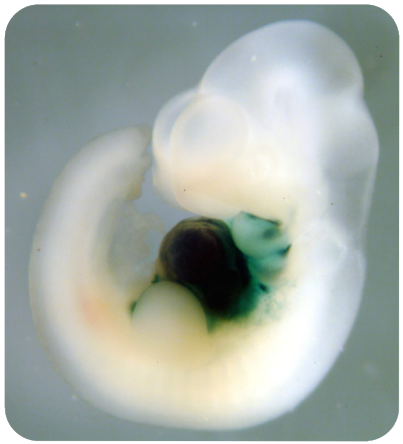
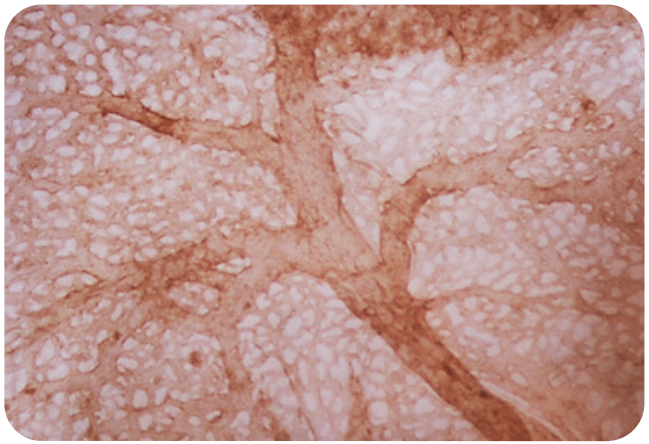
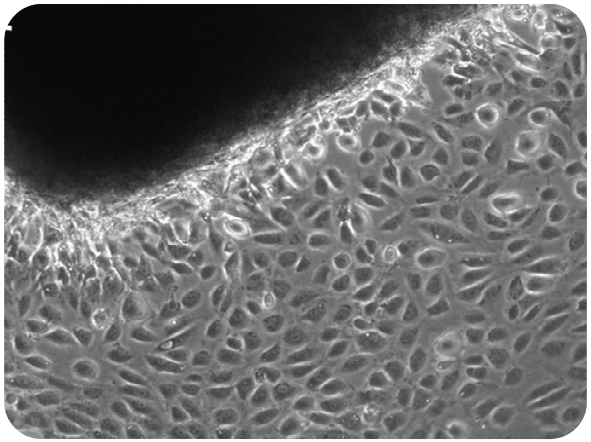
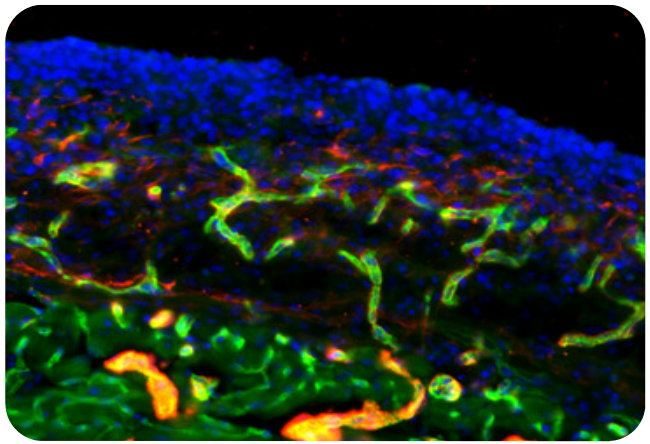
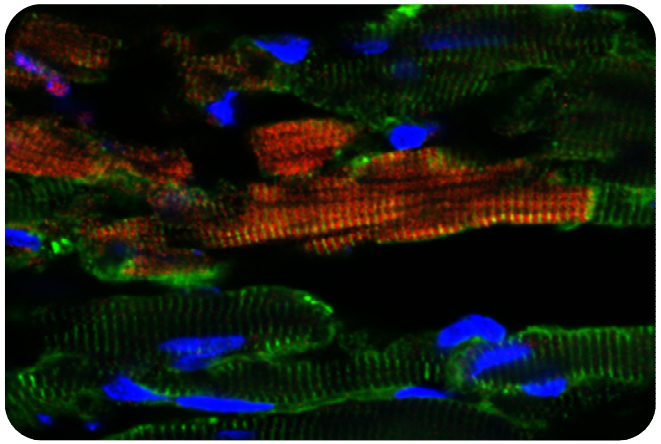
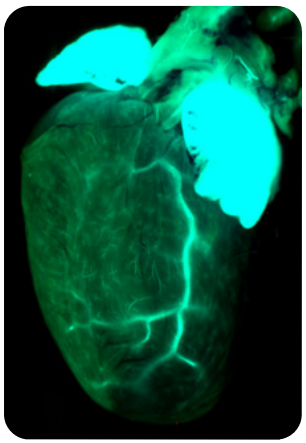







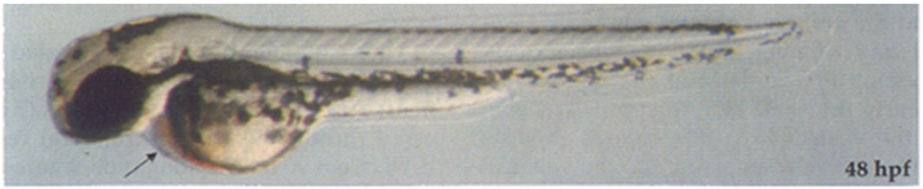
Heart Development: Implications for Regeneration

Dr Nicola Smart

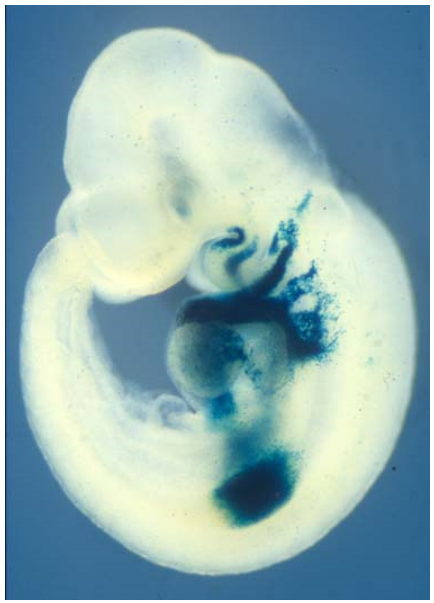
UNIVERSITY OF OXFORD

Why study heart development?

