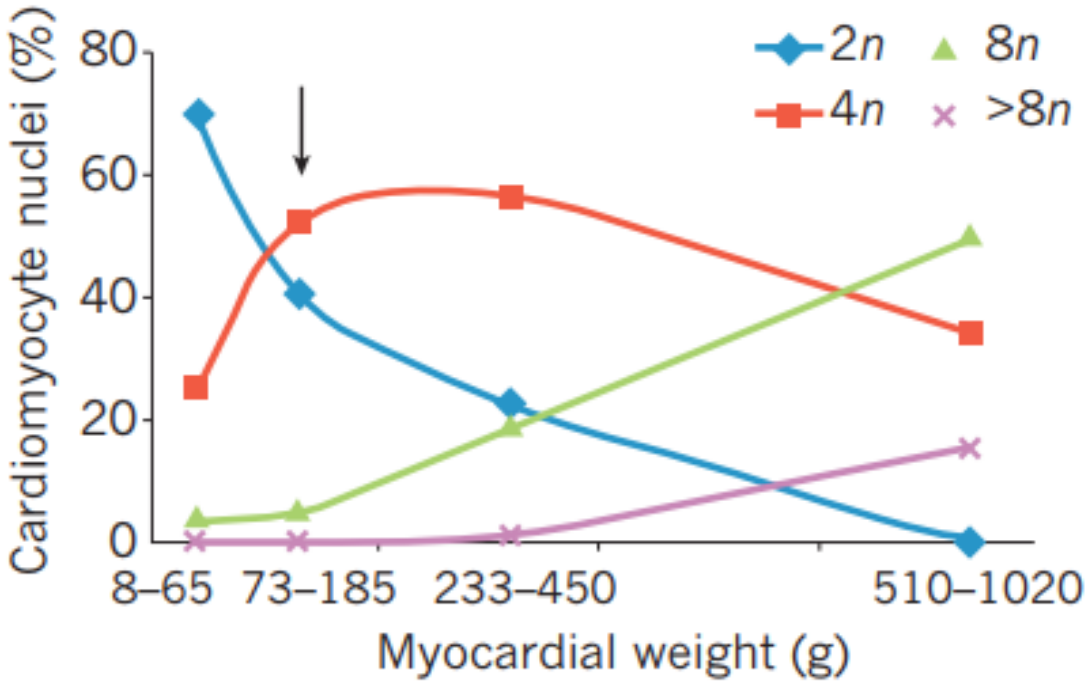
Cell turnover of cardiomyocytes through ontogeny





Steinhauser ML & Lee RT. Regeneration of the heart. *EMBO Molecular Medicine*. 2011. 3, 1–12
Laflamme MA & Murry CE. Heart Regeneration. *Nature*. 2011. 473; 326-335.

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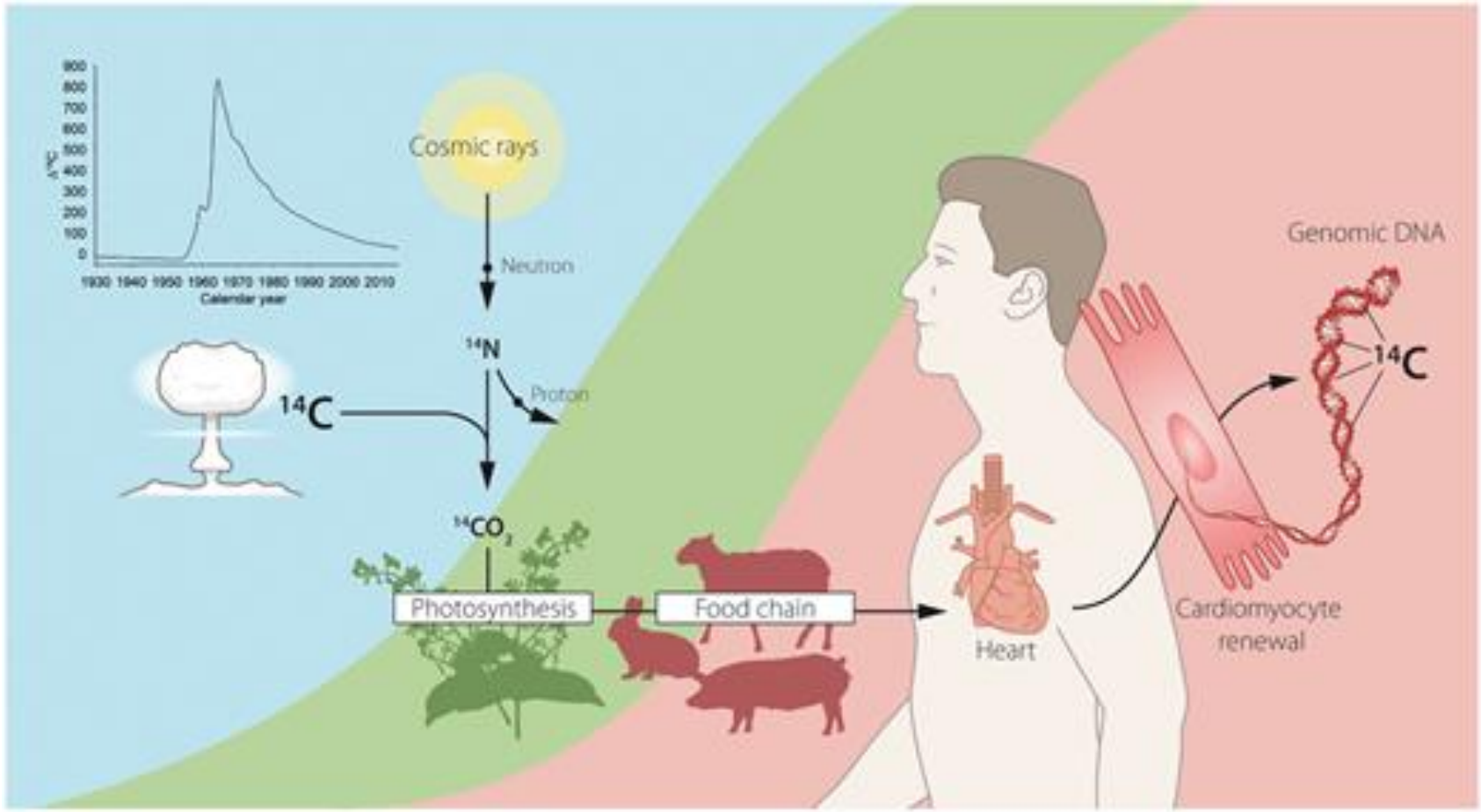
Cell turnover of cardiomyocytes in adulthood

Evidence for Cardiomyocyte Renewal in Humans

Science
AAAS

Olaf Bergmann,[1]* Ratan D. Bhardwaj,[1]* Samuel Bernard,[2] Sofia Zdunek,[1] Fanie Barnabé-Heider,[1] Stuart Walsh,[3] Joel Zupicich,[1] Kanar Alkass,[4] Bruce A. Buchholz,[5] Henrik Druid,[4] Stefan Jovinge,[3,6] Jonas Frisén[1]†



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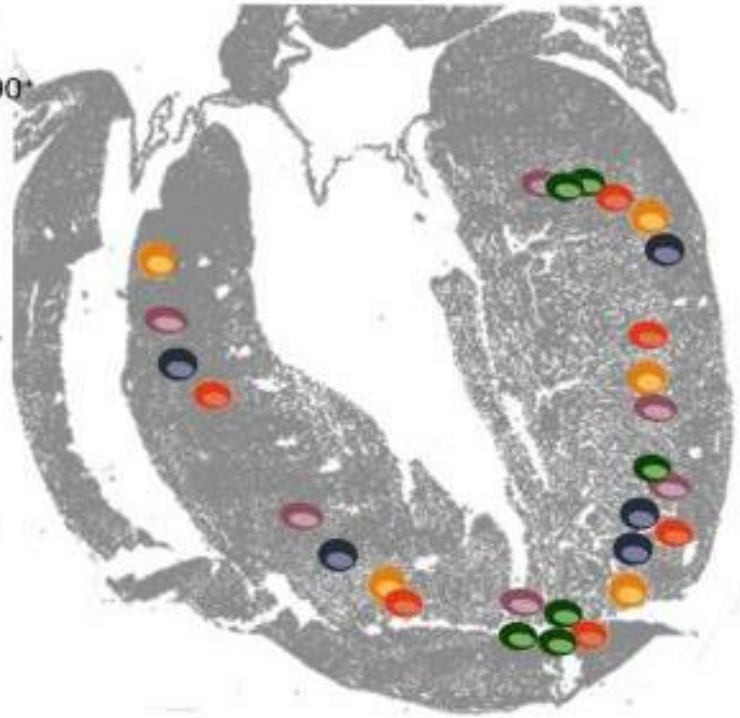
What is the origin of the newly formed cardiomyocytes?

Stem cells in the adult mammalian heart

[1]**Sca-1**$^-$ **c-Kit**$^-$ CD34$^-$ Flk-2$^-$ Thy1.1$^-$
[2]**Sca-1**$^+$ Abcg2$^+$ ckit^{low} CD45^{low} CD34^{low} CD31$^-$
[3]**Sca-1**$^+$ **c-Kit**$^-$ CD31$^-$ CD45$^-$ CD44$^-$ CD34$^-$
[4]**Sca-1**$^+$ **c-Kit**$^-$ VE-cadherin$^-$ CD34$^+$ CD73$^+$ CD90$^+$ CD105$^+$ CD45$^-$

Side population



Thymosin β4 primed Wt-1$^+$ *epicardial progenitors*

[13]**Sca-1**$^+$ **c-Kit**$^-$ CD31$^-$ Flk-1$^-$

CADUCEUS

Sphere formation

[5]**c-Kit**$^+$ **Sca-1**$^+$ CD34$^+$ CD31$^+$ Flk-1$^+$
[6]**Sca-1**$^+$ **c-Kit**$^-$ CD-45$^-$ CD34$^-$ CD31$^-$ CD29^{low} CD133$^-$ Flk-1$^-$

SCIPIO

c-Kit$^+$ *cells*

[7]**c-Kit**$^+$ CD45$^-$ CD34$^-$ CD20$^-$ CD45RO$^-$ CD8$^-$ TER-119$^-$
[8]**c-Kit**$^+$ CD29$^+$ CD44$^+$ CD105$^+$ CD90$^+$

Sca-1$^+$ *cells*

[9]**Sca-1**$^+$ **c-Kit**$^-$ Flt-1$^-$ Flk-1$^-$ CD34$^-$ CD31$^+$ CD45$^-$
[10]**Sca-1**$^+$ **c-Kit**$^-$ CD34$^-$ CD31$^-$ CD45$^-$ CD90$^+$ CD105$^+$ CD29$^+$ CD44$^+$ CD106$^+$ CD73$^+$ CD13$^+$
[11]**Sca-1**$^+$ PDGFRα$^+$ CD31$^-$ CD45$^-$ CD90$^+$ CD105$^+$ CD29$^+$ CD44$^+$ Flk-1$^-$
[12]**Sca-1**$^+$ **c-Kit**$^-$ CD34$^-$ CD31$^-$ CD45$^-$ CD29$^+$

Freire A* & Nascimento DS*, et. al. (2014) *Stem Cells & Development*

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Stem cells in the adult mammalian heart

Home / News & Opinion

Dozens of Retractions Requested for Heart Stem Cell Studies

Harvard and Brigham and Women's Hospital disavow the work by former faculty member Piero Anversa.

c-kit^{+} CPCs

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Stem cells in the adult mammalian heart

Cardiac Sca-1$^+$ Cells Are Not Intrinsic Stem Cells for Myocardial Development, Renewal, and Repair

Lu Zhang, Nishat Sultana, Jianyun Yan, Fan Yang, Fuxue Chen, Elena Chepurko, Feng-Chun Yang, Qinghua Du, Lior
Mingjiang Xu, Lei Bu, Chen-Leng Cai

Genetic Lineage Tracing of Sca-1$^+$ Cells Reveals Endothelial but Not Myogenic Contribution to the Murine Heart

Ronald J. Vagnozzi, Michelle A. Sargent, Suh-Chin J. Lin, Nathan J. Palpant, Charles E. Murry, Jeffery D. Molkentin

Evidence for Minimal Cardiogenic Potential of Stem Cell Antigen 1–Positive Cells in the Adult Mouse Heart

Lauren E. Neidig, Florian Weinberger, Nathan J. Palpant, John Mignone, Amy M. Martinson, Daniel W. Sorensen, Ingrid Bender, Natsumi Nemoto, Hans Reinecke, Lil Pabon, Jeffery D. Molkentin, Charles E. Murry, Jop H. van Berlo

Absence of Cardiomyocyte Differentiation Following Transplantation of Adult Cardiac-Resident Sca-1$^+$ Cells Into Infarcted Mouse Hearts

Mark H. Soonpaa, Pascal J. Lafontant, Sean Reuter, John A. Scherschel, Edward F. Srour, Marc-Michael Zaruba, Michael Rubart-von der Lohe, Loren J. Field

Fate Mapping of Sca1$^+$ Cardiac Progenitor Cells in the Adult Mouse Heart

Juan Tang, Yan Li, Xiuzhen Huang, Lingjuan He, Libo Zhang, Haixiao Wang, Wei Yu, Wenjuan Pu, Xueying Tian, Yu Nie, Shengshou Hu, Qing-Dong Wang, Kathy O. Lui, Bin Zhou

Originally published 17 Dec 2018 | https://doi.org/10.1161/CIRCULATIONAHA.118.036210 | Circulation. 2018;138:2967–2969

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Circulation

Sca-1$^+$ CPCs

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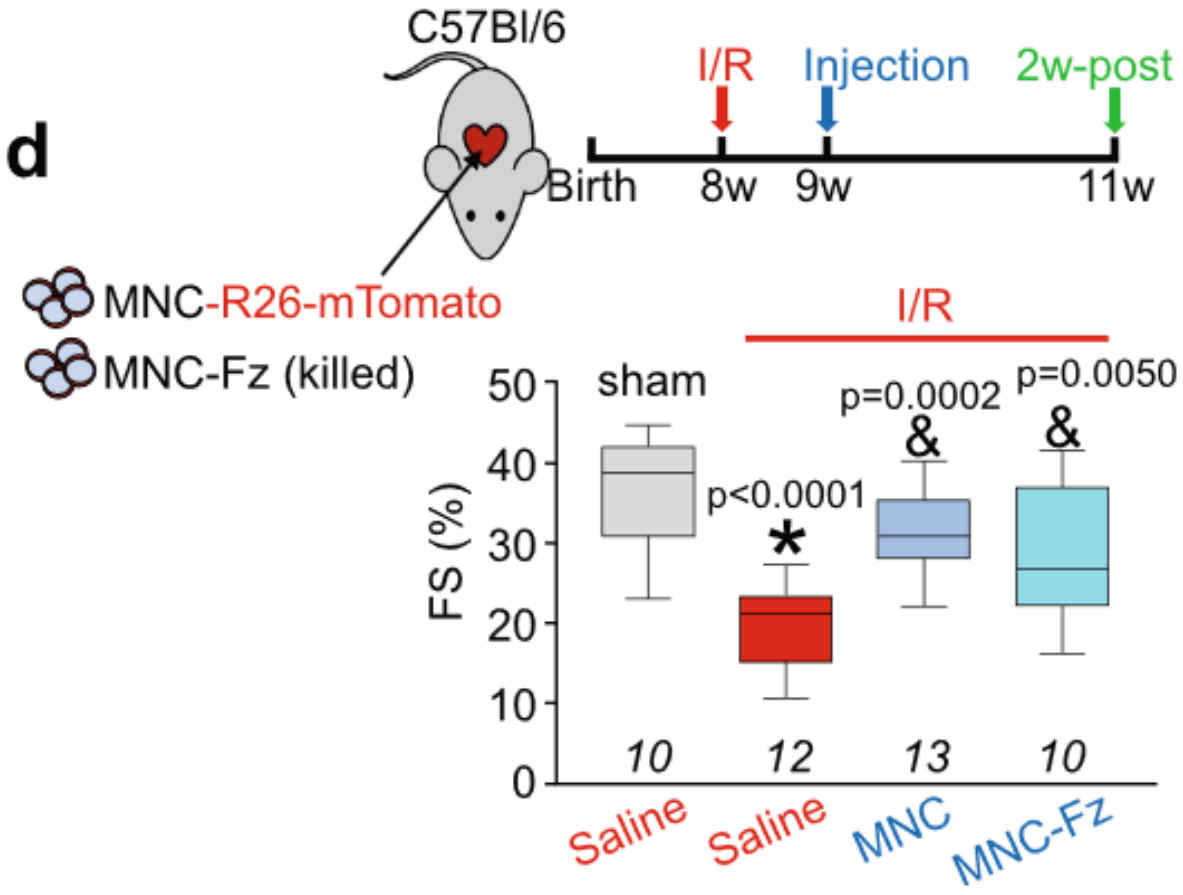
Stem cells in the adult mammalian heart



nature

We'd like to understand how you use our websites in order to impr

Article | Published: 27 November 2019

An acute immune response underlies the benefit of cardiac stem cell therapy

Ronald J. Vagnozzi, Marjorie Maillet, Michelle A. Sargent, Hadi Khalil, Anne Katrine Z. Johansen, Jennifer A. Schwanekamp, Allen J. York, Vincent Huang, Matthias Nahrendorf, Sakthivel Sadayappan & Jeffery D. Molkentin

Nature **577**, 405–409(2020) | Cite this article

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Stem cells DO NOT contribute to cardiomyocyte renewal

Cell cycle re-entry of preexisting cardiomyocytes

Differentiation of Cardiac Progenitor Cells (CPCs)