Fly

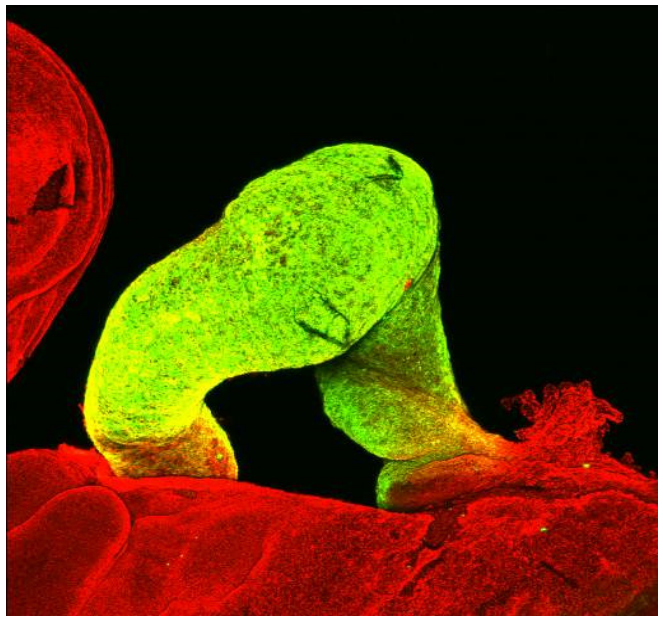


Zebrafish



Mouse

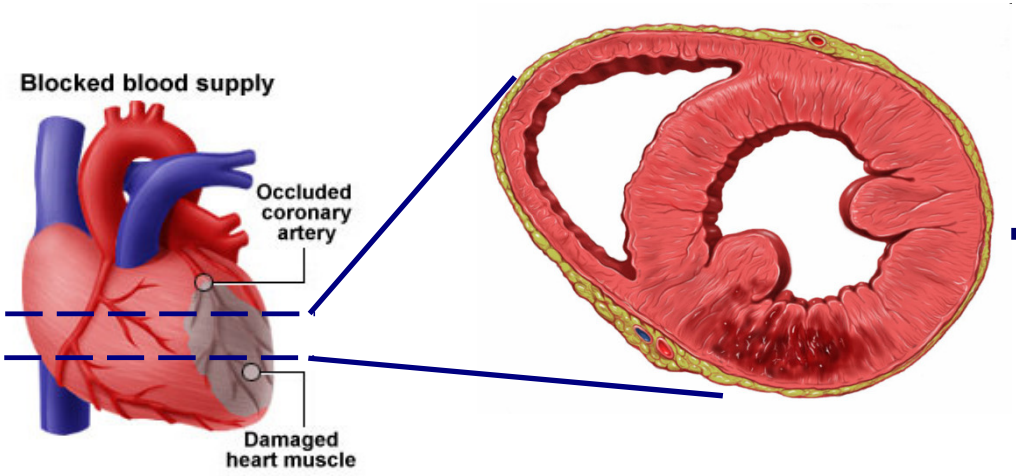
Human



Chicken

- **Origin of congenital heart defects**
- **Production of cardiac progenitor cells**

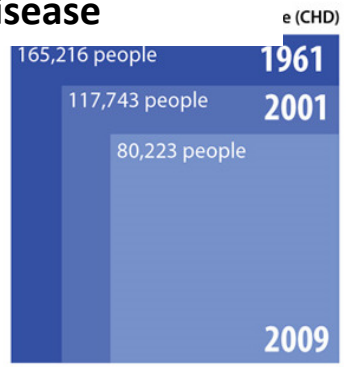
Heart Failure: The Evolving Epidemic

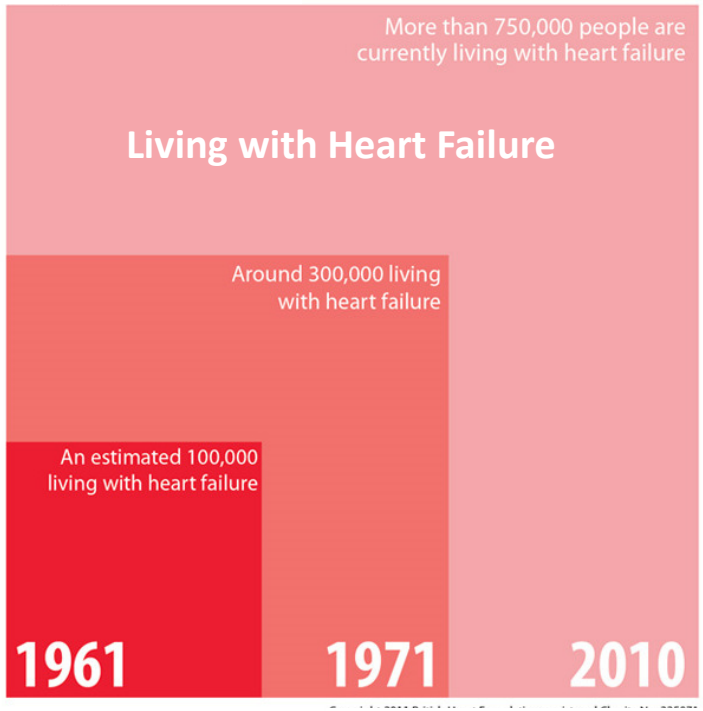


Loss of cardiomyocytes (1 billion; 25%)