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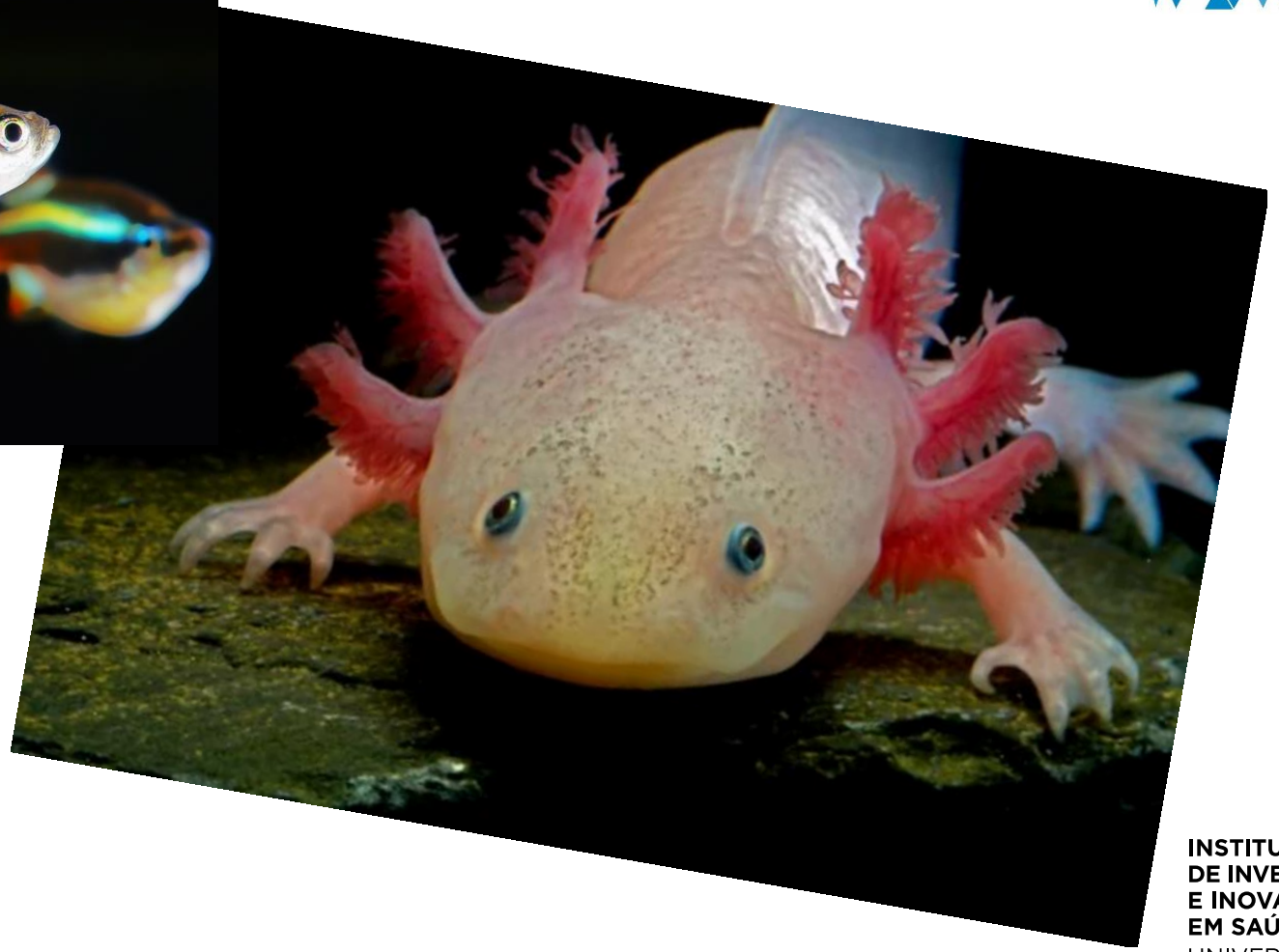
Fish and amphibian species can regenerate their hearts



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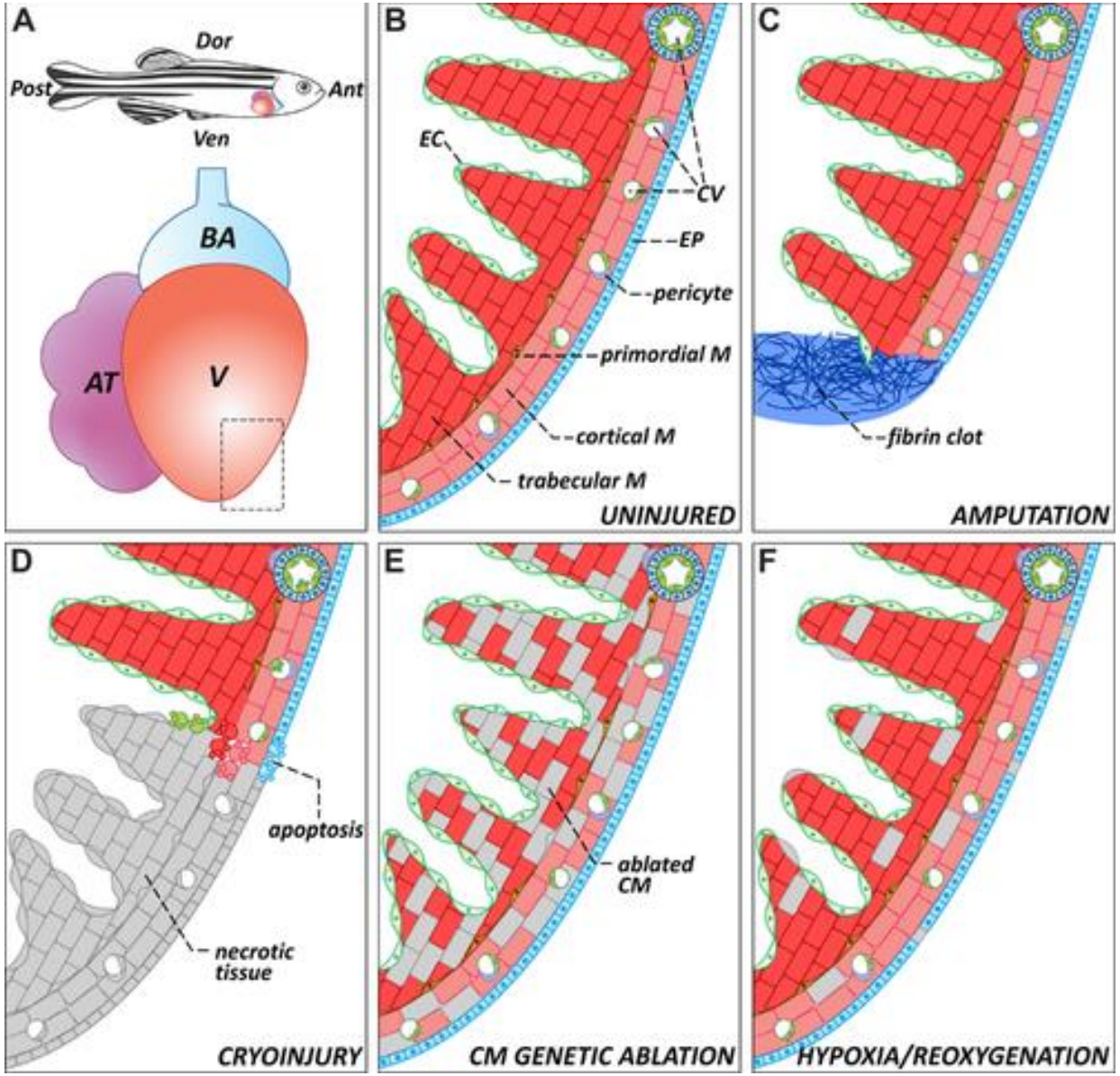
Fish and amphibian species can regenerate their hearts



González-Rosa JM et al. Zebrafish Heart Regeneration: 15 Years of Discoveries. *Regeneration*. 2017 Sep 28;4(3):105-123.

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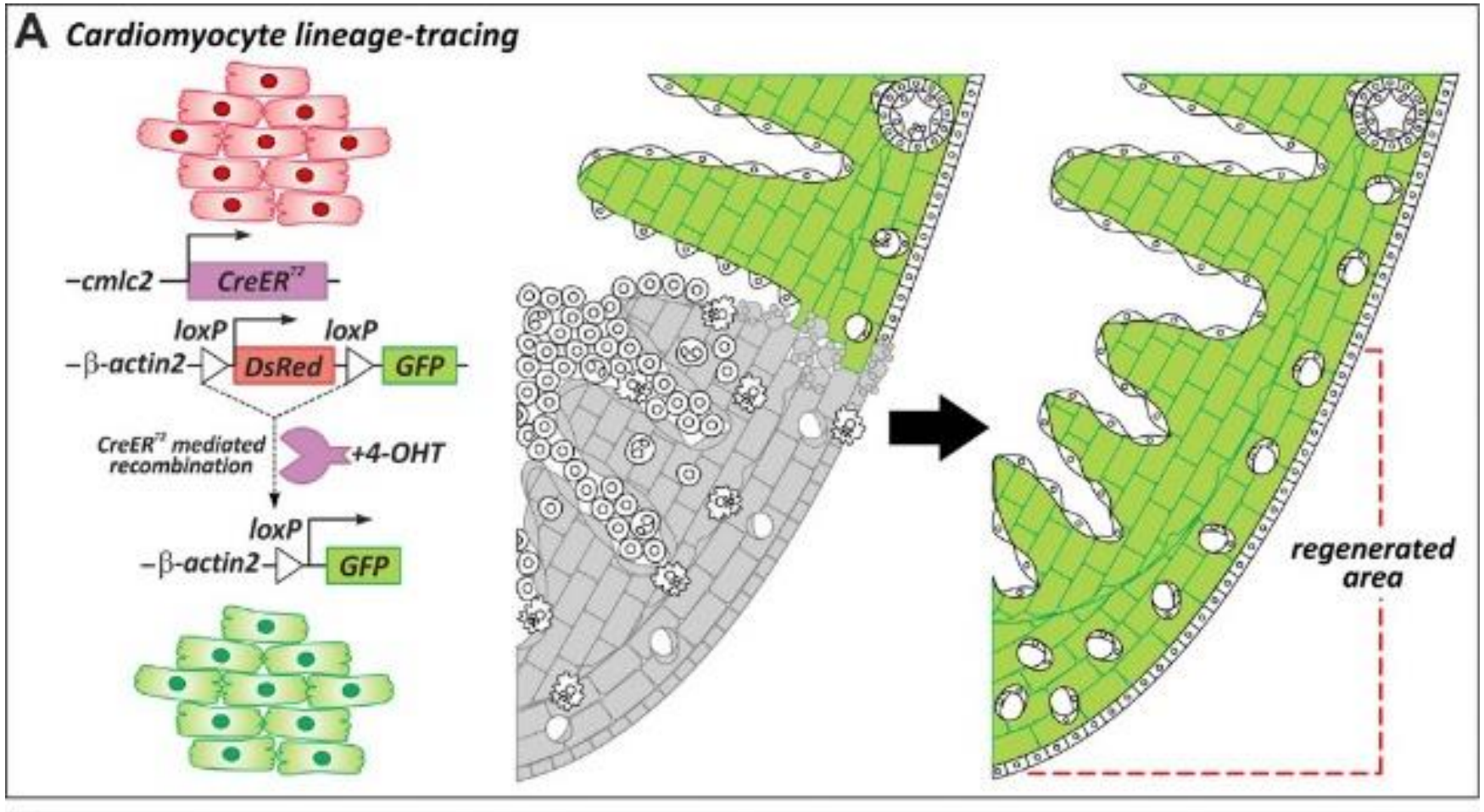
Fish and amphibian species can regenerate their hearts



González-Rosa JM et al. Zebrafish Heart Regeneration: 15 Years of Discoveries. *Regeneration*. 2017 Sep 28;4(3):105-123.

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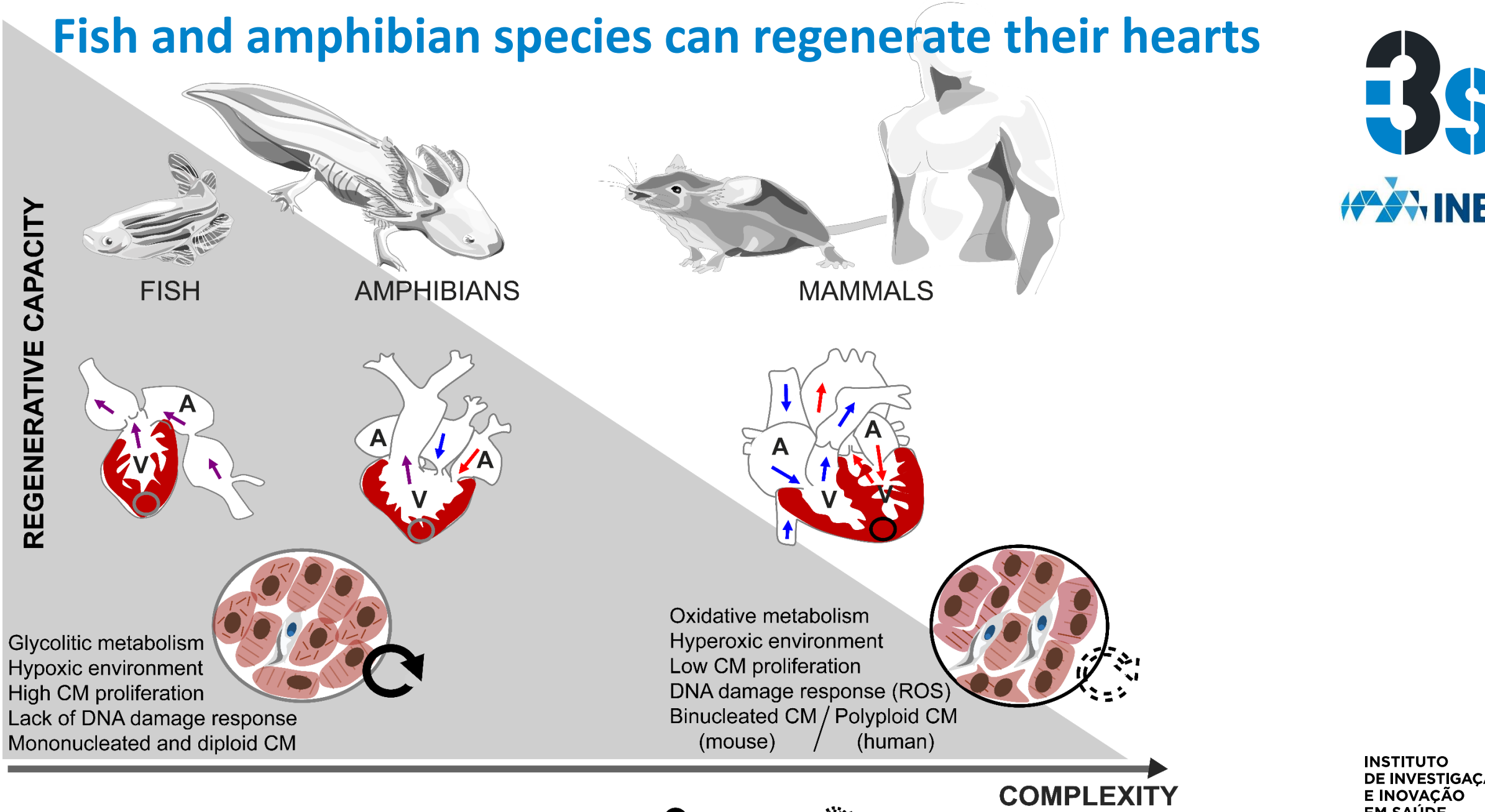
Fish and amphibian species can regenerate their hearts



A, atrium; V, ventricle; , mixture of arterial and venous blood; , venous blood; , arterial blood; , high proliferation; , low proliferation; , mononucleated cardiomyocytes; , binucleated cardiomyocytes; , fibroblasts; iM, immature myocardium; mM, mature myocardium

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Does the regenerative capacity of the heart change throughout life?

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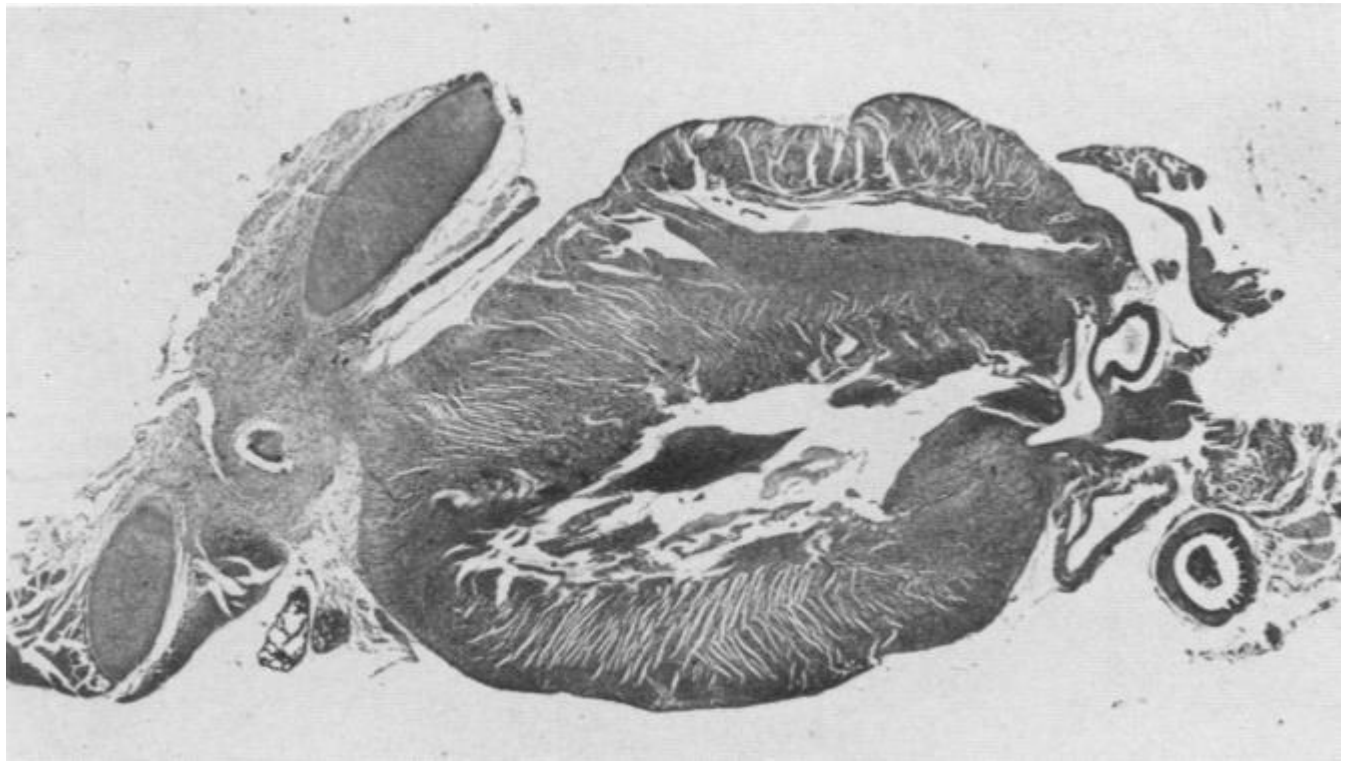
An ontogenic-specific window for cardiac regeneration

MYOCARDIAL REGENERATION IN YOUNG RATS*

MARIO ROBLEDO, M.D.†

From the Department of Pathology, University of Michigan Medical School, Ann Arbor, Mich.