Myocardial Infarction

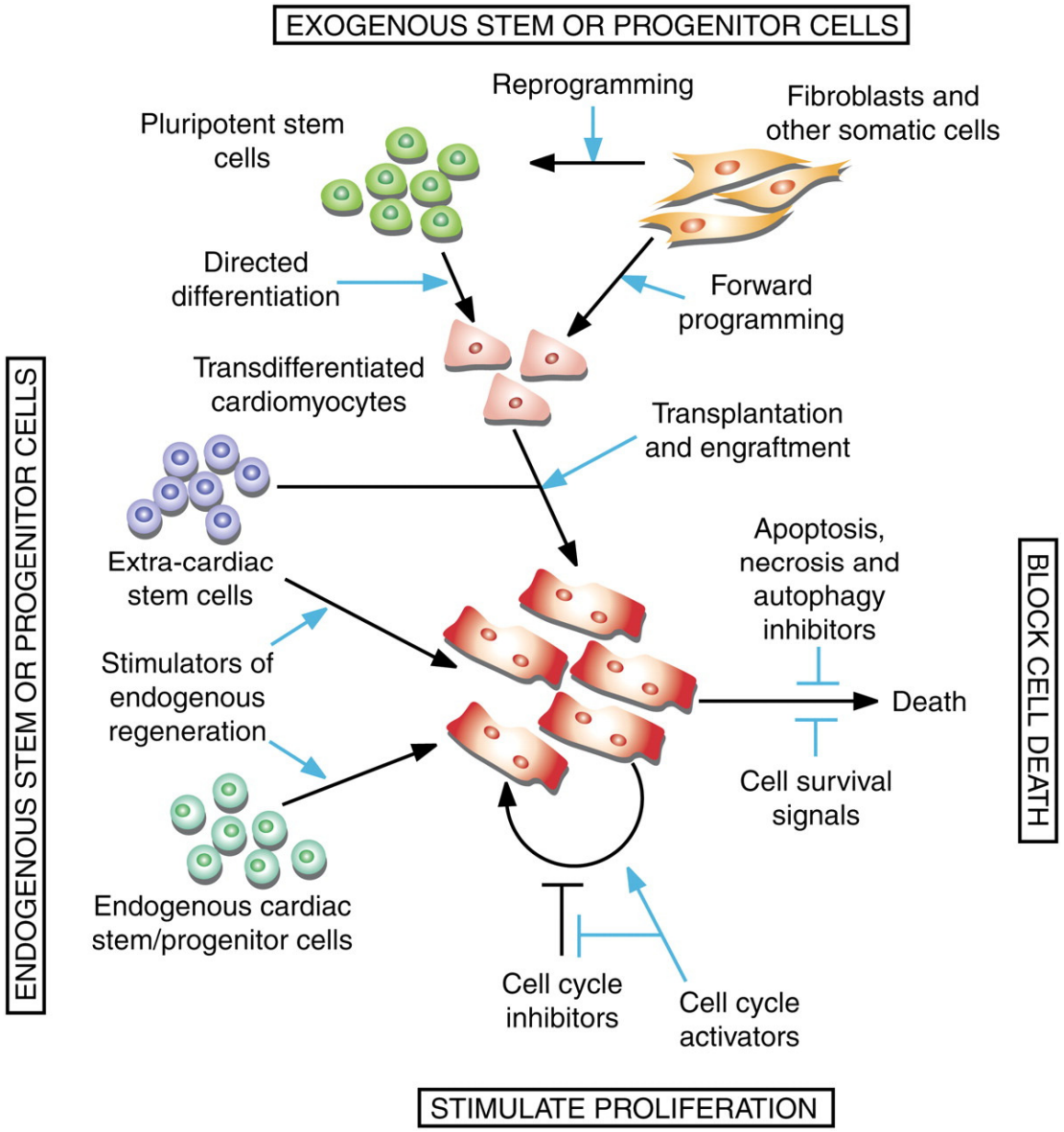
Deaths from Coronary Heart Disease





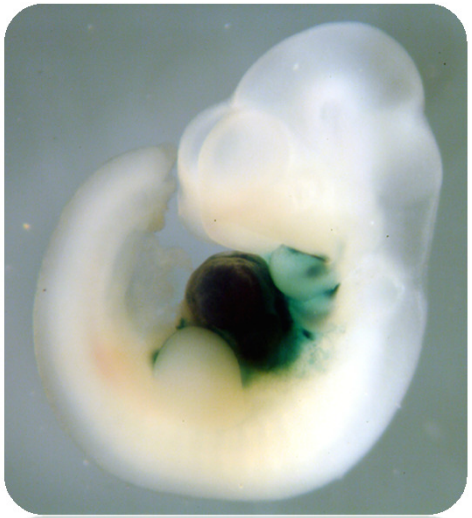
Source: BHF

Strategies to increase cardiomyocyte number following injury



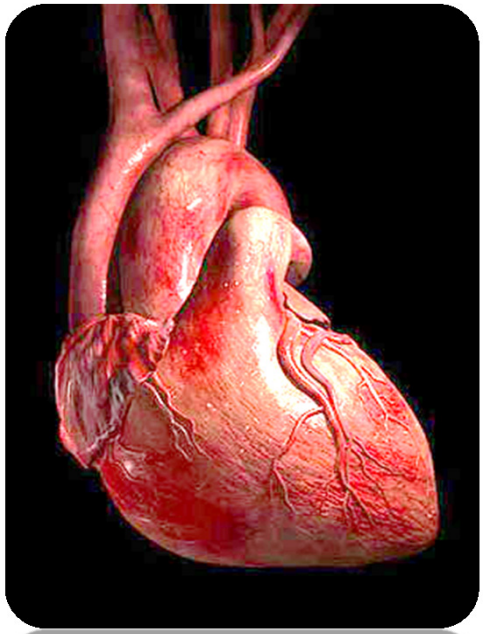
Mercola M et al. Genes Dev. 2011;25:299-309

The Embryonic Paradigm for Cardiac Repair

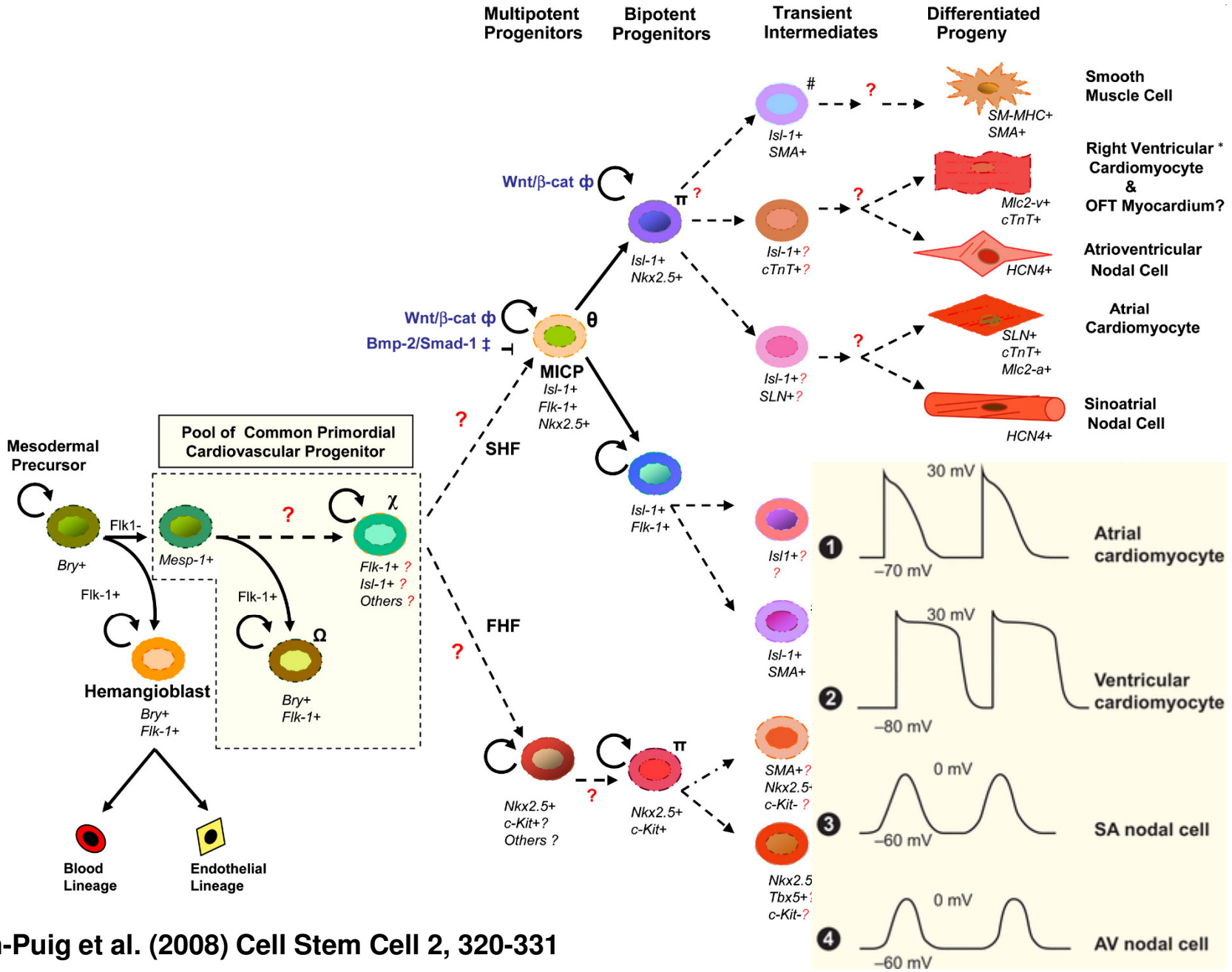


how to make a heart ?

how to repair a heart ?



A Blueprint for Cardiac Regeneration

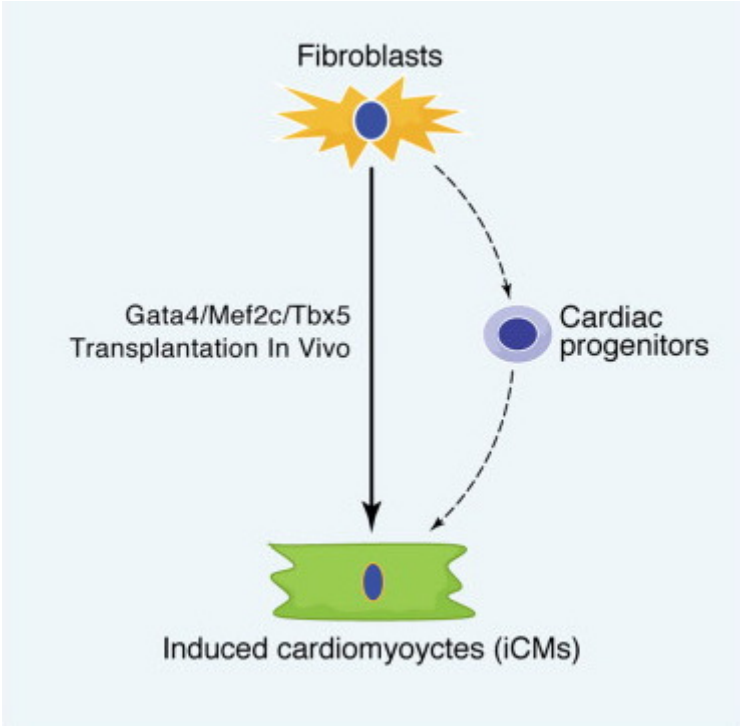


Martin-Puig et al. (2008) Cell Stem Cell 2, 320-331

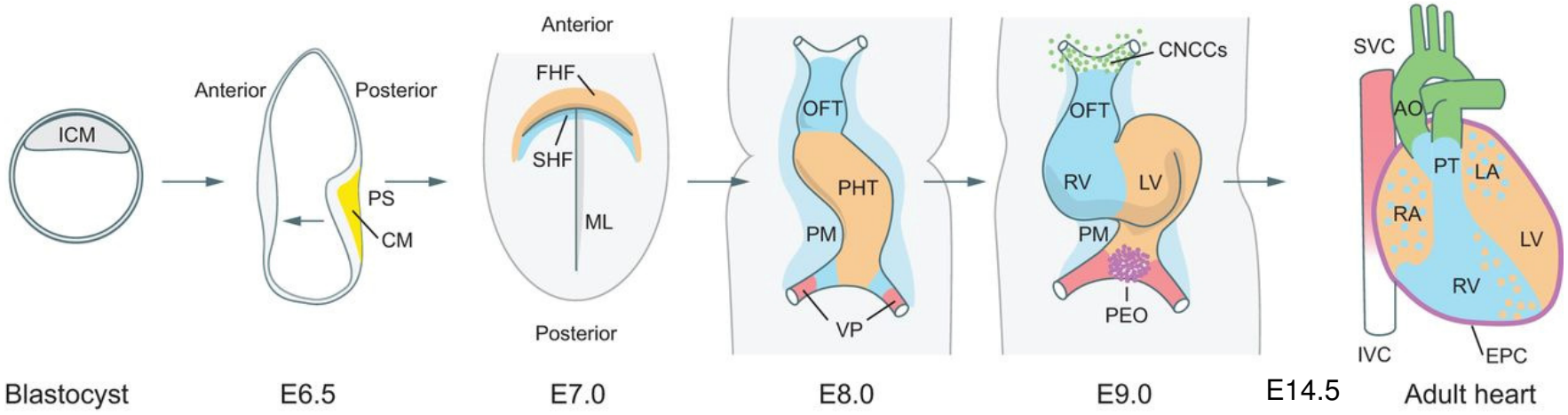
Cell

Direct Reprogramming of Fibroblasts into Functional Cardiomyocytes by Defined Factors

Masaki Ieda,[1,2,3,6,*] Ji-Dong Fu,[1,2,3] Paul Delgado-Olguin,[1,2,4] Vasanth Vedantham,[1,5] Yohei Hayashi,[1] Benoit G. Bruneau,[1,2,4] and Deepak Srivastava[1,2,3,*]
[1]Gladstone Institute of Cardiovascular Disease



Cardiac development in the mouse embryo

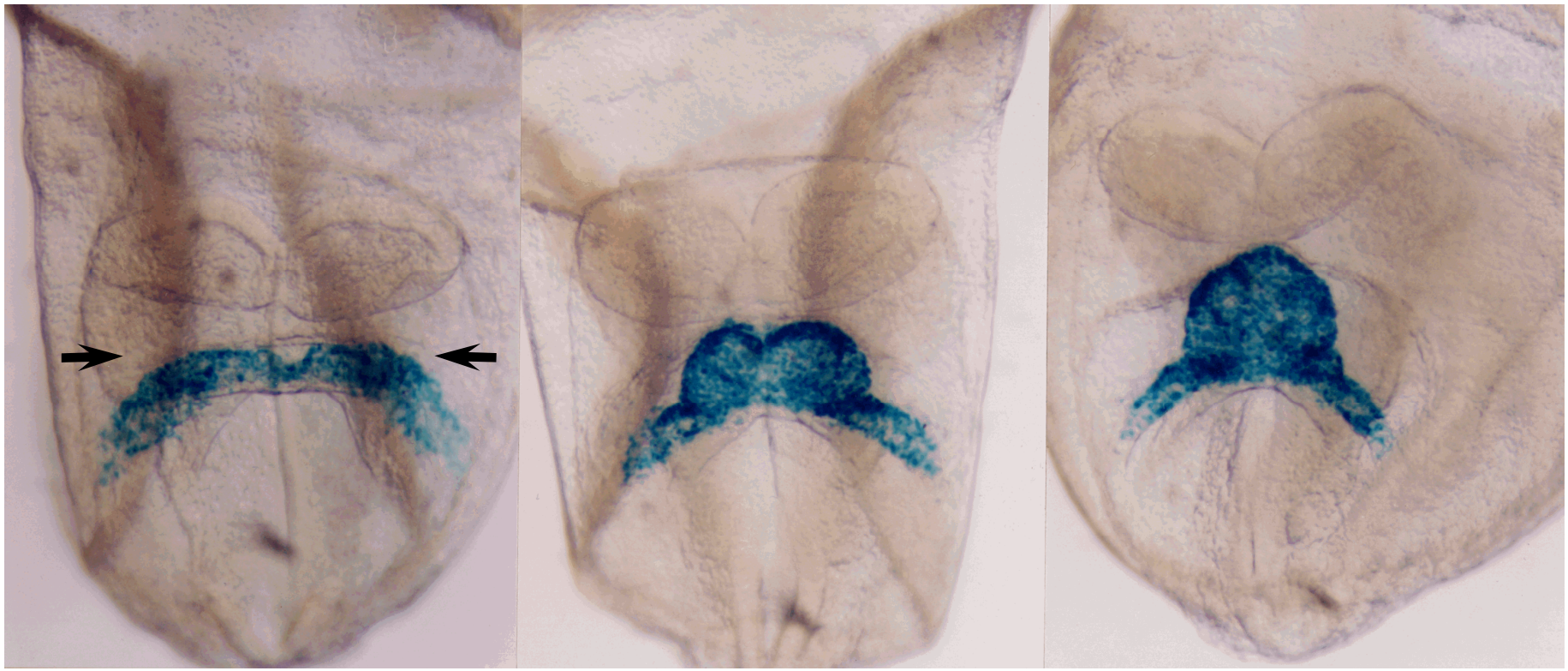


Human **Day 15** **Day 21** **Day 28** **Day 50**

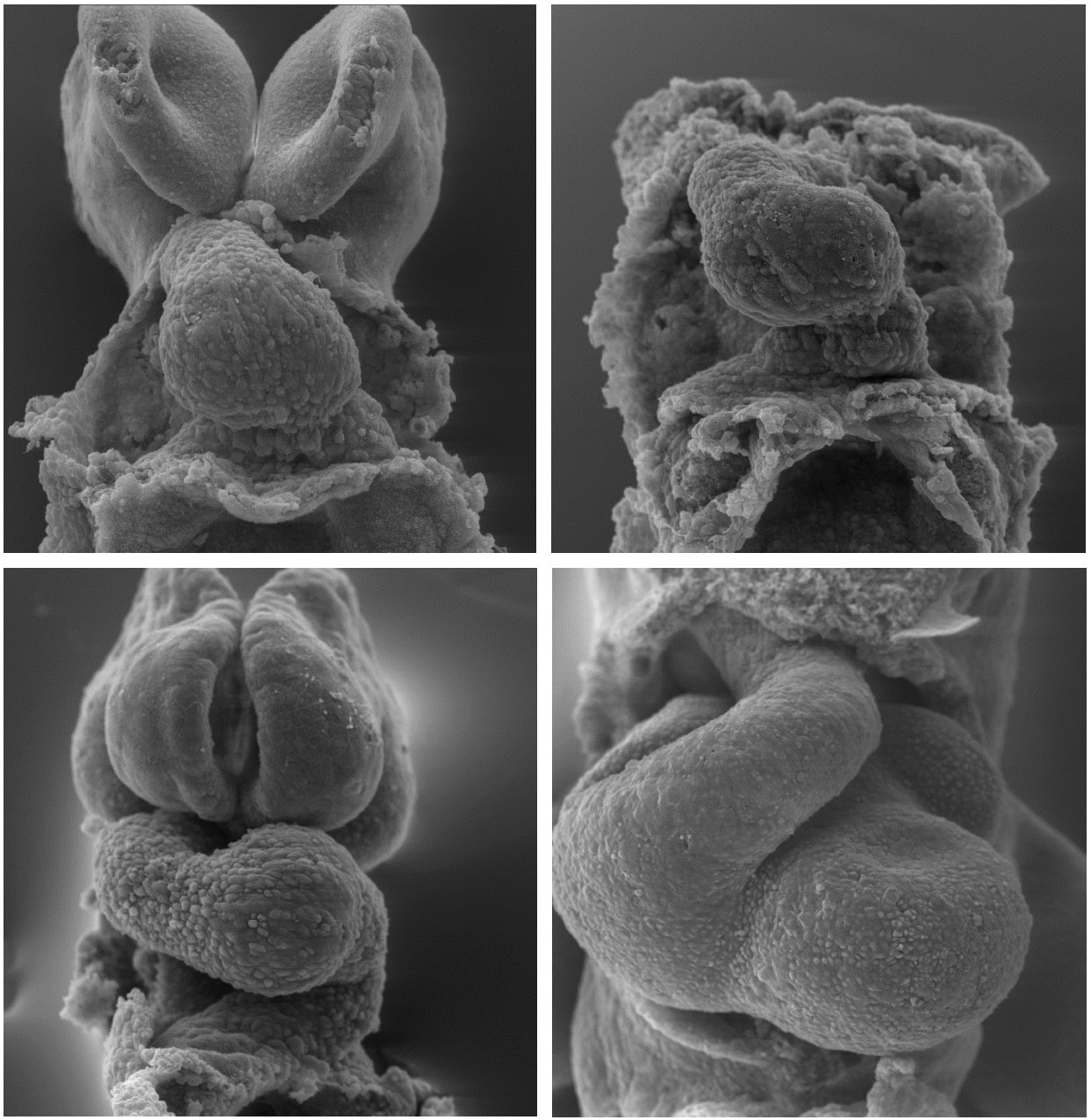
Daniela Später et al. Development 2014;141:4418-4431