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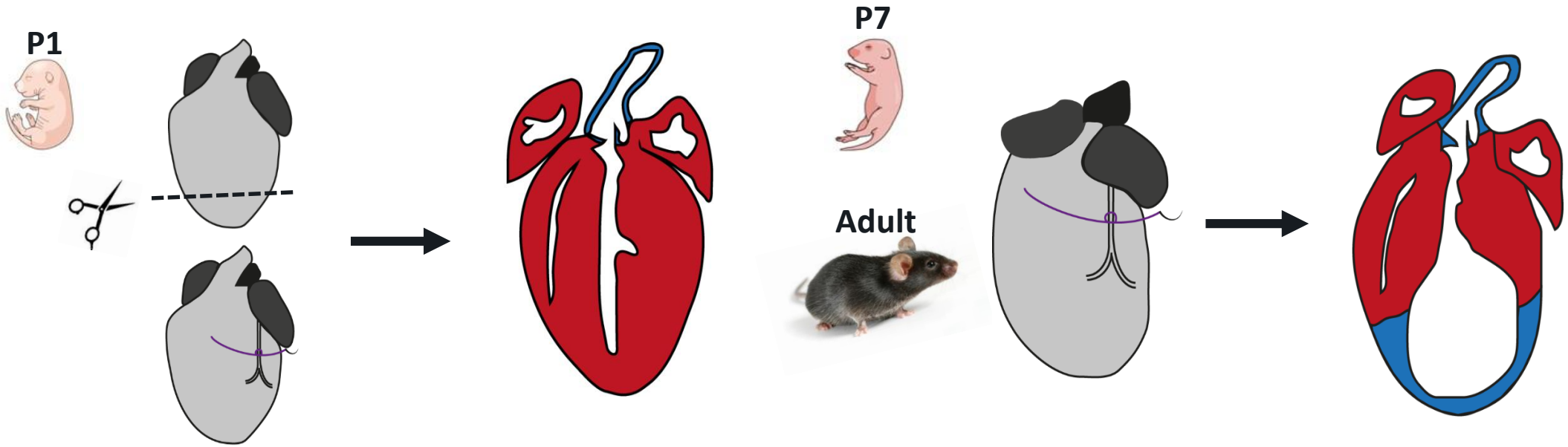
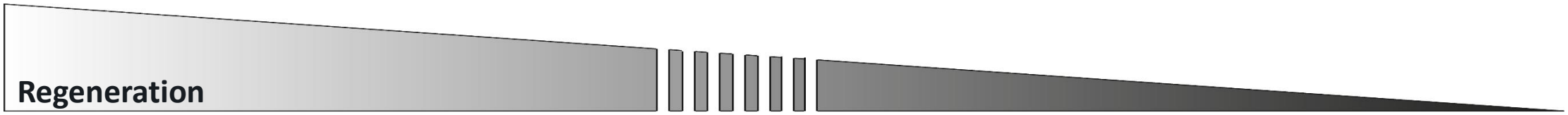
An ontogenic-specific window for cardiac regeneration

Science
AAAS

Transient Regenerative Potential of the Neonatal Mouse Heart
Enzo R. Porrello *et al.*
Science **331**, 1078 (2011);
DOI: 10.1126/science.1200708





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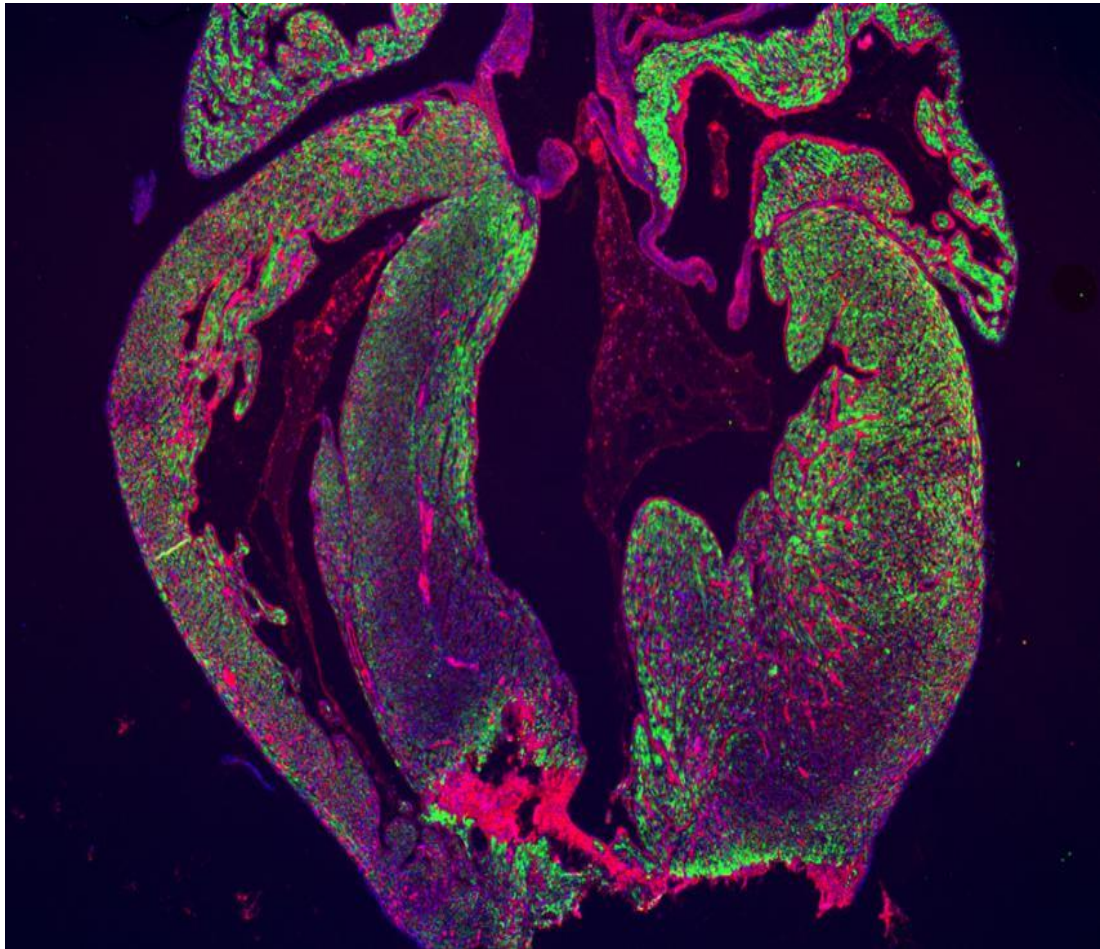
Do neonatal mouse hearts regenerate?

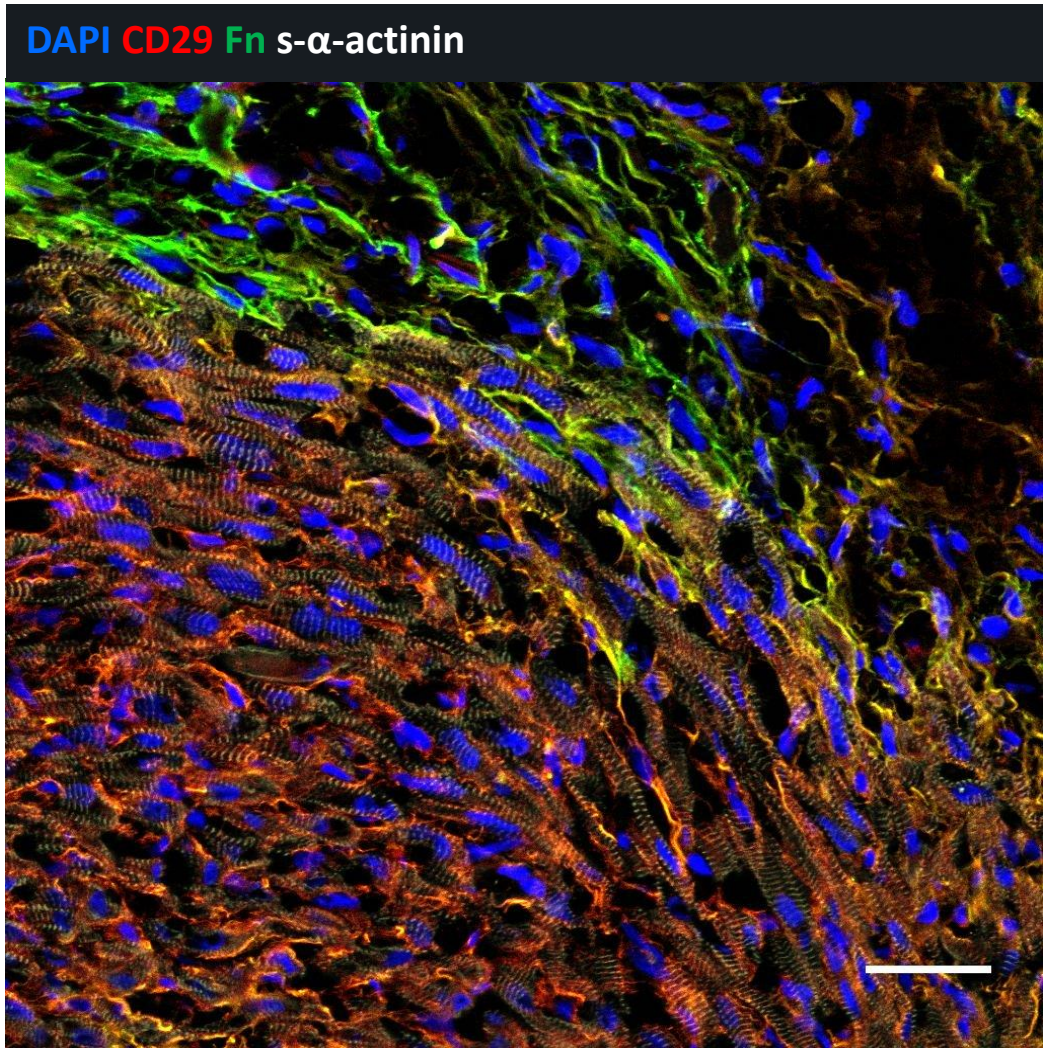
Stem Cell Reports
Report
OPEN ACCESS

Do Neonatal Mouse Hearts Regenerate following Heart Apex Resection?

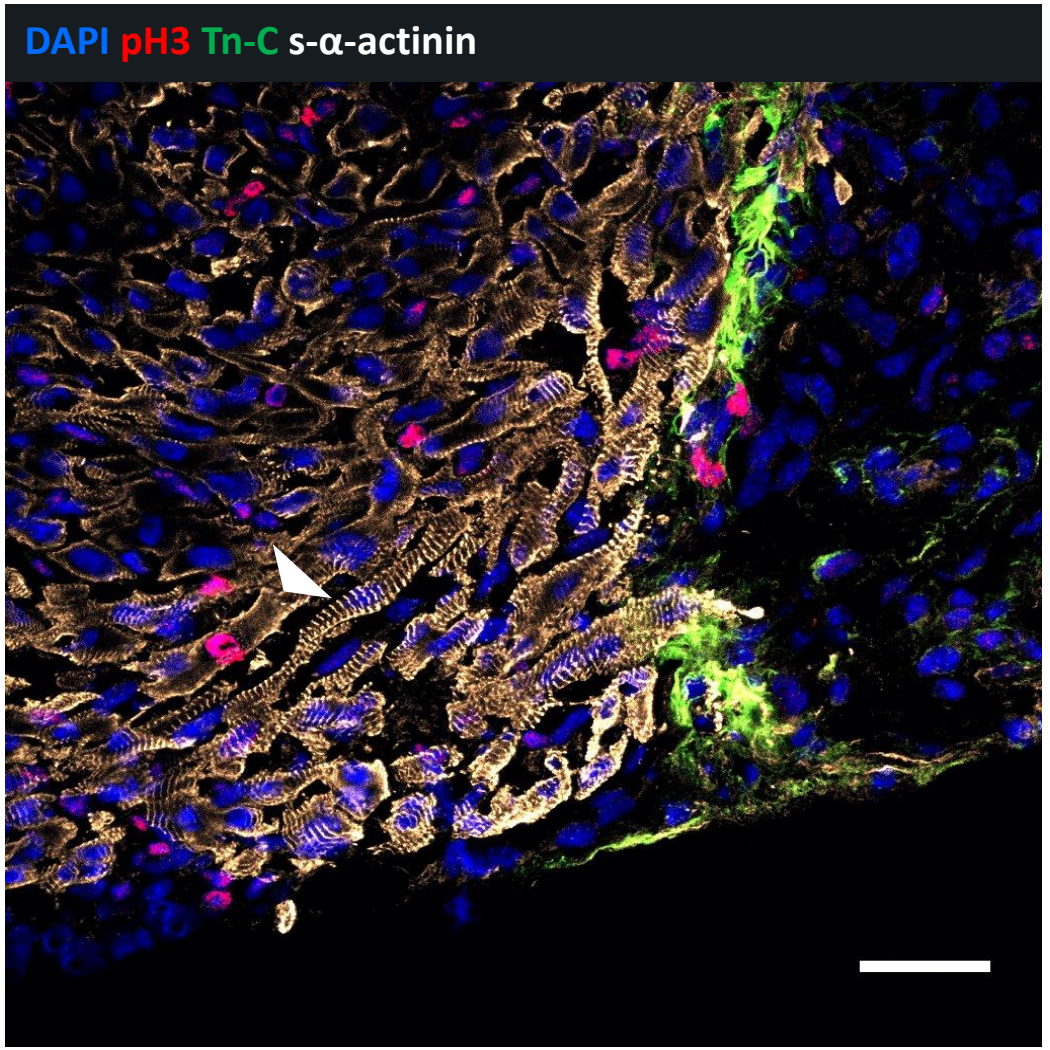
Ditte Caroline Andersen,[1,2,*] Suganya Ganesalingam,[1,3] Charlotte Harken Jensen,[1] and Søren Paludan Sheikh[1,3,*]
[1]Laboratory of Molecular and Cellular Cardiology, Department of Clinical Biochemistry and Pharmacology, Odense University Hospital, Winsloewparken 21[3rd], 5000 Odense C, Denmark
[2]Clinical Institute, University of Southern Denmark, 5000 Odense C, Denmark
[3]Institute of Molecular Medicine, University of Southern Denmark, 5000 Odense C, Denmark
*Correspondence: dandersen@health.sdu.dk (D.C.A.), soeren.sheikh@rsyd.dk (S.P.S.)
http://dx.doi.org/10.1016/j.stemcr.2014.02.008



Dynamic deposition of extracellular matrix instructs the myocardium upon injury



Scale bar: 30 µm



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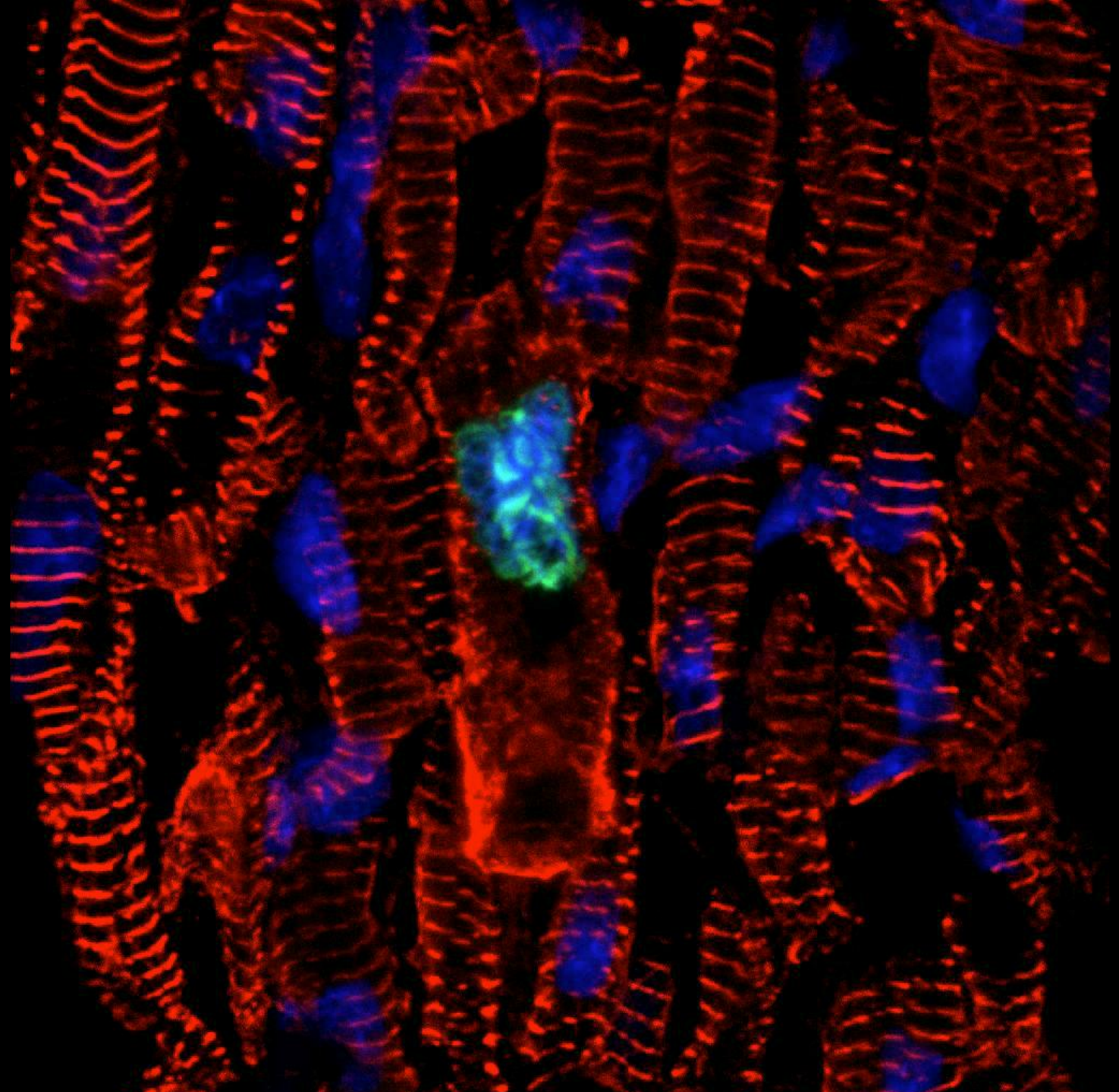
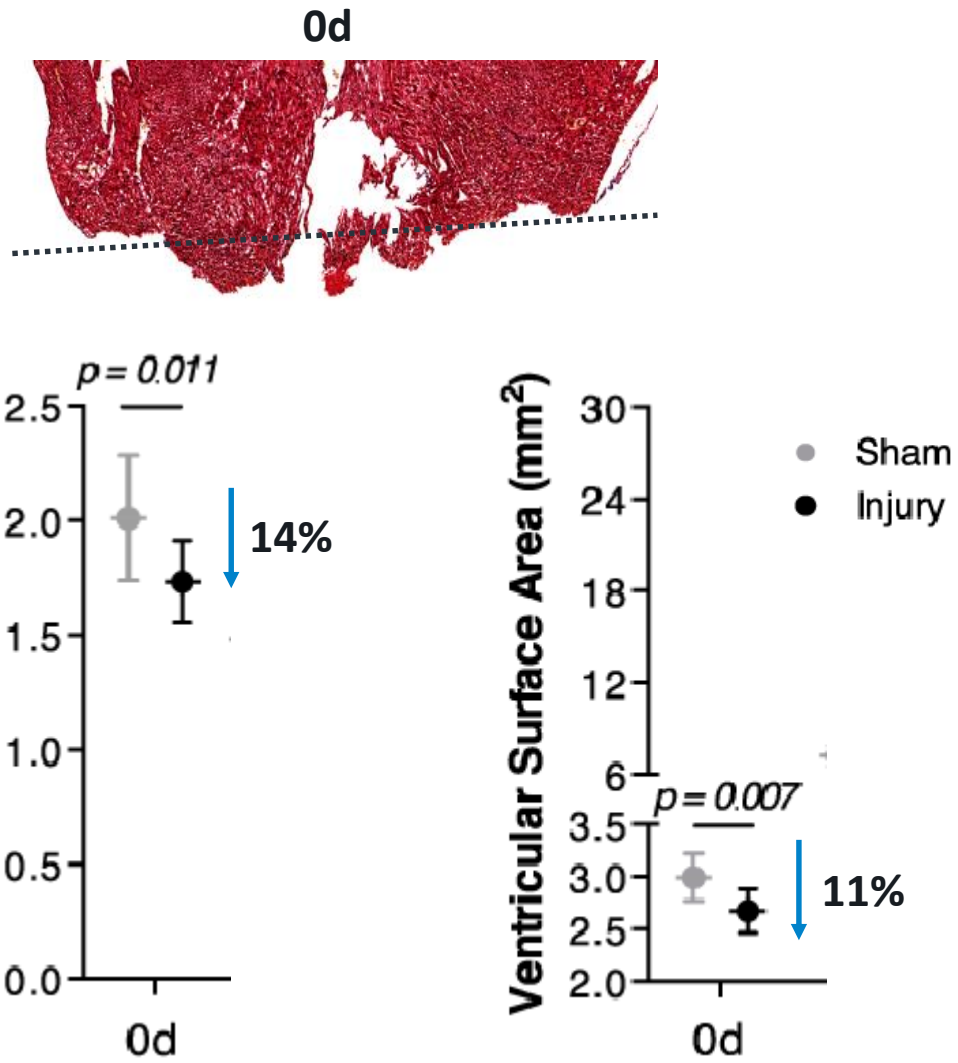
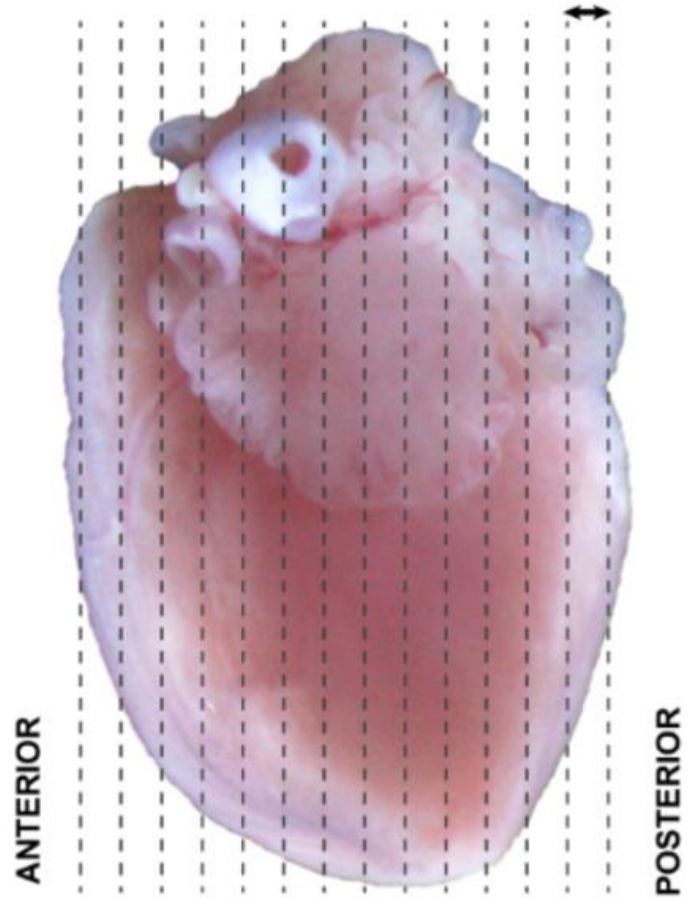
Sampaio-Pinto V* et al. *Stem Cell Reports* 2018


DAPI
pH3
α-s-actinin

Neonatal apex resection in mice





40 µm (0d)
50 µm (7d)
70 µm (14d)
90 µm (21d)
130 µm (60d, 180d)

Sampaio-Pinto V* et al. *Stem Cell Reports* 2018

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Hearts are not fully restored at the histological level

Sampaio-Pinto V* et al. *Stem Cell Reports* 2018

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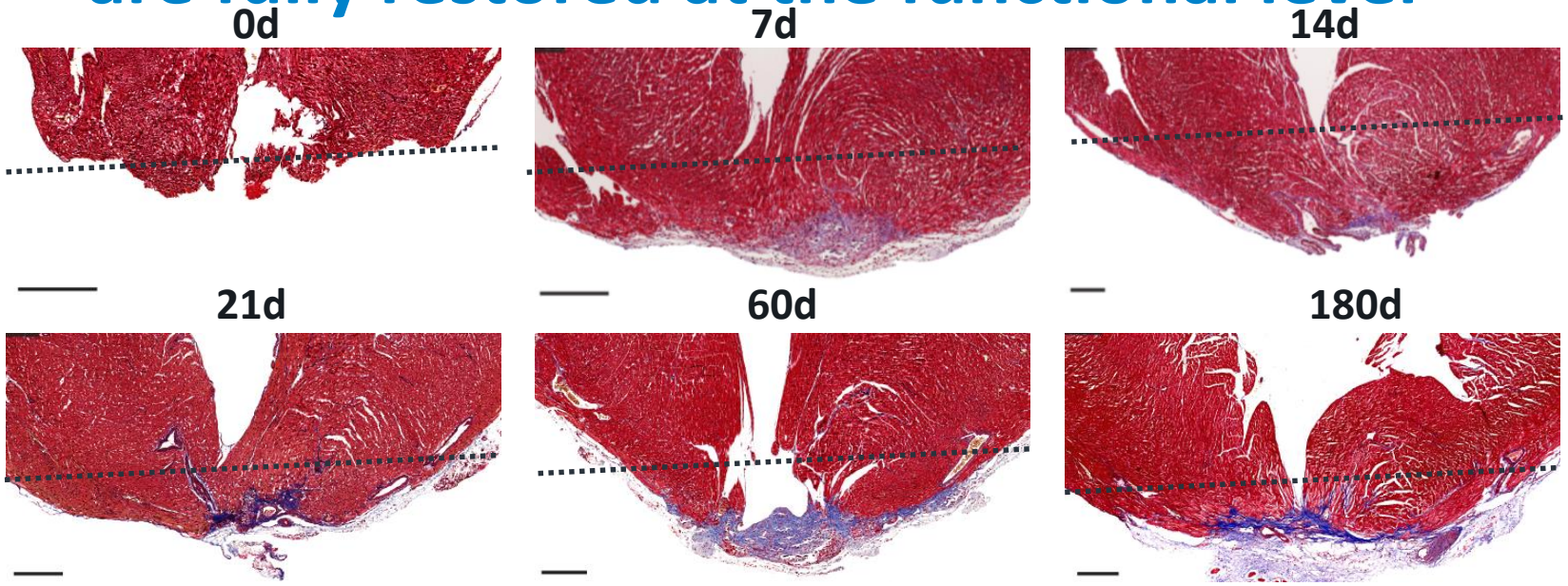
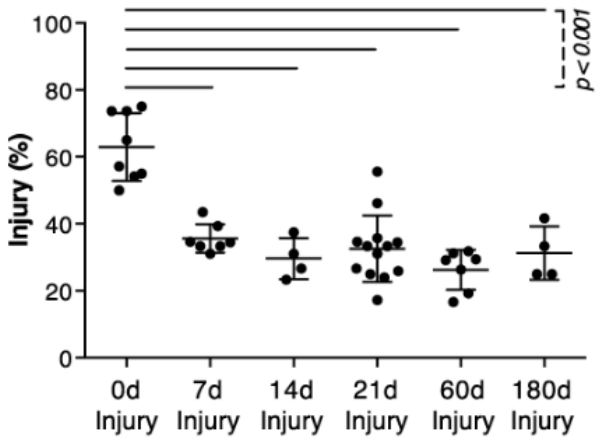
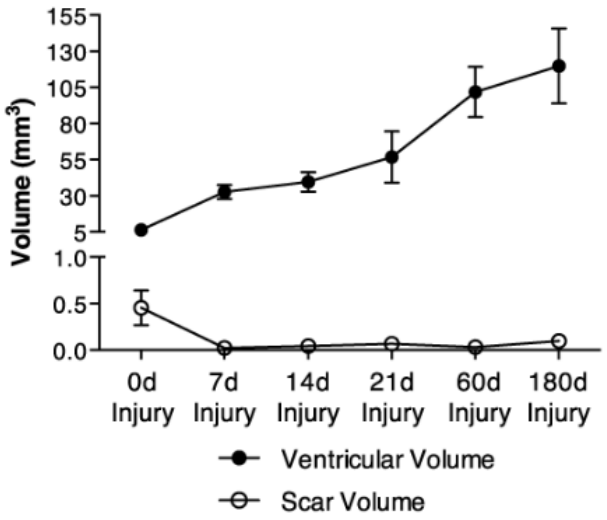
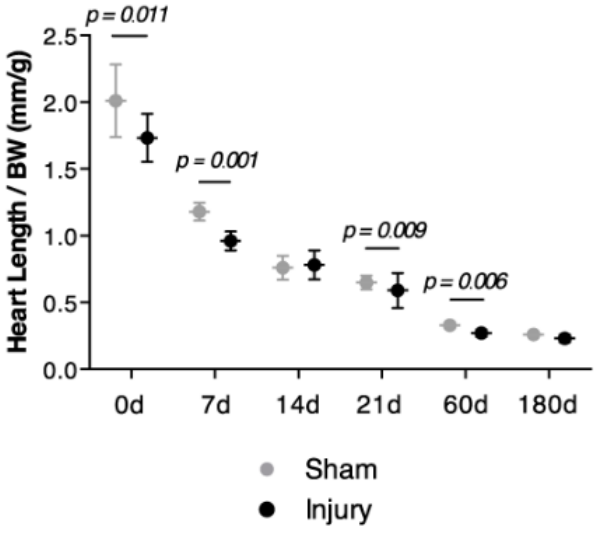
Hearts are not fully restored at the histological level but are fully restored at the functional level









Sampaio-Pinto V* et al. *Stem Cell Reports* 2018

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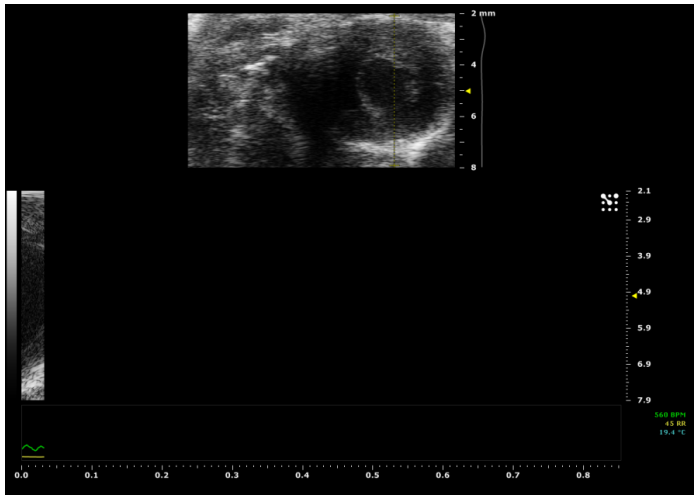
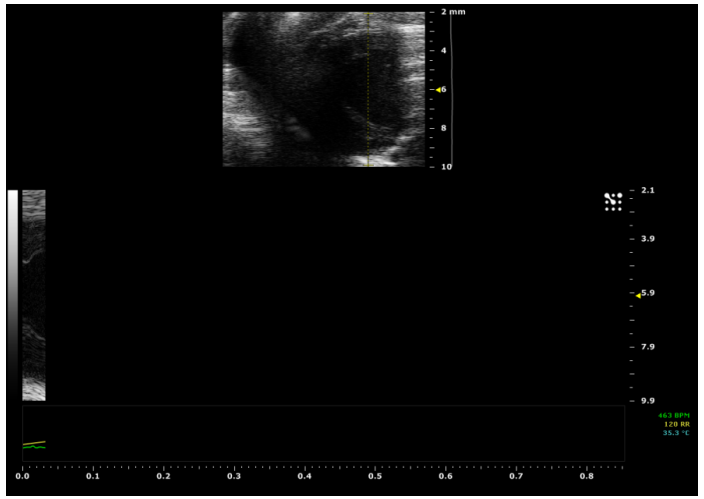
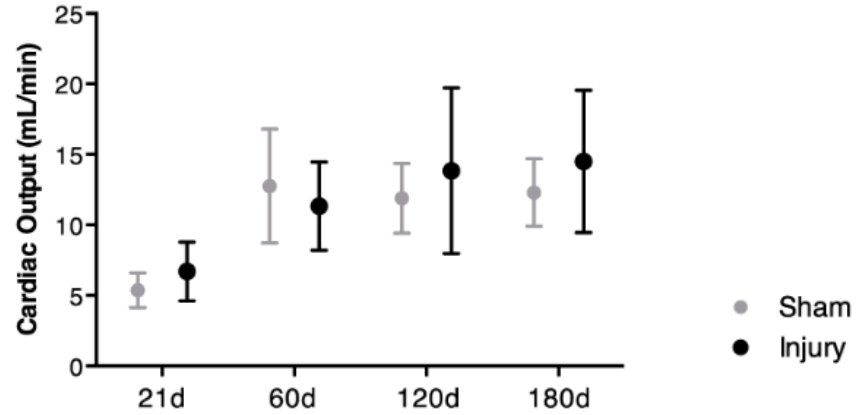
Hearts are not fully restored at the histological level but are fully restored at the functional level