THE COMPANY OF Biologists
Published by The Company of Biologists Limited
Development
dev.biologists.org

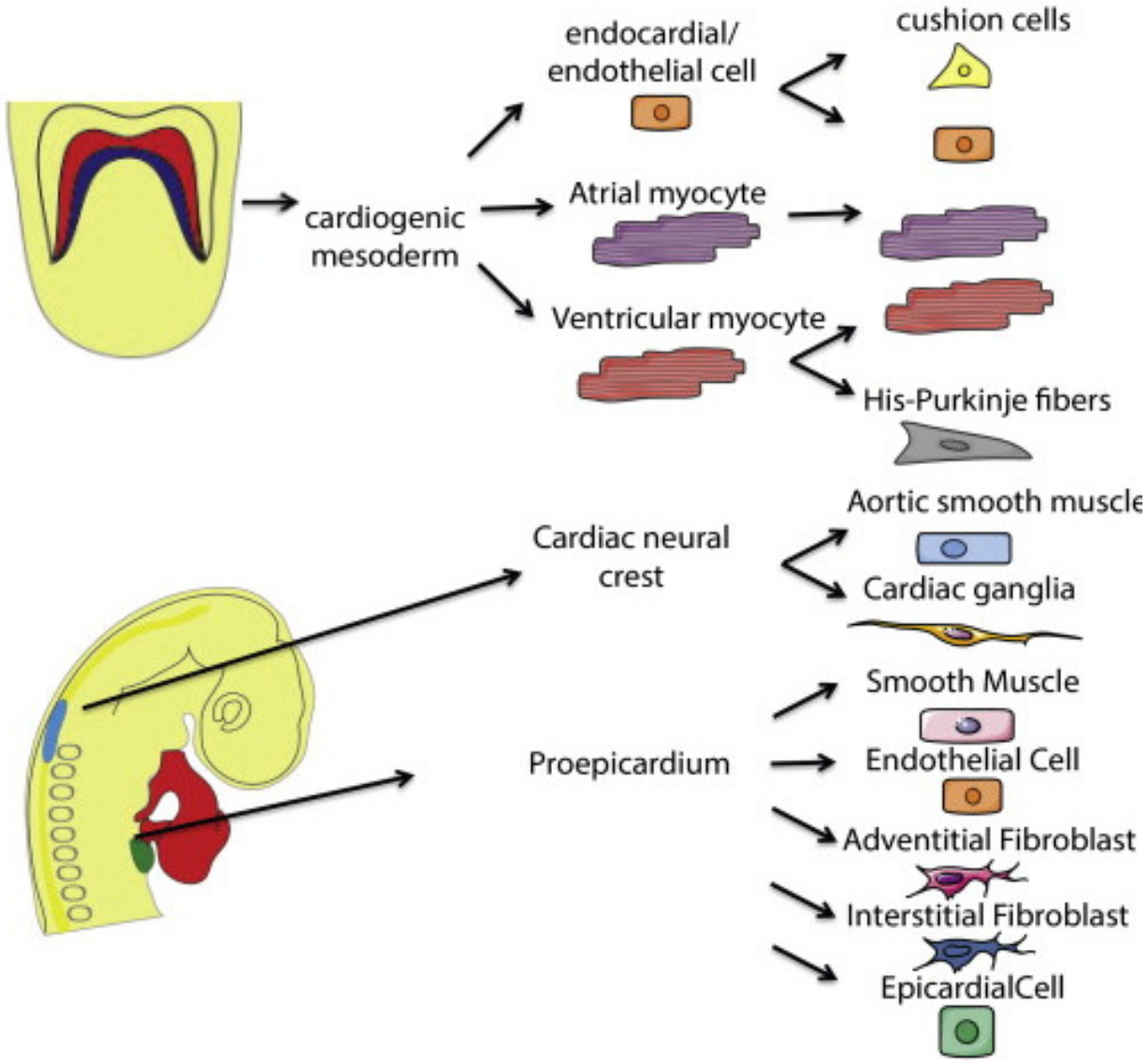
E7.0-7.5 Mouse Embryo: Cardiac Primordium