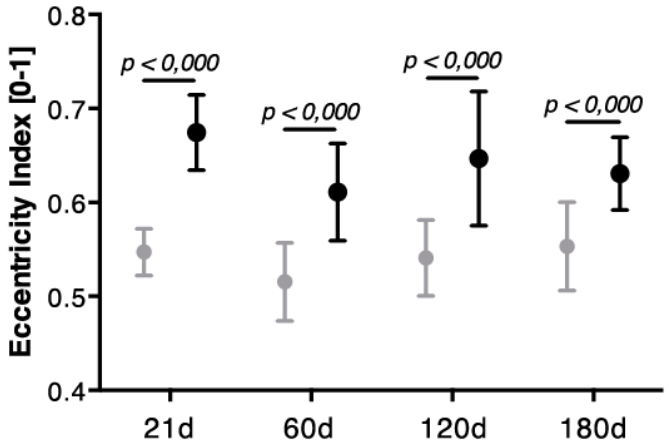




Sham

Injury





Sampaio-Pinto V* et al. *Stem Cell Reports* 2018

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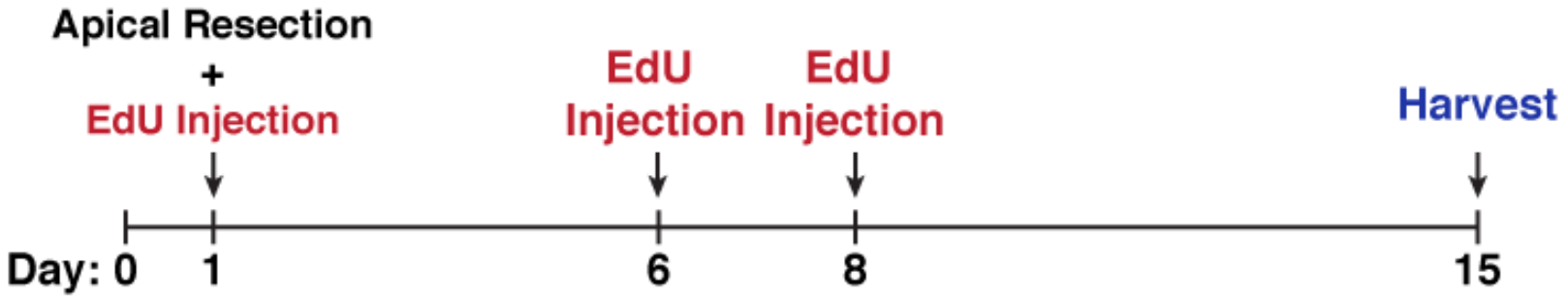
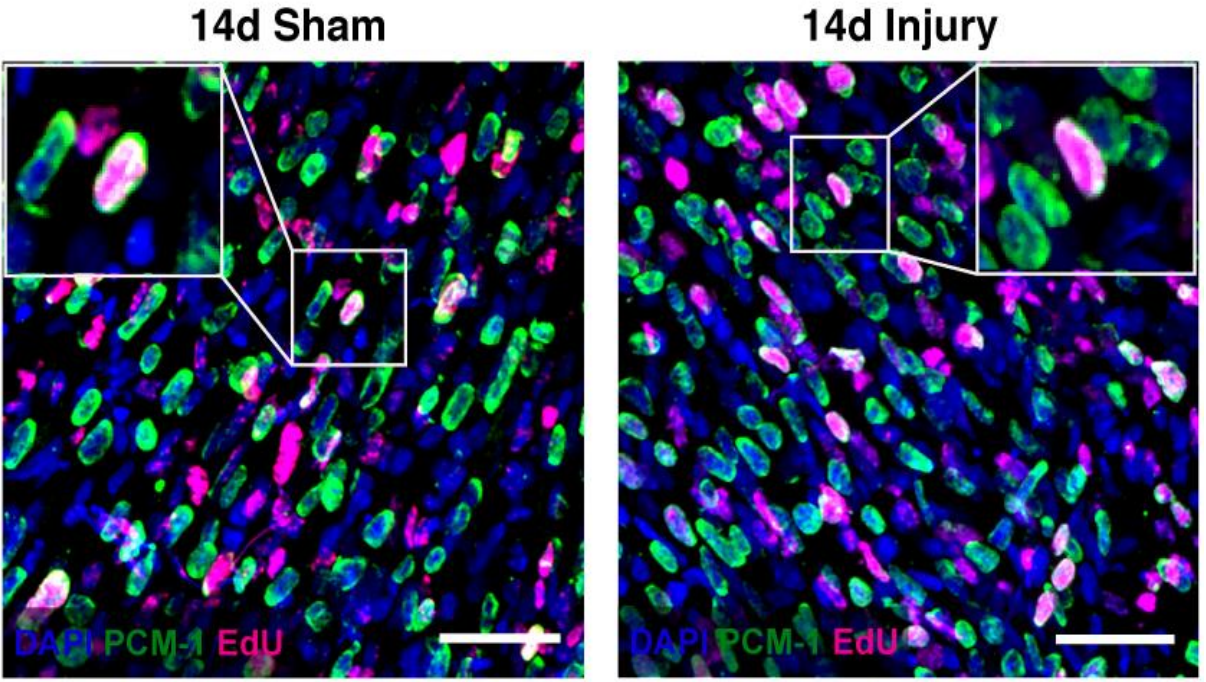
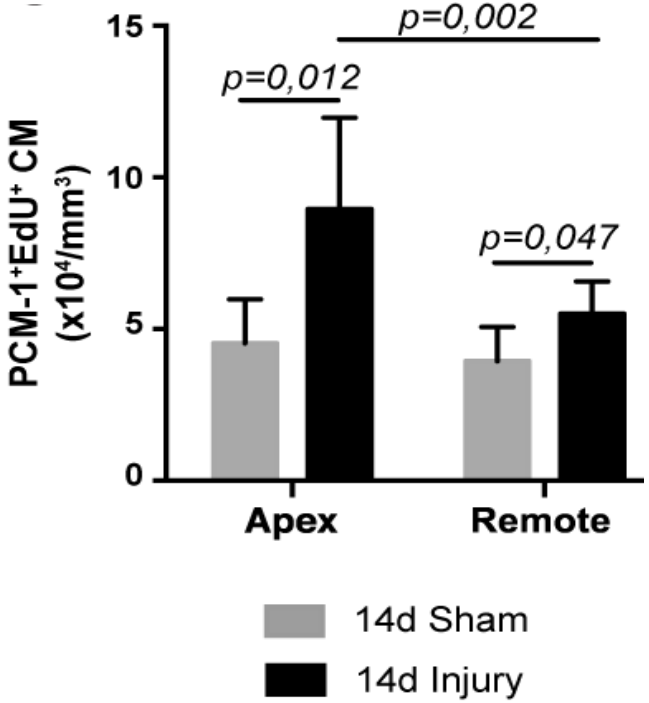
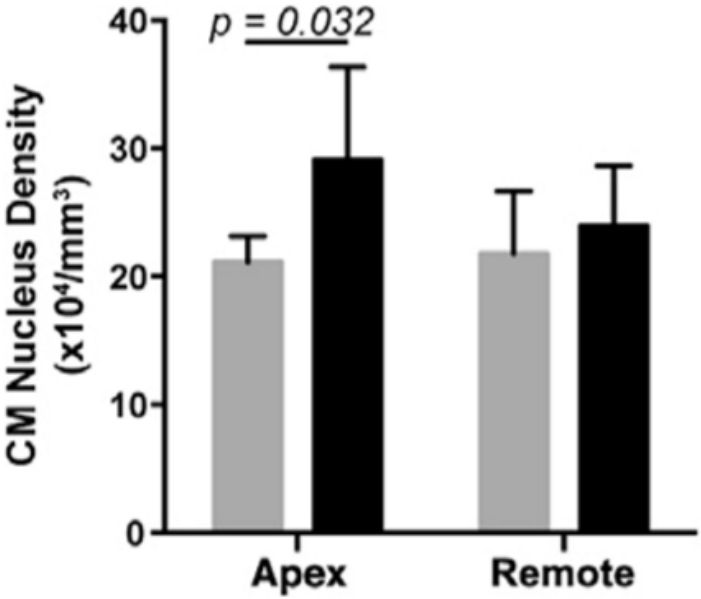
Resected hearts have more cardiomyocytes in the LV









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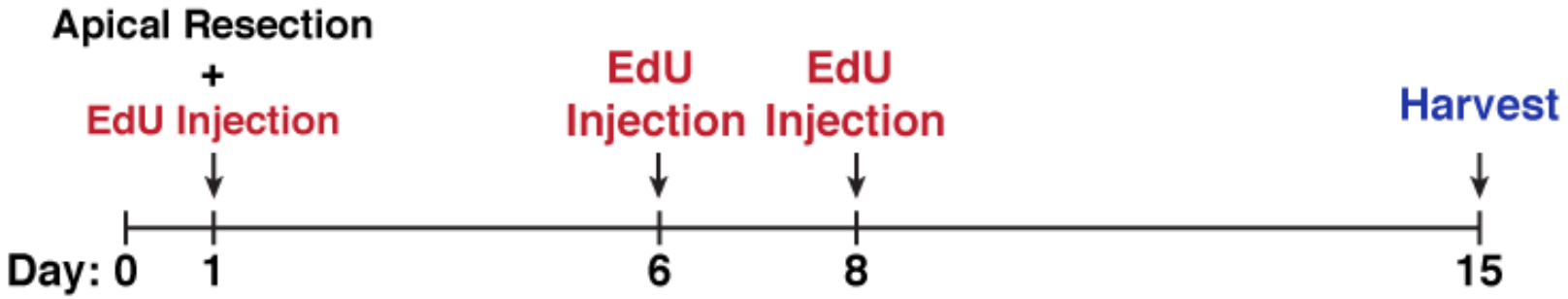
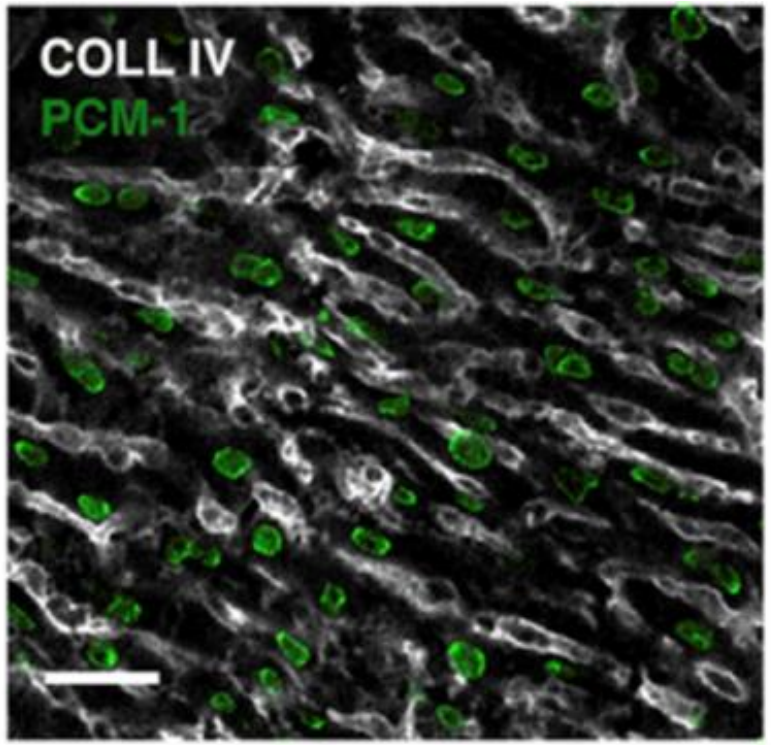
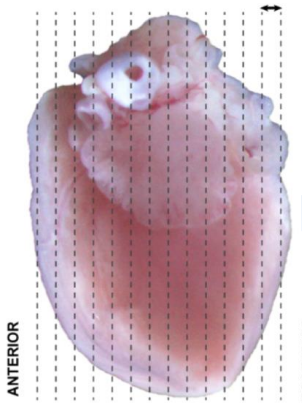
Resected hearts have more cardiomyocytes in the LV

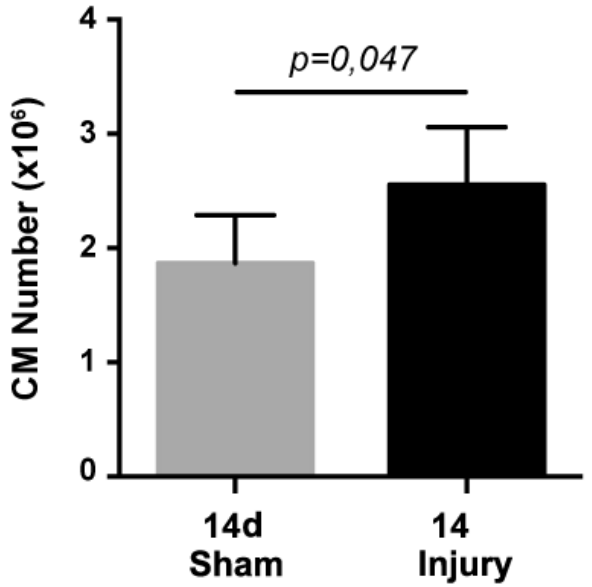






VOLUME

BINUCLEATION RATE



Sampaio-Pinto V* et al. *Stem Cell Reports* 2018

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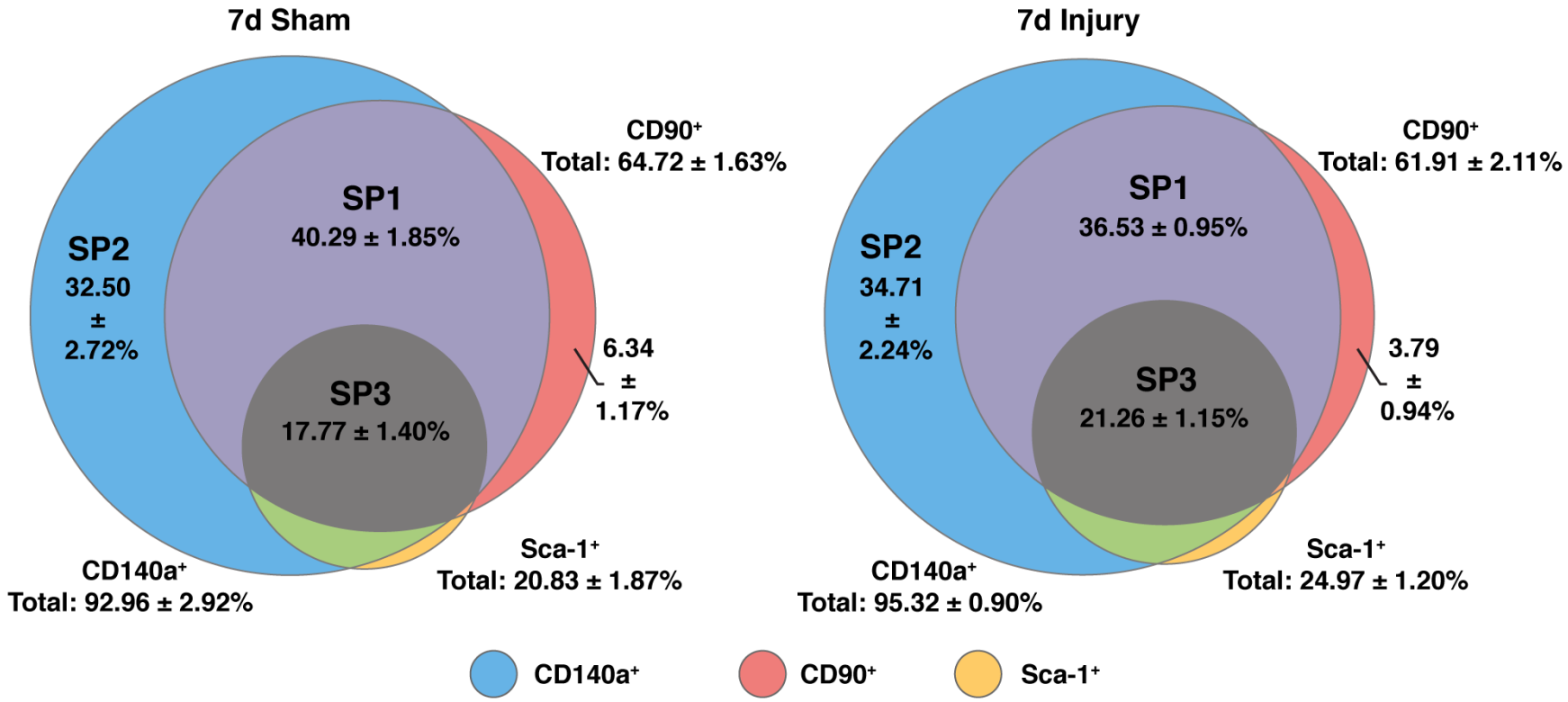
Short-Term Response to Cardiac Injury Involves ECM Remodeling and Fibroblast Activation



Sampaio-Pinto V* et al. *Stem Cell Reports* 2018

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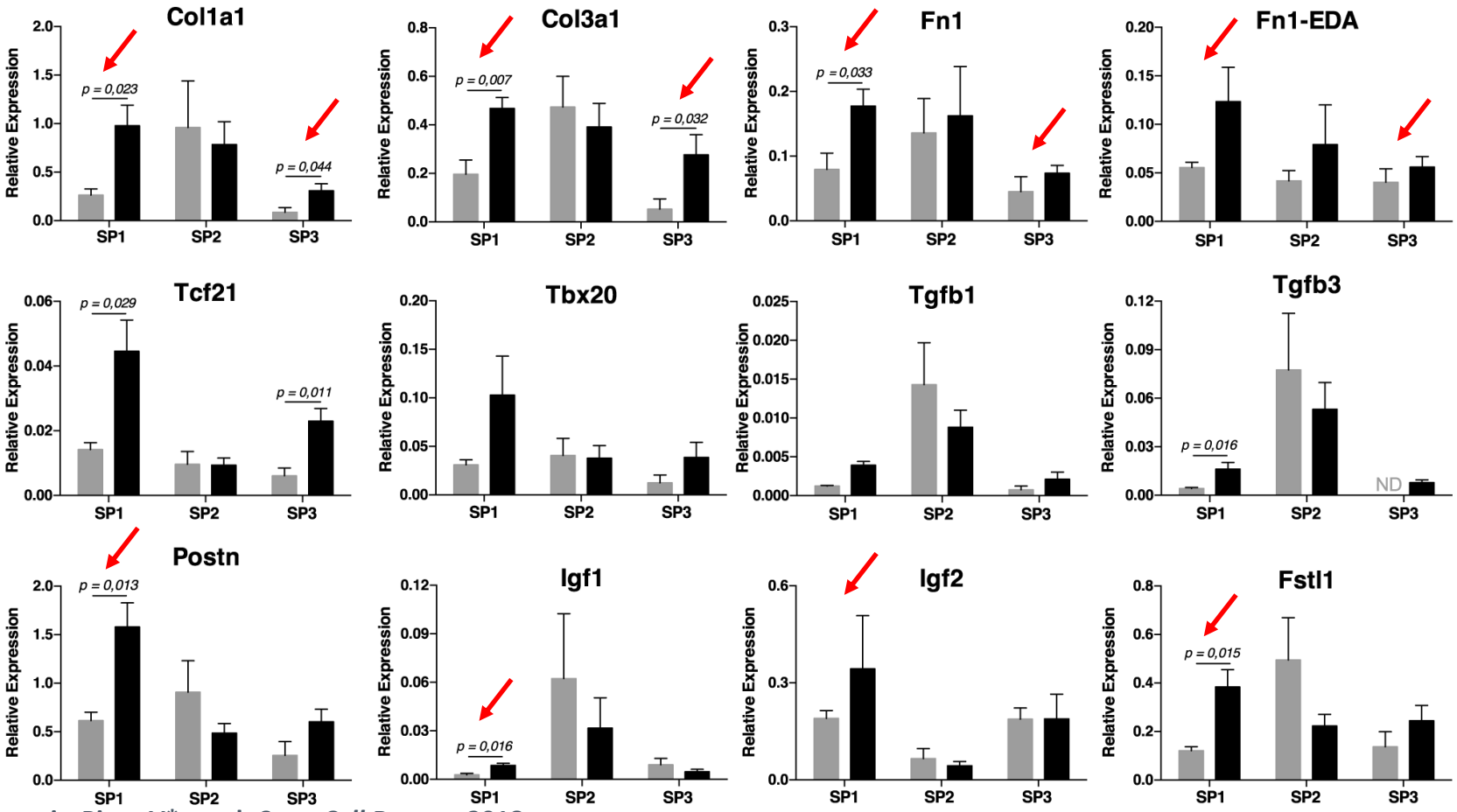
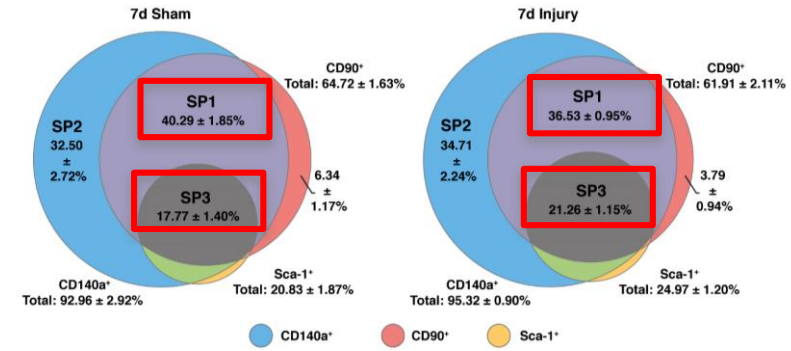
Short-Term Response to Cardiac Injury Involves ECM Remodeling and Fibroblast Activation





SP1 CD140a⁺CD90⁺Sca-1⁻
SP2 CD140a⁺CD90⁻Sca-1⁻
SP3 CD140a⁺CD90⁺Sca-1⁺

7d Sham
7d Injury

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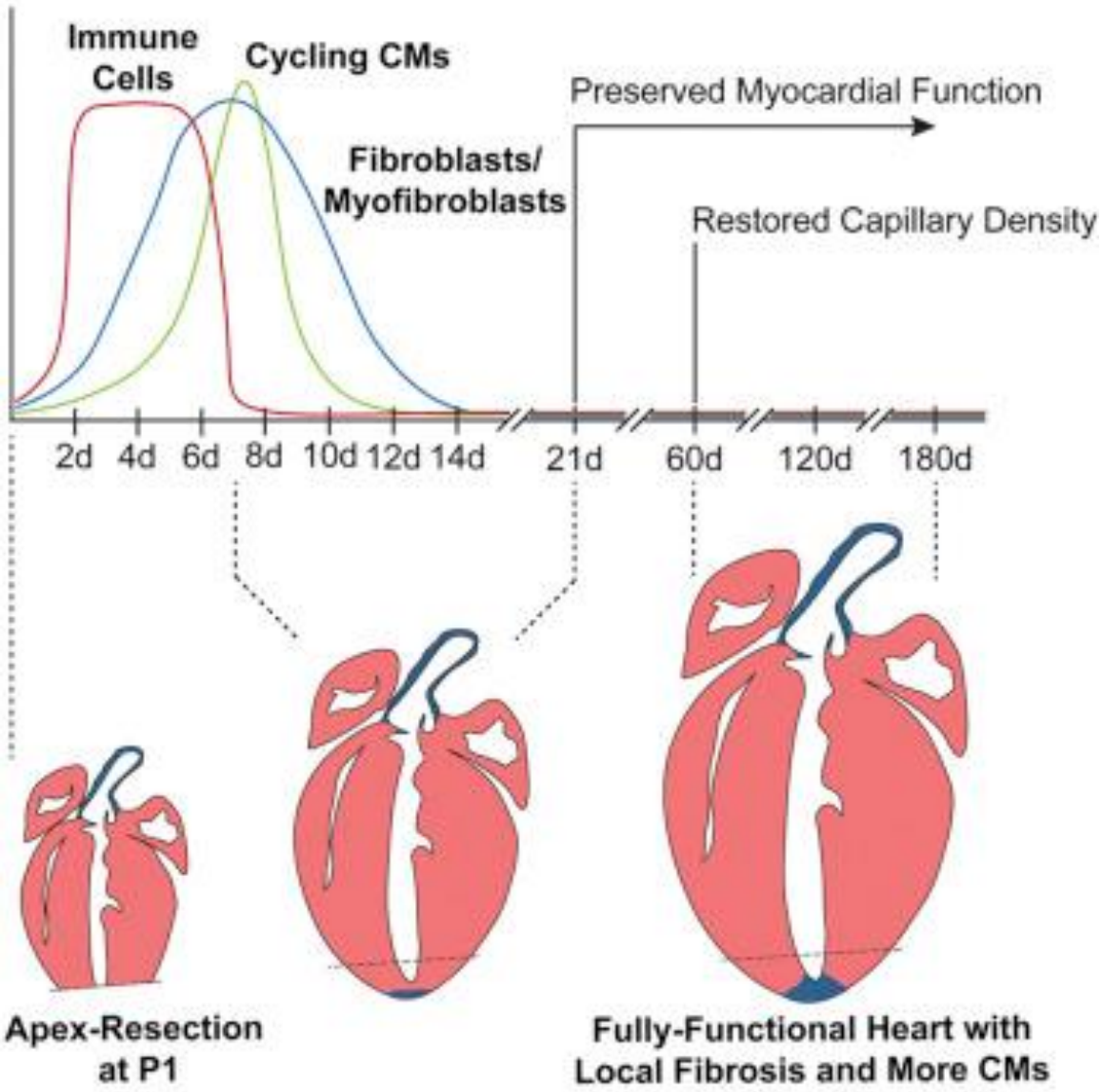

Regeneration and fibrotic deposition are both activated upon apex resection

Cardiac fibroblasts seem to be involved in both processes

Sampaio-Pinto V* et al. *Stem Cell Reports* 2018

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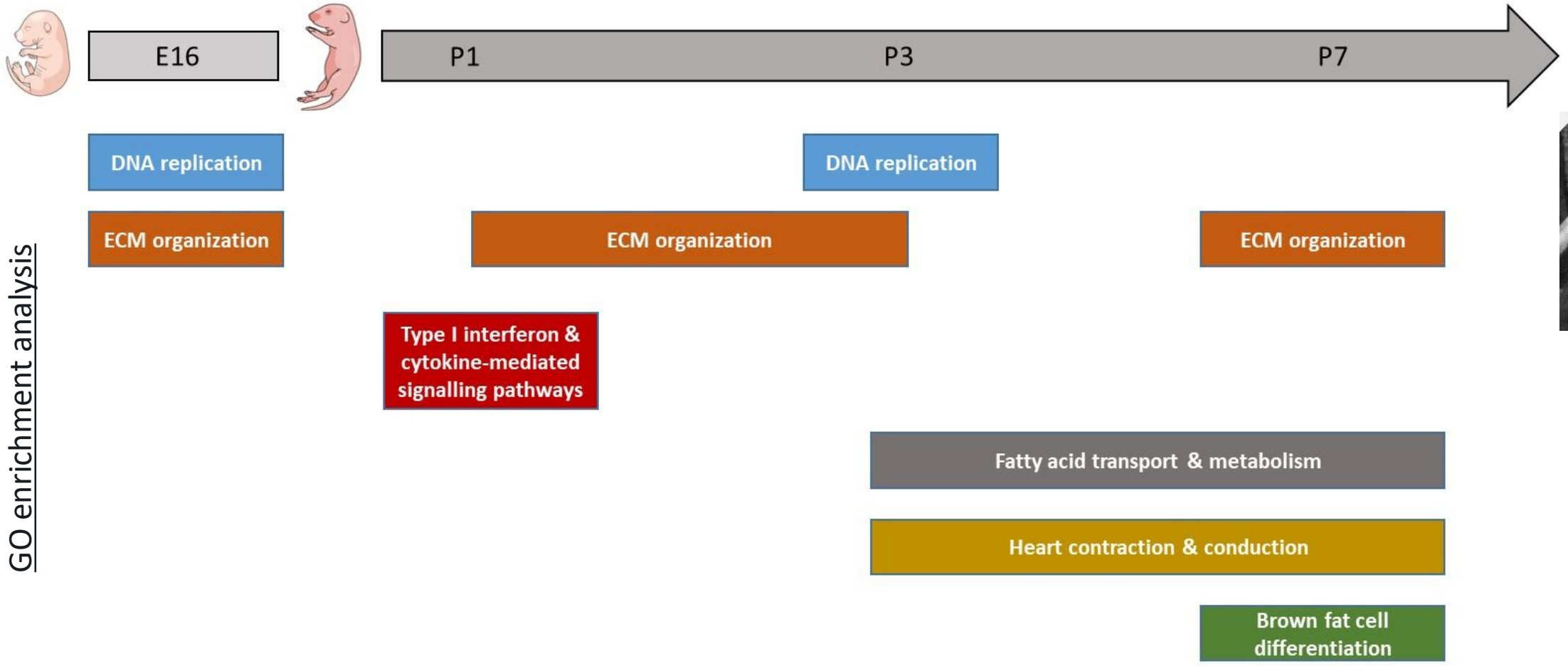
Transcriptomic alterations during the neonatal period



GO enrichment analysis

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Transcriptomic alterations during the neonatal period

ECM organization

Mdk
Mfap4
Ambp
Slit2
Bmp2
Matn4
Plau
Sfrp2
Col12a1
Serpinf2
Cx3cl1
Wnt2b
Col9a3
Igfbp3
Edil3
P4ha1
Spp1
Fbln5
Ptn
Col16a1
Sema5b
Lgi2
Spon2

Lox
Col9a1
Sema4g
Sema3d
Col2a1
Lamb3
Hapln1
Thbs2
Bmp7
Fgf11
Scube1
Emilin3
Plxna3
Serpinc1
Igfbp2
Ltbp2
Wnt5a
Gpc3
Serpina6

ECM organization

Lgals4
Stfa1
S100a9
Sfrp1
Timp4
Ccl9
Adamts6
Fam132b
Col23a1
Mst1
Wnt4
S100a8
Serpinb6b
Smoc1
Pik3ip1
Oit3
Fgf12
Fgb
Fras1

Loxl1
Mfap4
Nov
Col1a2
Plxdc1
Plau
Sfrp2
Fgf9
Gpc6
Col5a3
Adamts2
Pcolce
Smoc2
Emilin2
Cxcl9
Sdc3
Igfbp7
Vwa1
Postn
Sparcl1
Cd109

Spon2
Clec3b
Col14a1
Vtn
Wisp2
Thbs2
Lum
Serpine2
Col3a1
Fndc1
Tll2
Cilp
Pcolce2
Tnc
Col15a1
Pcsk6

ECM organization

Adamts10
Lgals12
Mfap4
C1qtnf7
Cxcl13
Ctsf
Hmcn2
Lgals4
Fbln1
Crispld2
Cilp2
Fbln5
Adamtsl4
Abi3bp
Podn
Col28a1
Col11a2
Eln
Col8a1
S100a6
Comp

Adamtsl2
Mfap5
Gdf7
Anxa8
Papln
Ntng2
Vtn
Fst
Serpinf1
Clec3a
Scube1
Colec11
Htra3
Adipoq
Fgf10
Cilp
Clec11a
Col6a5
Pcolce2
Itih4
Chad
Tnfsf10
Pcsk6

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How does ECM from different stages of cardiac aging impact on cardiac cells?

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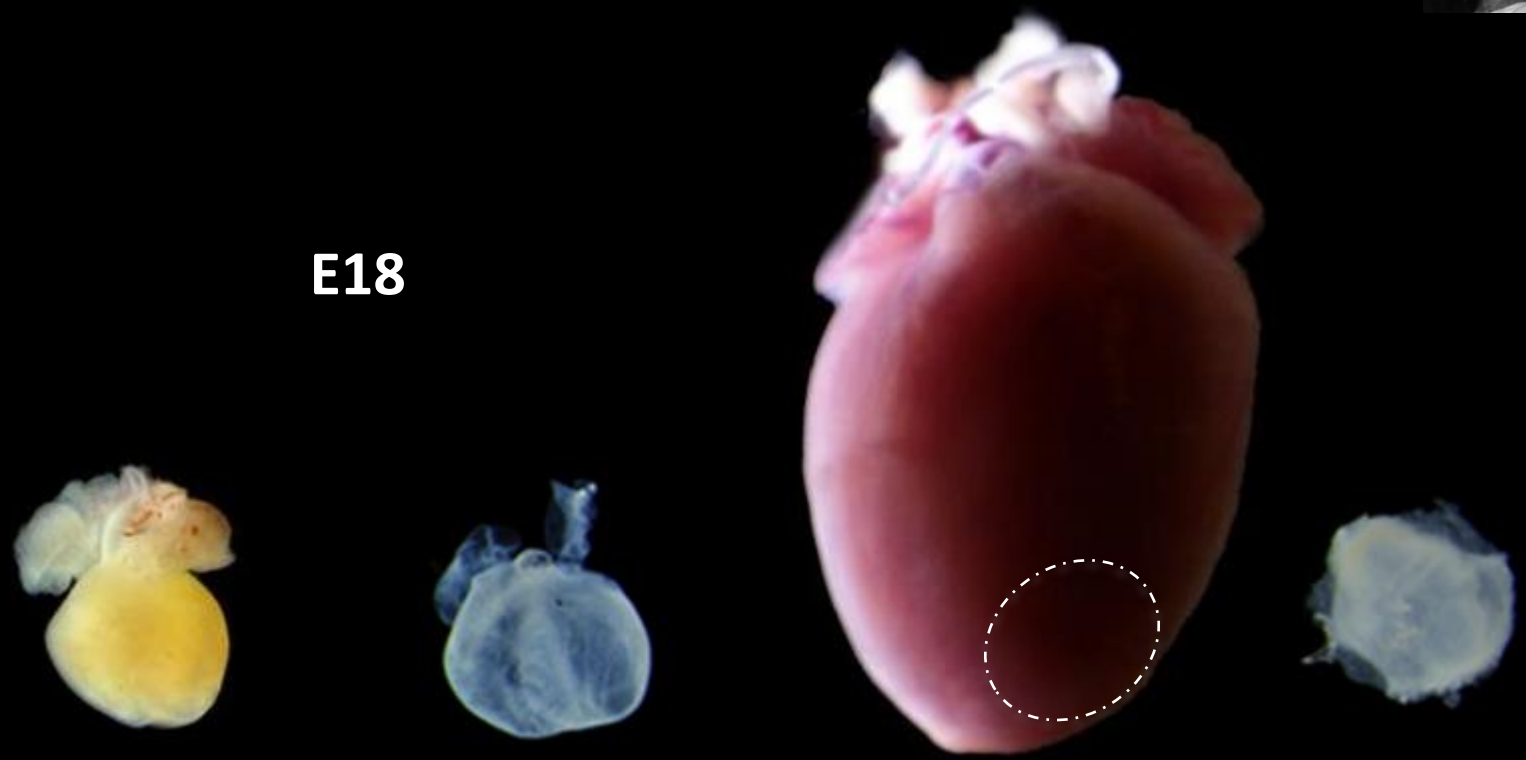
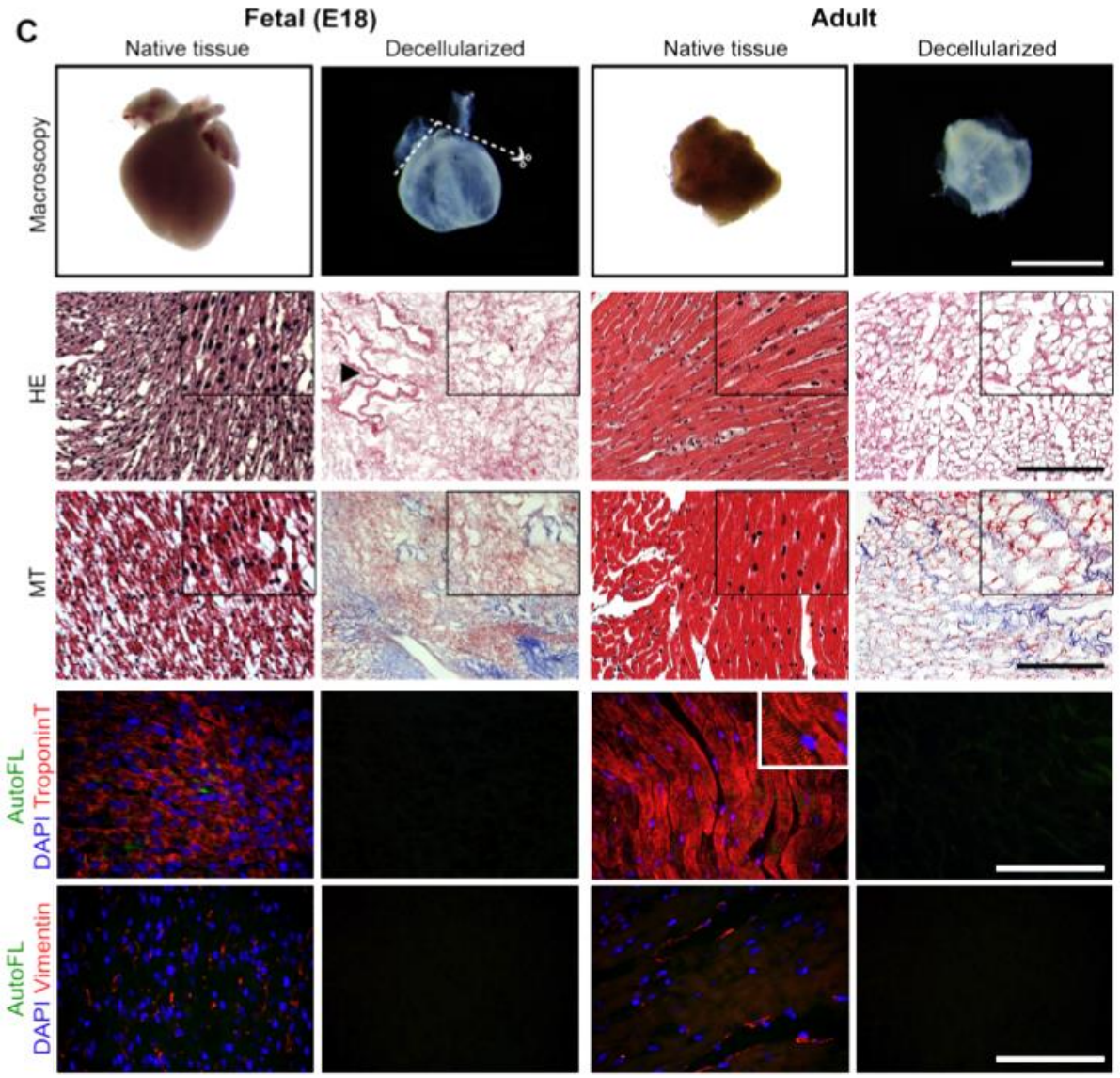
Adult

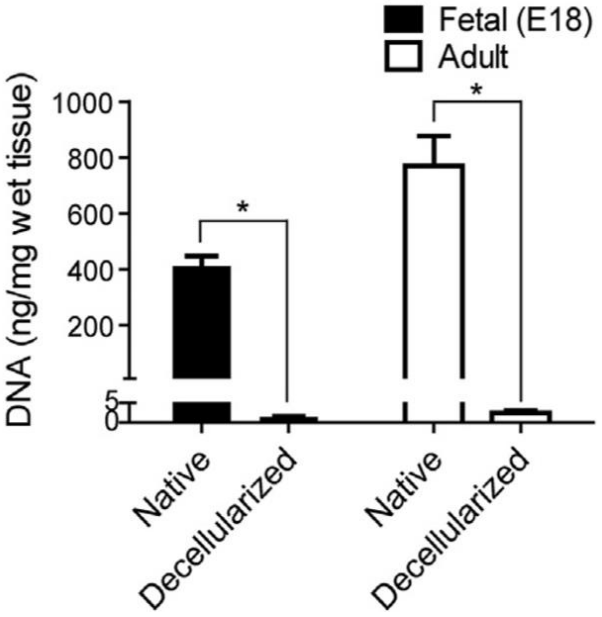
E18



Silva AC* et al. *Biomaterials* 2016; Silva AC et al J. Vis Exp 2019; Garlikova et al. Tissue Eng C 2018

Is the ECM a key player in heart regeneration?