S.E.M. Developing Mouse Heart E8.0-9.5

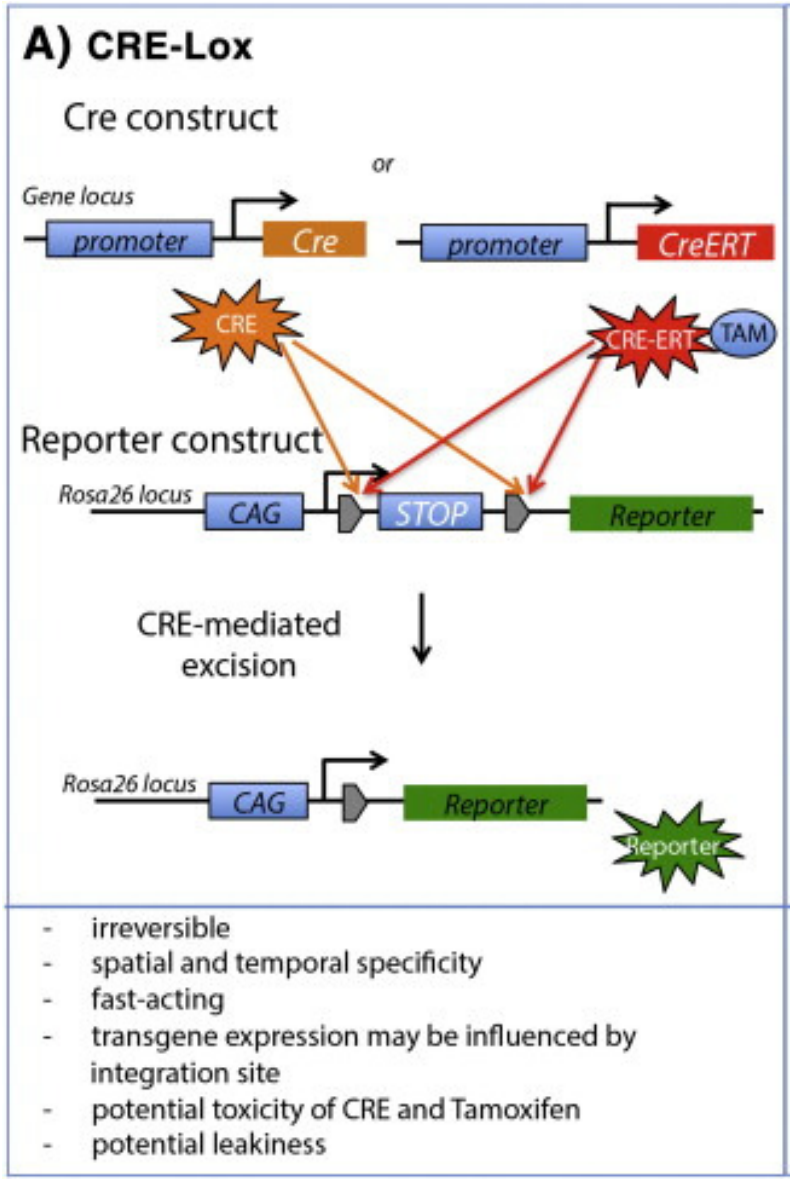


Origin and lineage relationship of cardiac cell types



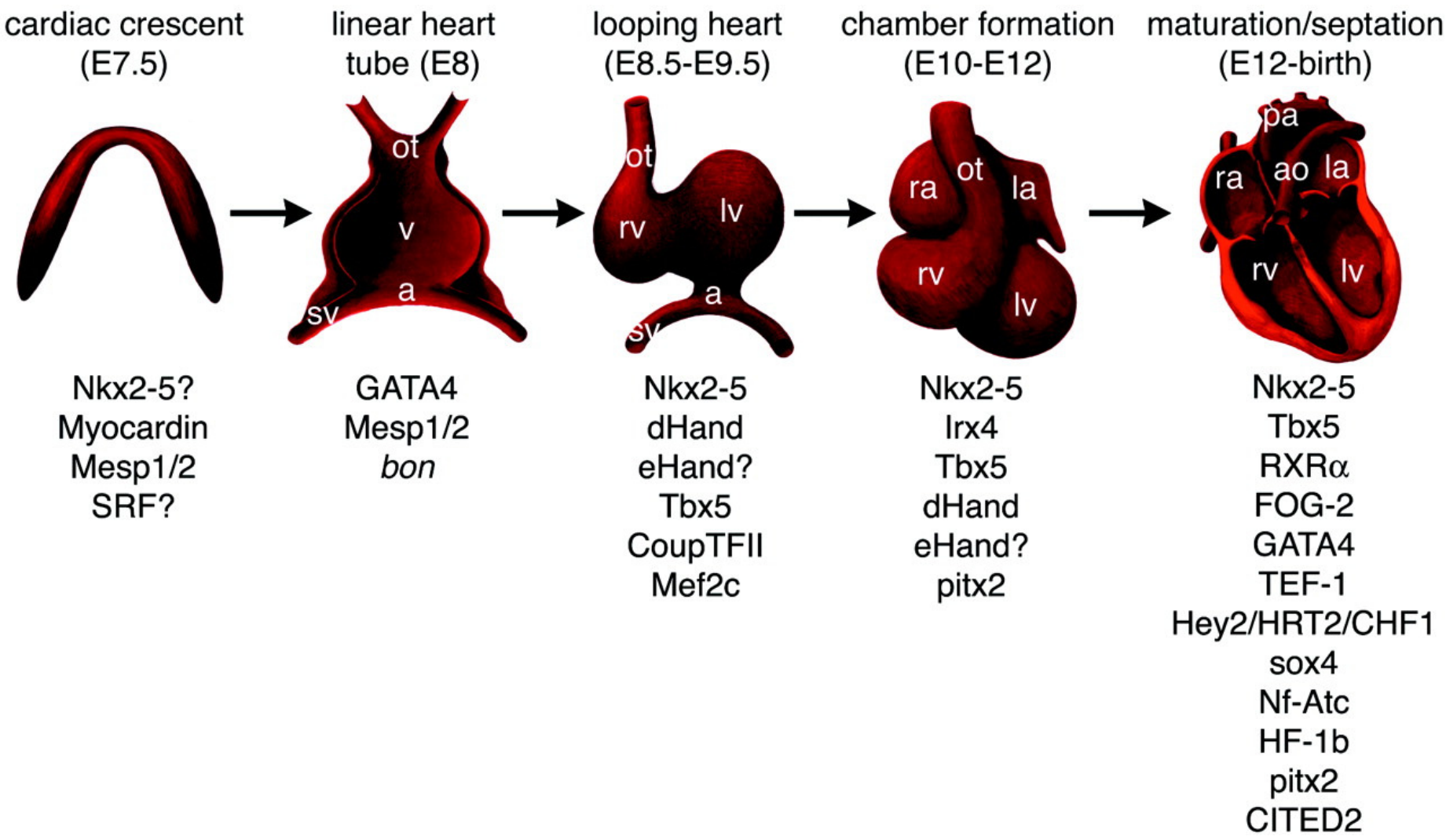
Chong et al. (2014) *Stem Cell Res* **13**, 592-614