Silva AC* et al. *Biomaterials* 2016

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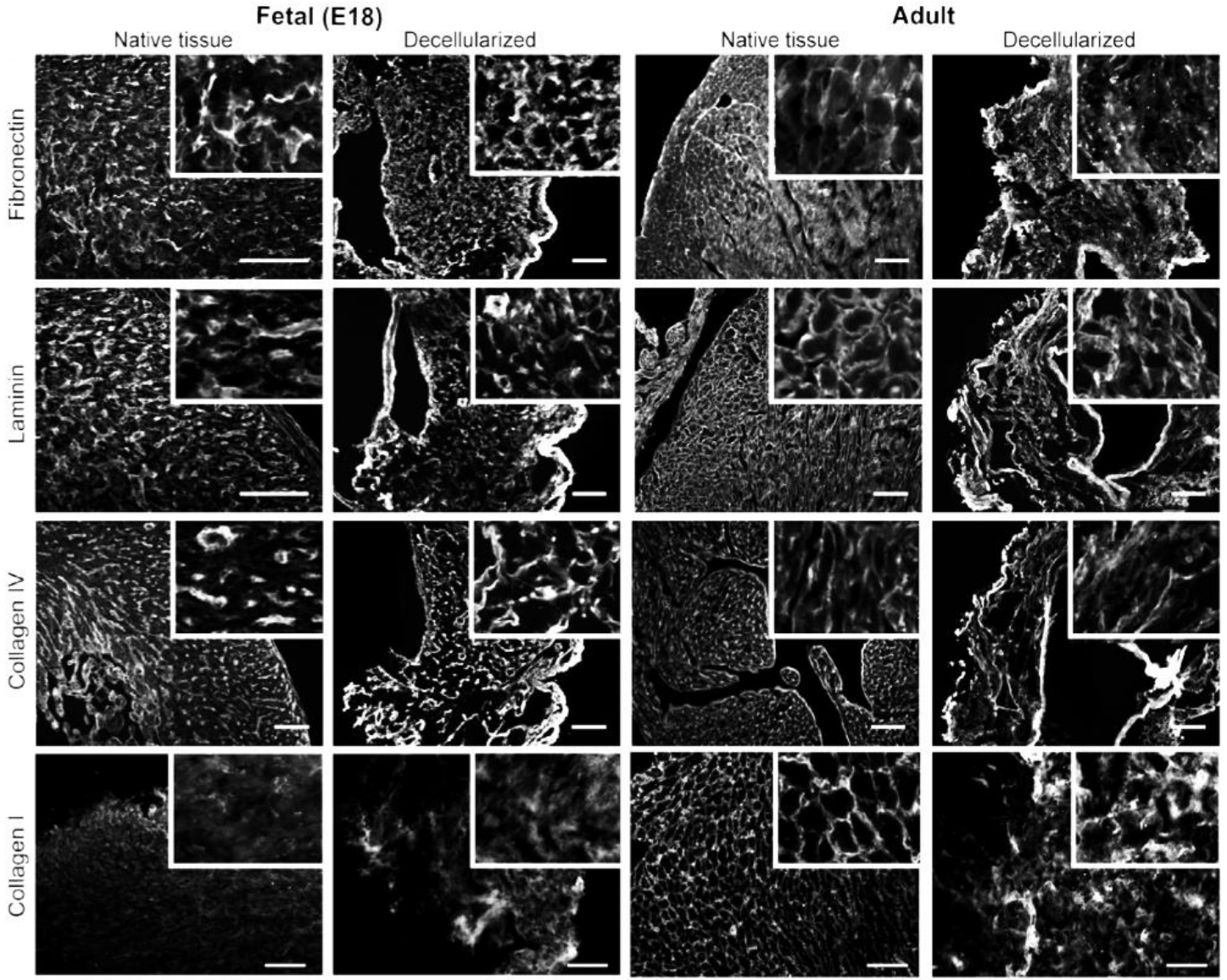
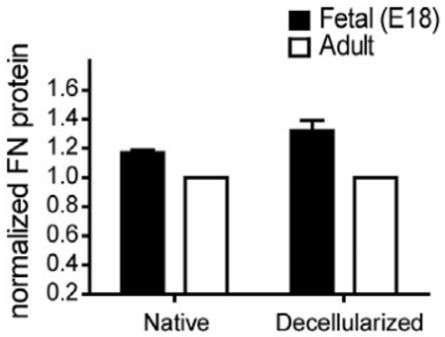
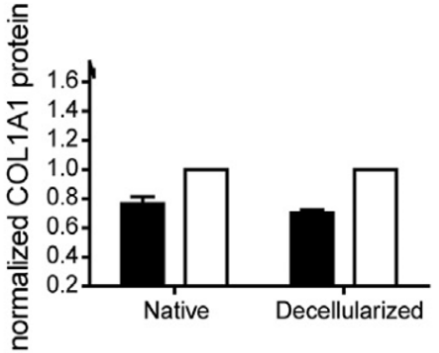
Is the ECM a key player in heart regeneration?







Silva AC* et al. *Biomaterials* 2016

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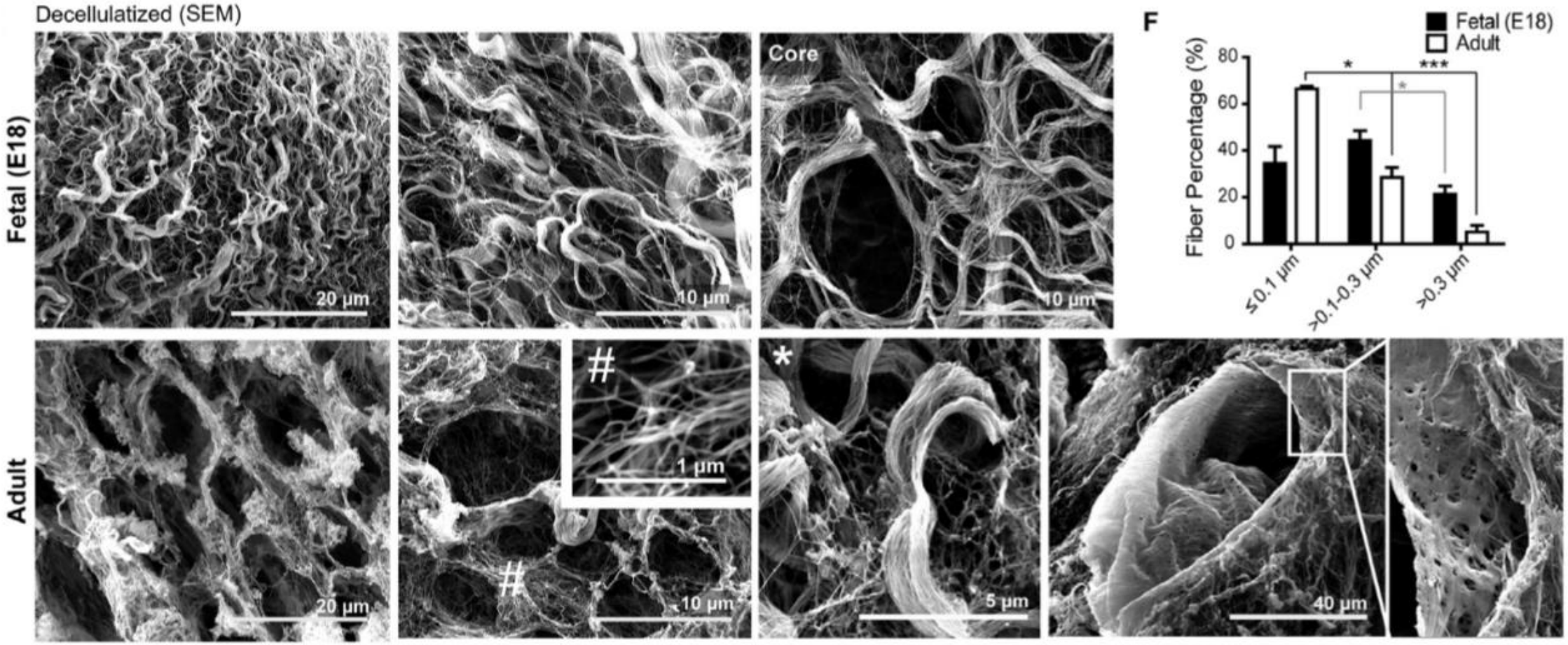
Is the ECM a key player in heart regeneration?



Silva AC* et al. *Biomaterials* 2016

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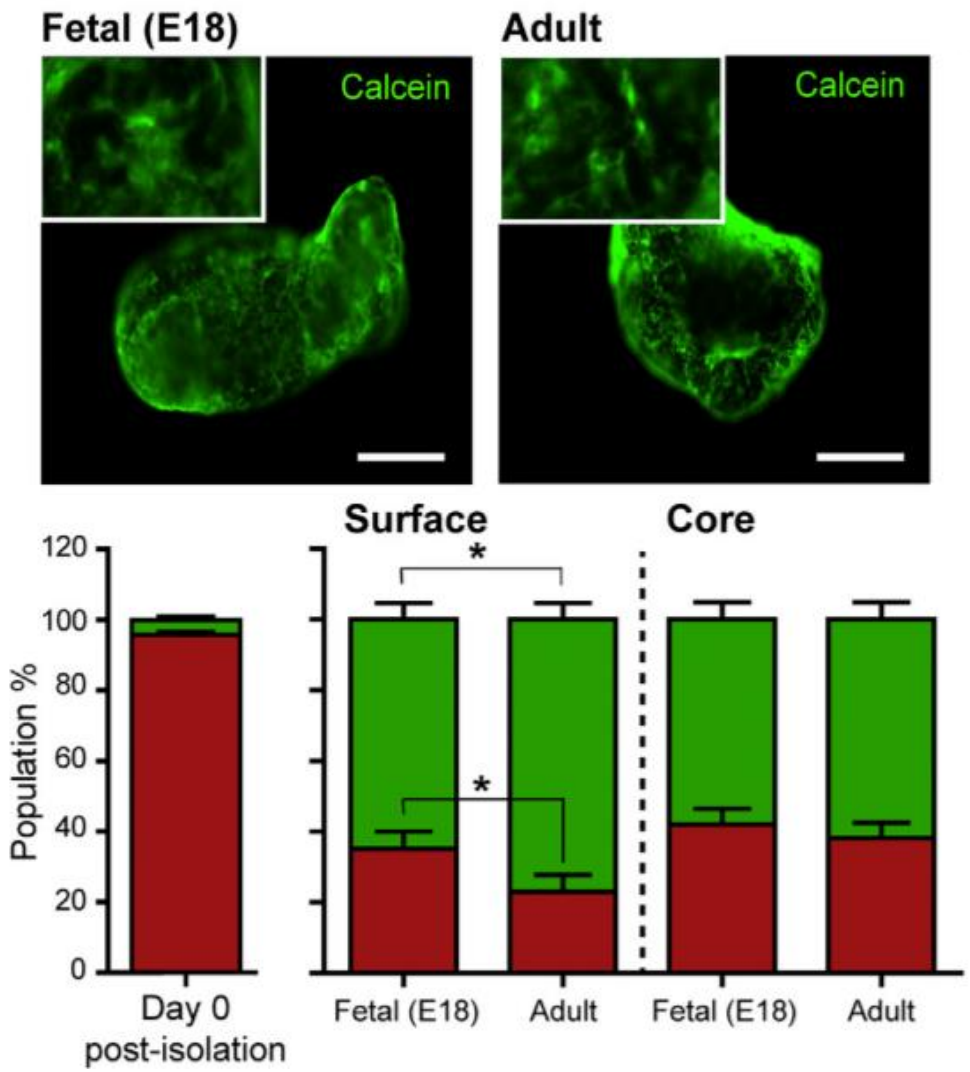
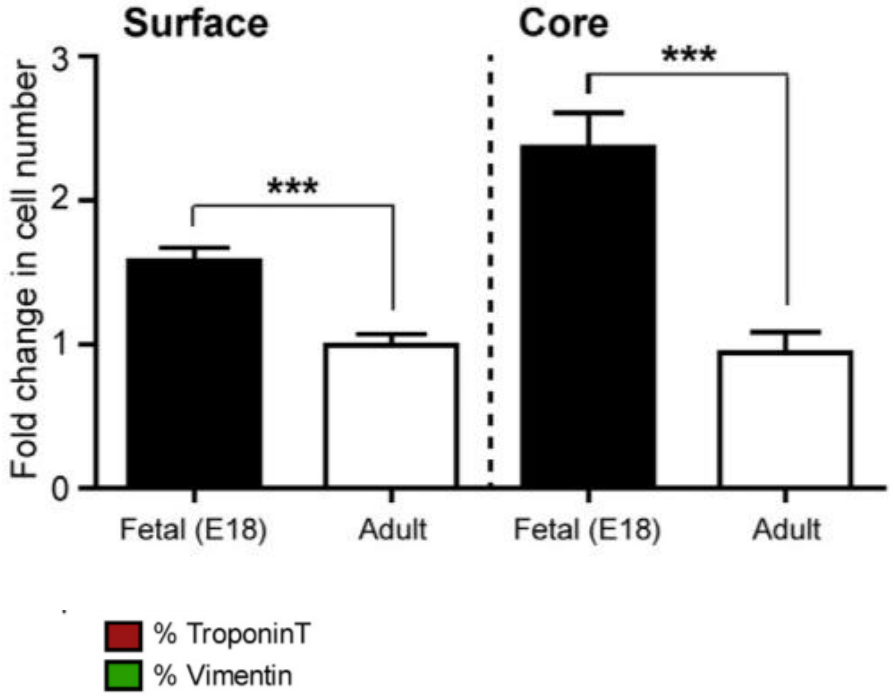
Is the ECM a key player in heart regeneration?

Repopulation with Neonatal cardiomyocytes (15 days)





Young cardiac ECM is a better environment for cardiomyocytes

Silva AC* et al. *Biomaterials* 2016

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Temporal Expression Properties of iPSC-Derived Cardiac Cells

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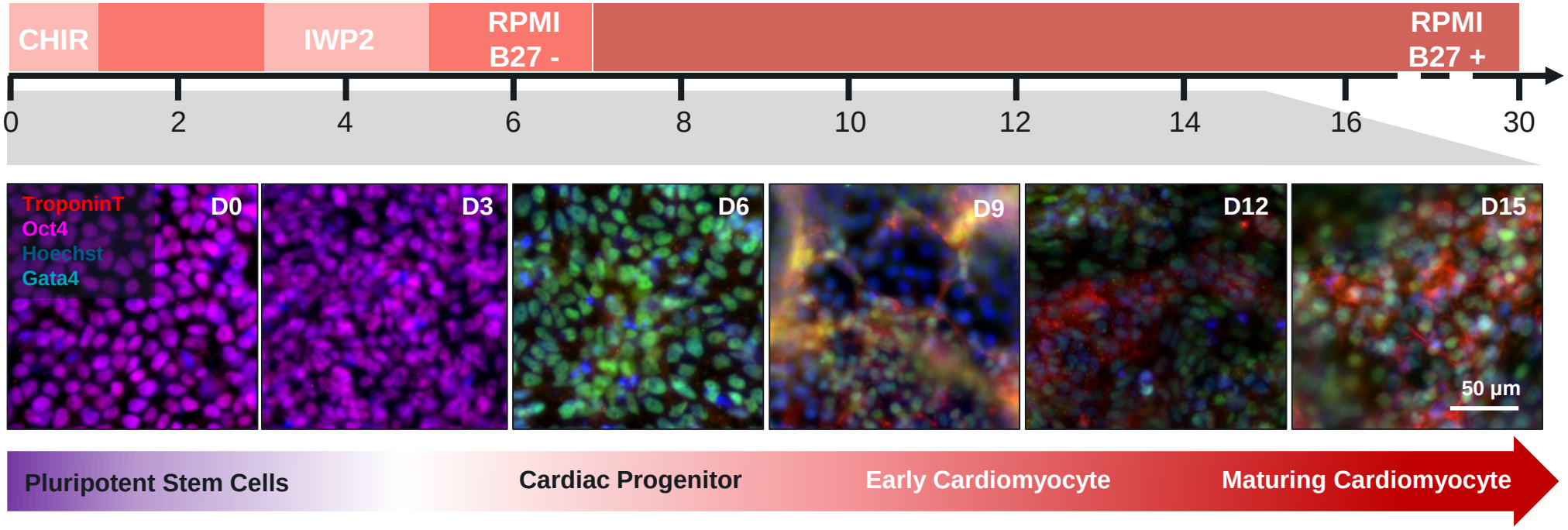