Genetic Fate Mapping

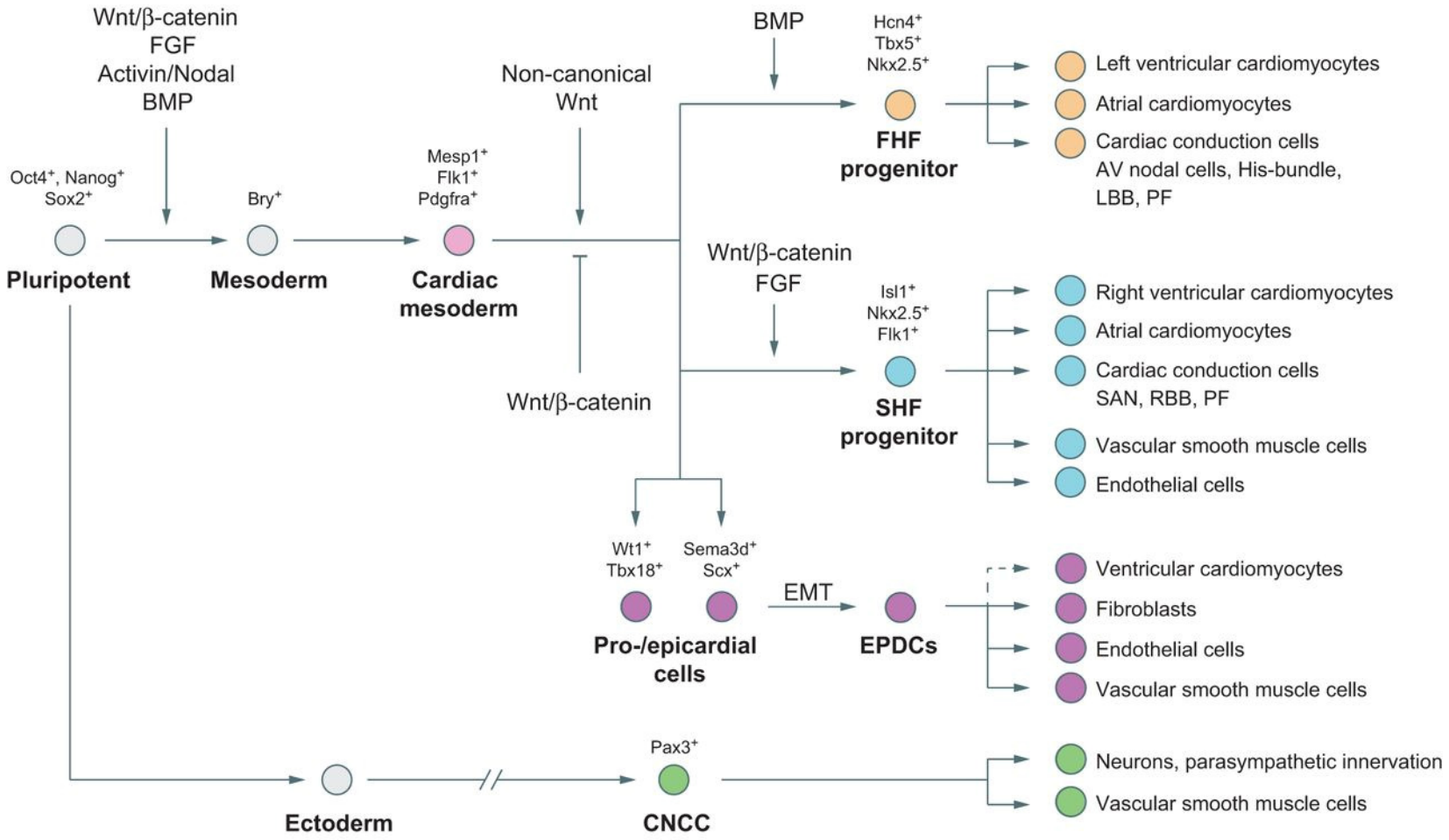


Chong et al. (2014) *Stem Cell Res* **13**, 592-614

Transcription Factors in Heart Development

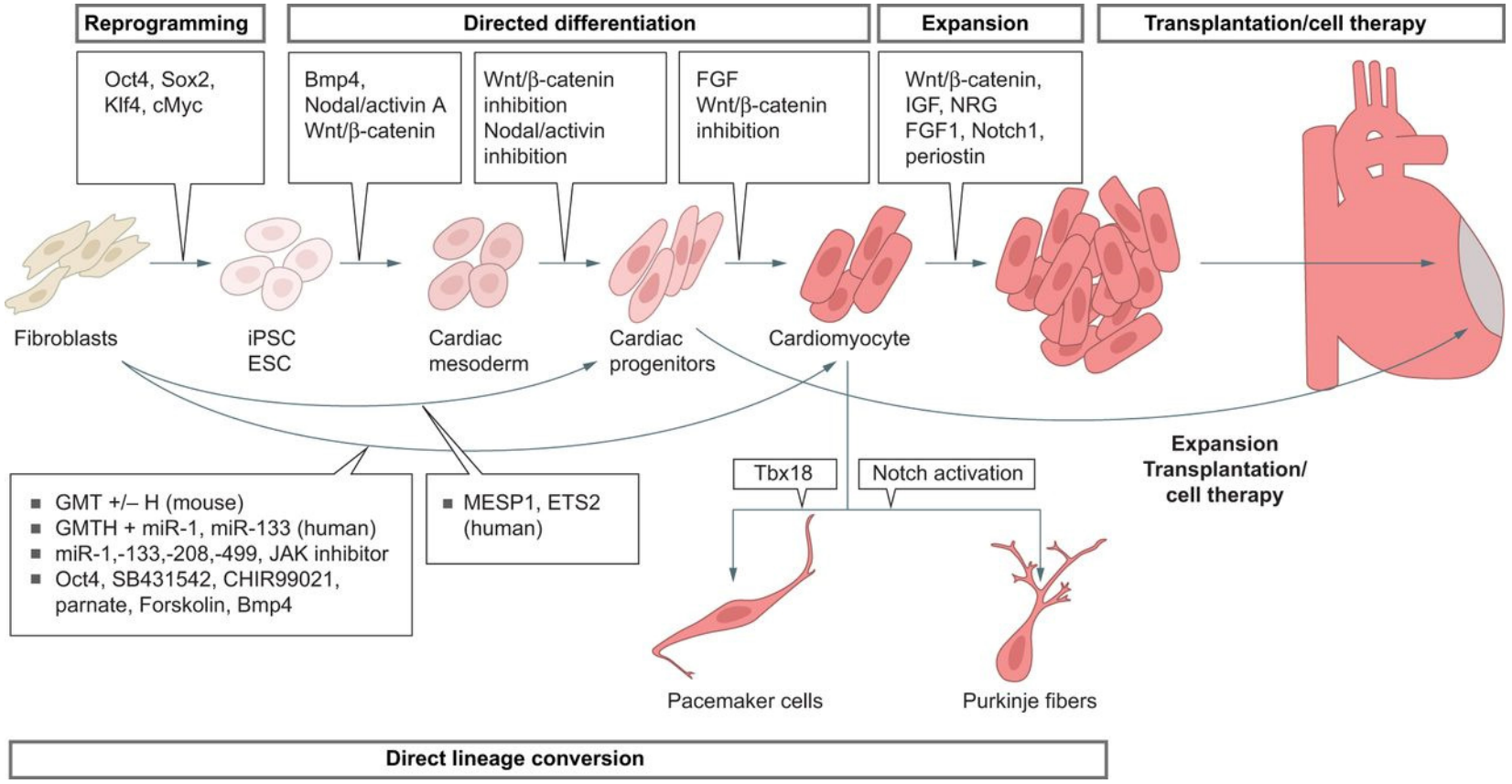


Specification and progression of the cardiac cell lineages during development



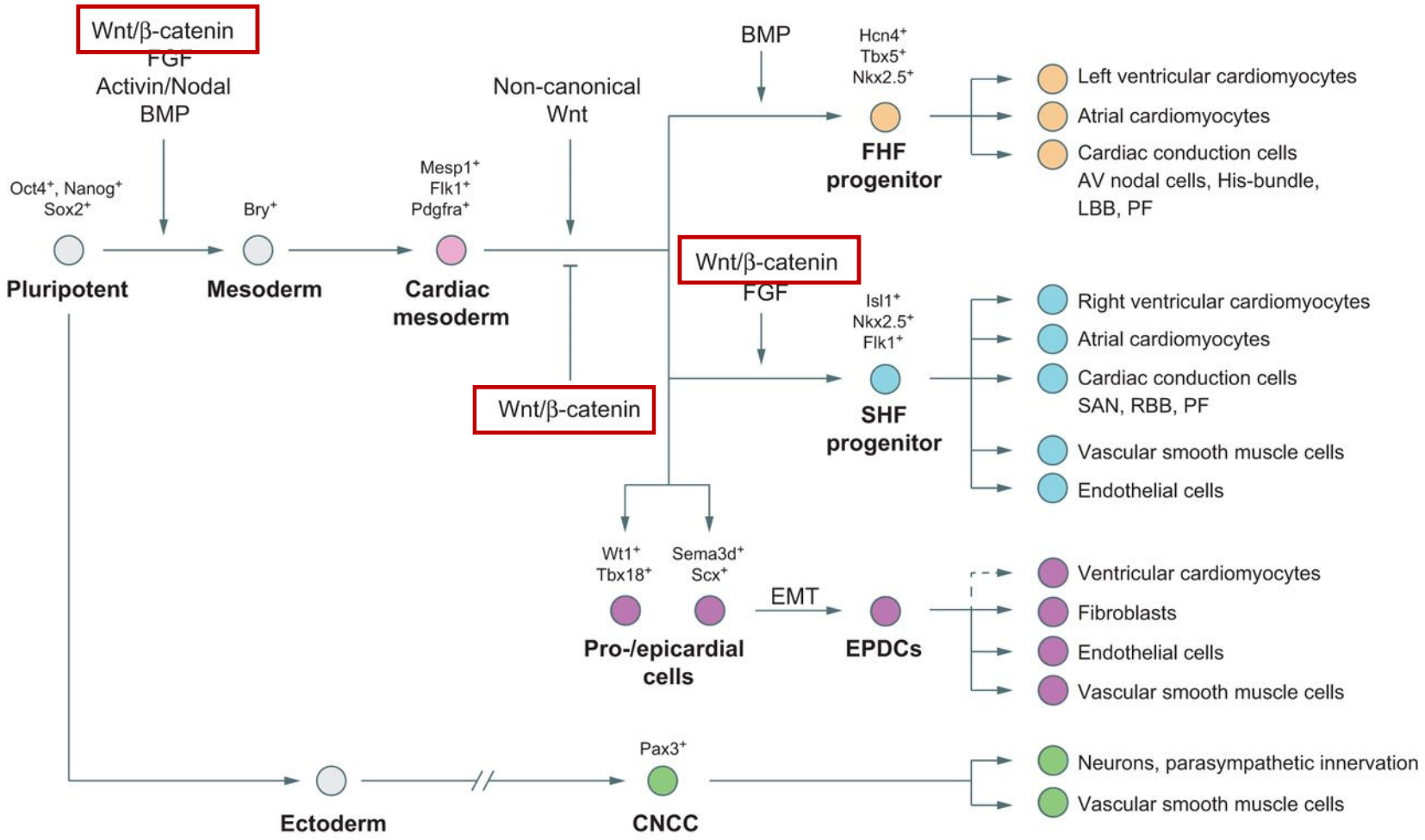
Daniela Später et al. Development 2014;141:4418-4431

Strategies to generate cardiomyocytes in vitro.