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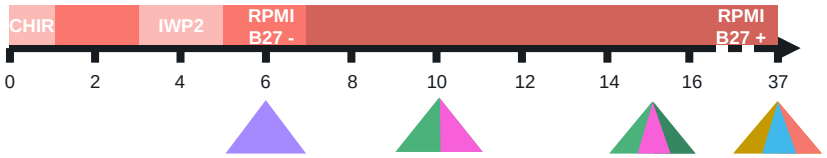
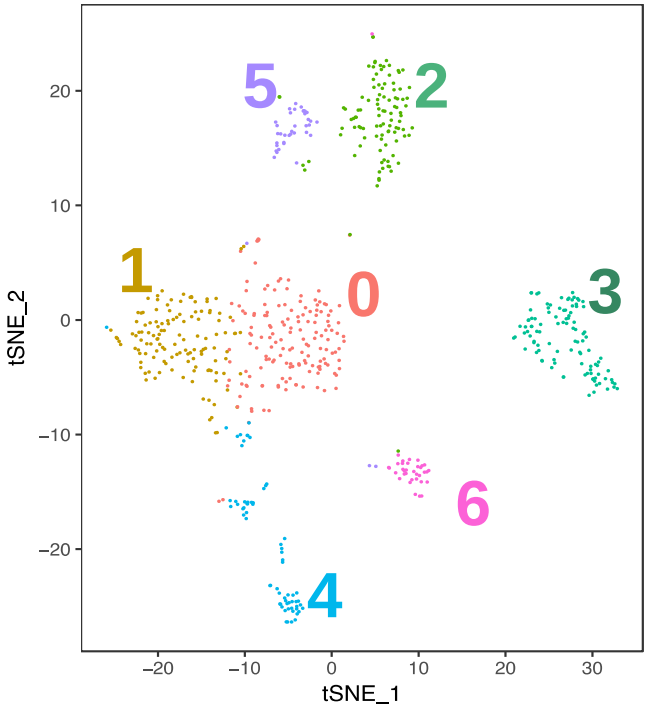
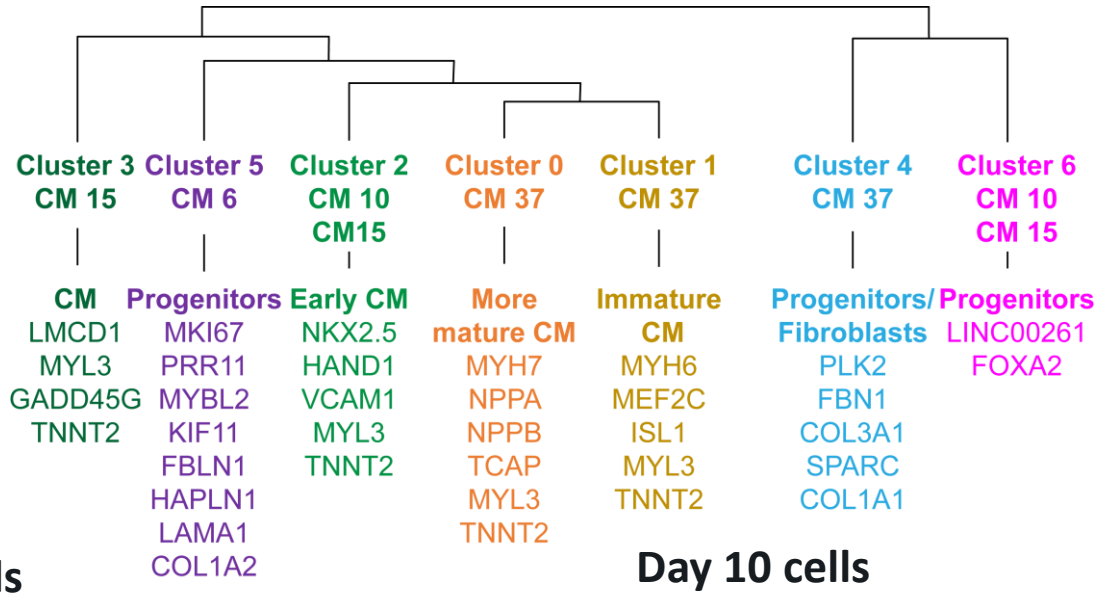
X Lian et al., PNAS 2012

iPSC-Derived Cardiac Cell Identity and Heterogeneity



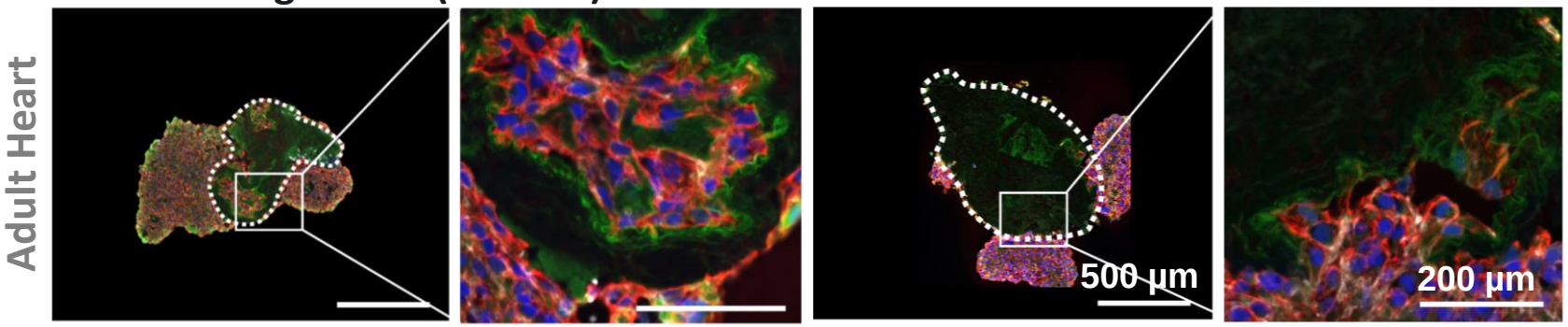


CM 6 – 5
CM 10 – 2, 6
CM 15 – 2, 3, 6,
CM 37 – 0, 1, 4



Day 5 cells
Cardiac Progenitors (iPSC-CP)

Day 10 cells
Early Cardiomyocytes (iPSC-eCM)



TroponinT Vimentin DAPI autoFL

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Fetal Heart ECM Promotes High Repopulation and Differentiation into Cardiomyocytes by iPSC-CP

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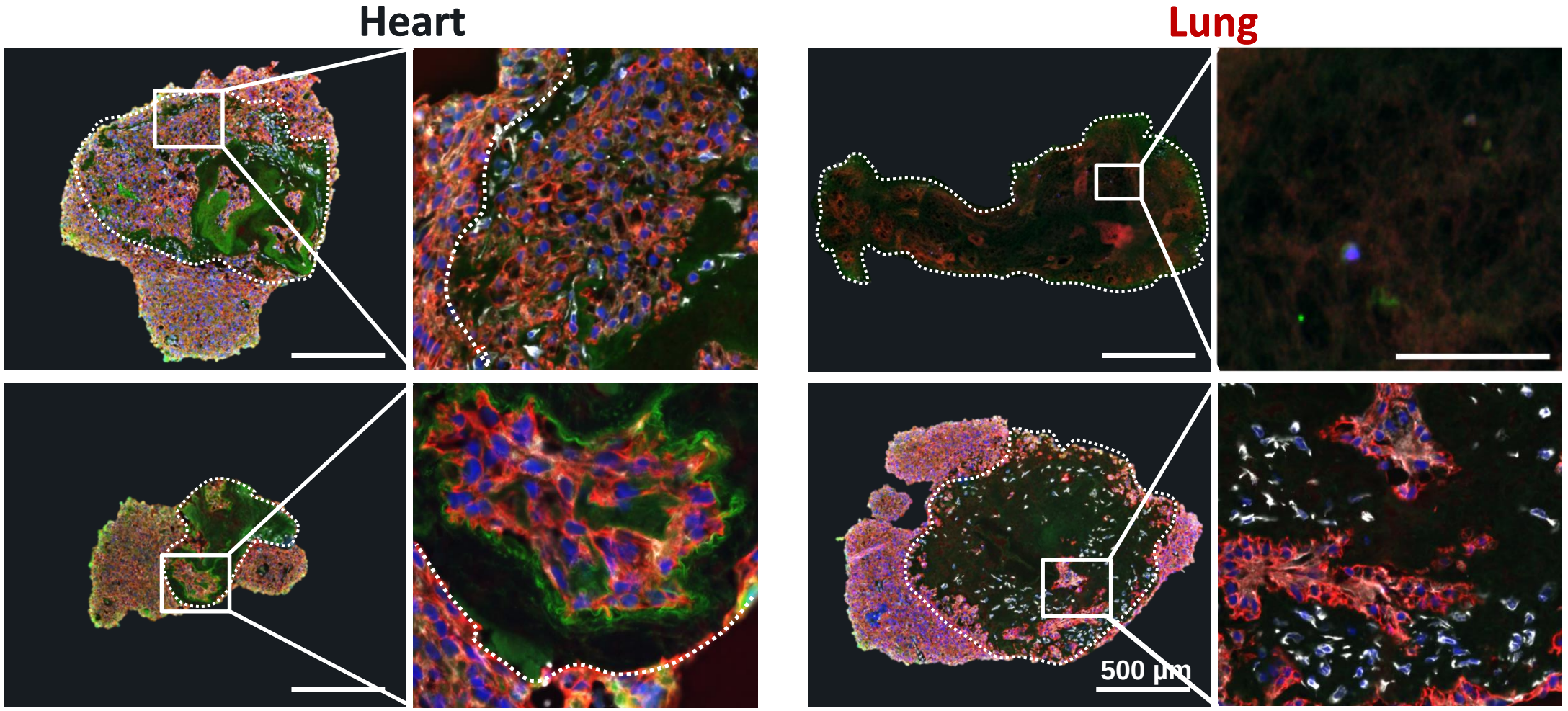

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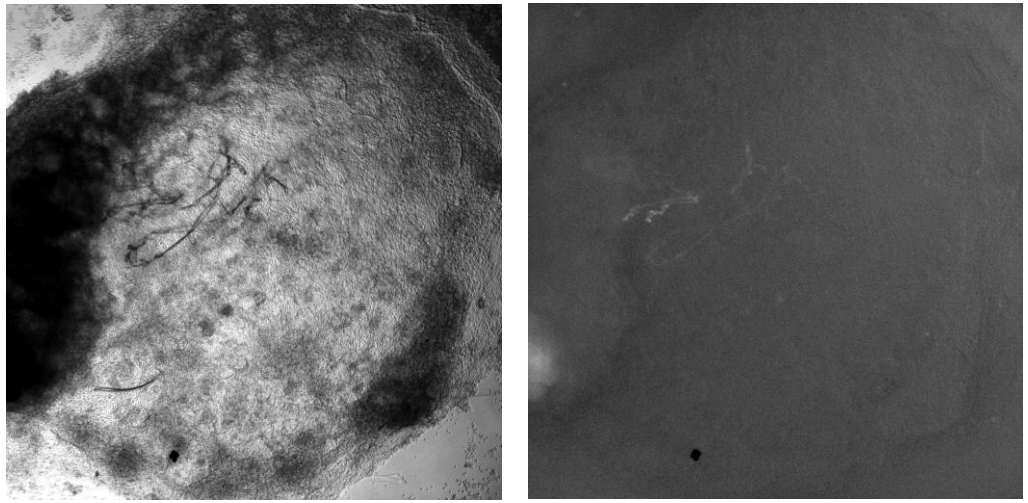
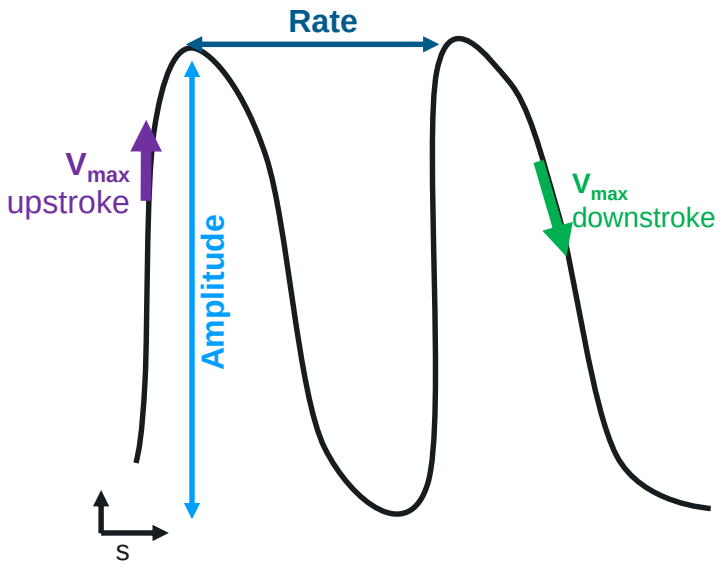
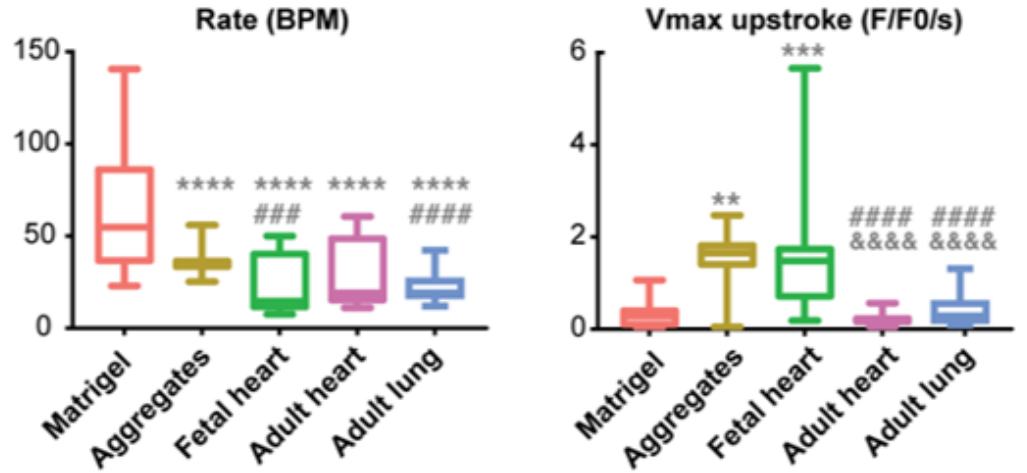
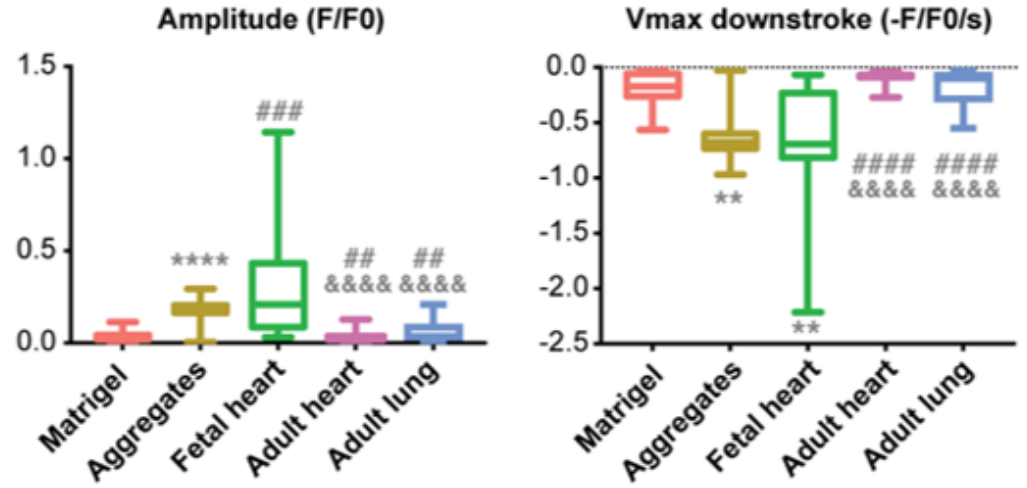
Cardiomyocytes Differentiated on Fetal Heart ECM Display Higher Functional Maturation









*p<0.05, **p<0.01, *** p<0.0005, ****p <0.0001, * vs Matrigel, # vs Aggregates, & vs Fetal Heart

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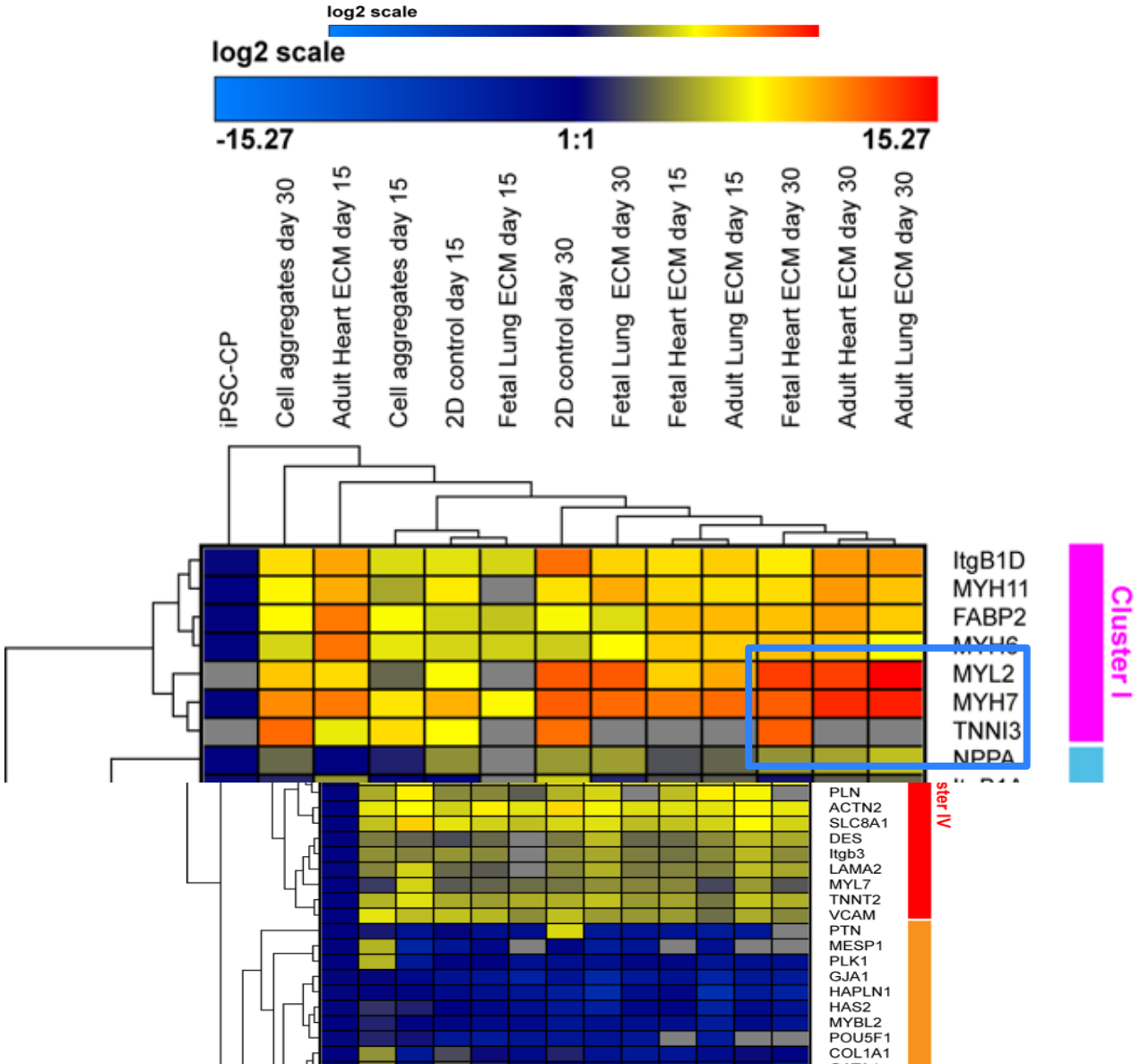
Decellularized Tissues Accelerate Cardiomyocyte Transcriptional Maturation



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-15.27 1:1 15.27

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- **Fetal ECM bioscaffolds promote better colonization rates of cardiac cells *in vitro***

- **Differentiation of iPSC-CP in ECM bioscaffolds accelerates maturation and specification into ventricular-like cells.**

- **Fetal heart ECM promotes improved CM calcium handling properties and CM maturation.**

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Acknowledgments

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Animal Facility

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André Maia, BioSciences Screening Unit

Rui Fernandes, HEMS

Paula Sampaio, ALM

Maria Lázaro, b.Image

Collaborators

Todd McDevitt

Sólveig Thorsteinsdóttir

Adelino Leite-Moreira

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