Daniela Später et al. Development 2014;141:4418-4431

Specification and progression of the cardiac cell lineages during development



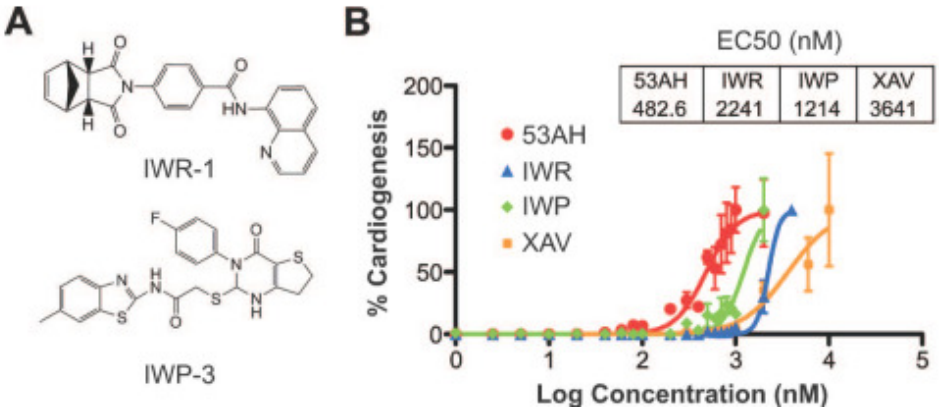
Daniela Später et al. Development 2014;141:4418-4431

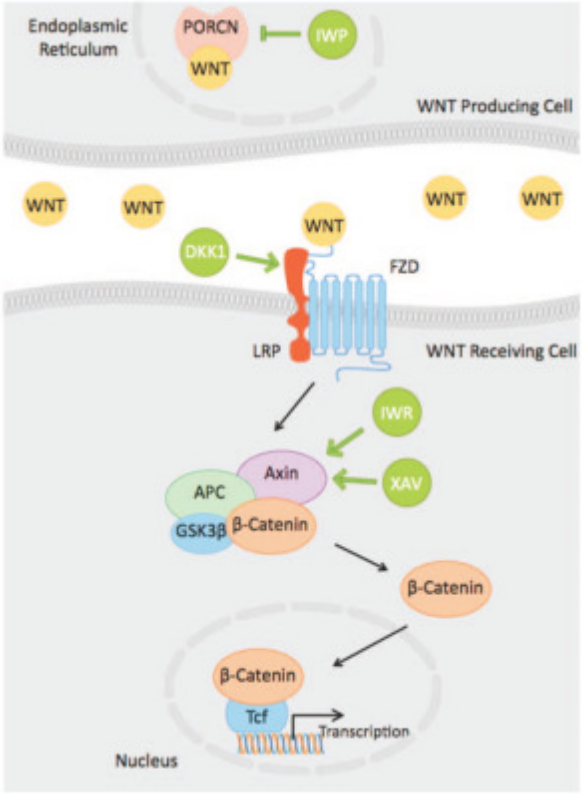
Applying this Knowledge…

Brief UltraRapid Communication

Small-Molecule Inhibitors of the Wnt Pathway Potently Promote Cardiomyocytes From Human Embryonic Stem Cell–Derived Mesoderm

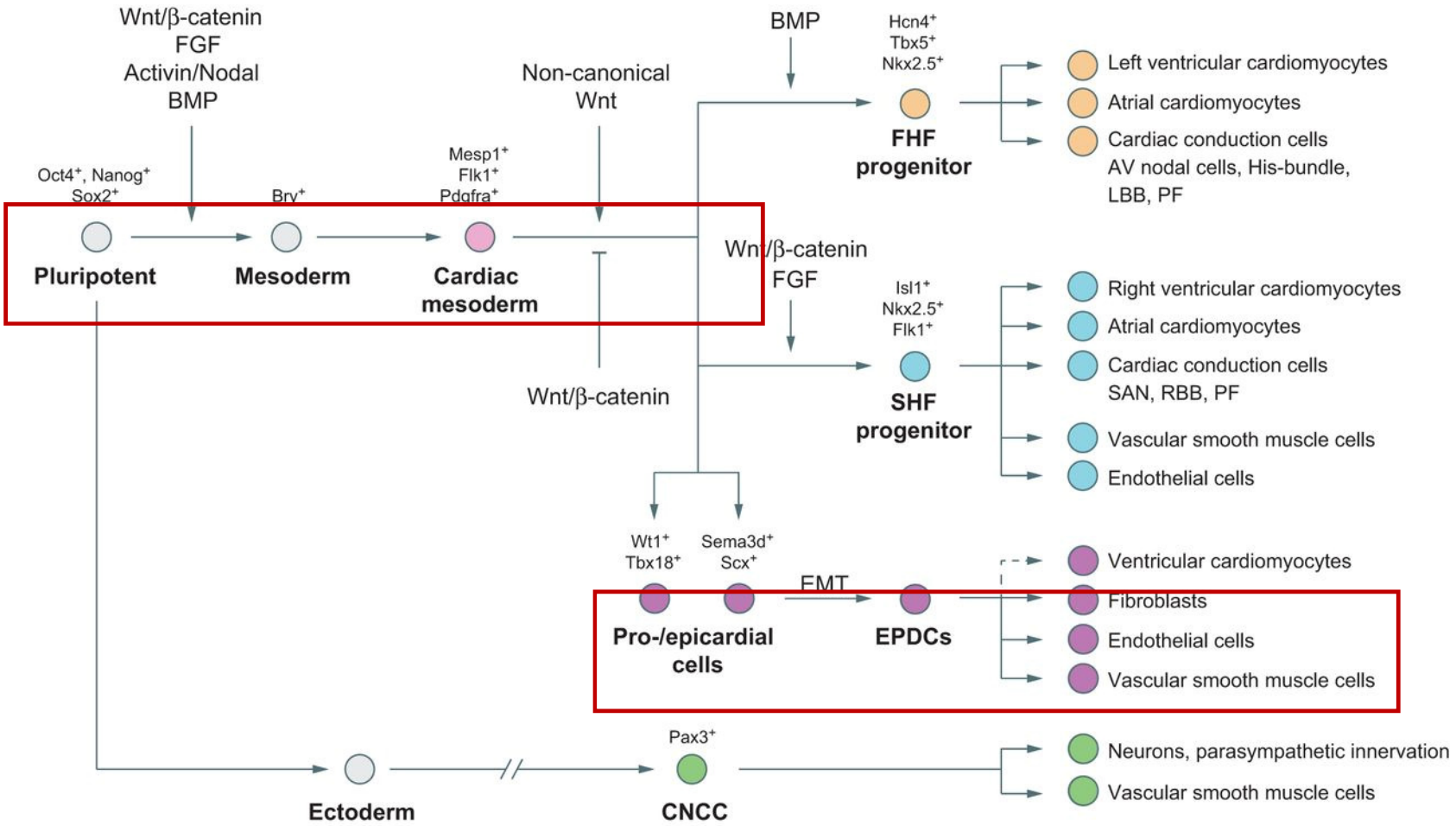
Erik Willems, Sean Spiering, Herman Davidovics, Marion Lanier, Zebin Xia, Marcia Dawson, John Cashman, Mark Mercola





Willems et al., Circ Res. 2011;109:360-364.

Specification and progression of the cardiac cell lineages during development



Daniela Später et al. Development 2014;141:4418-4431

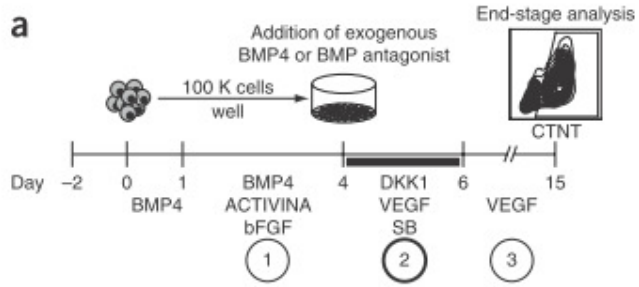
Epicardium from human iPSCs

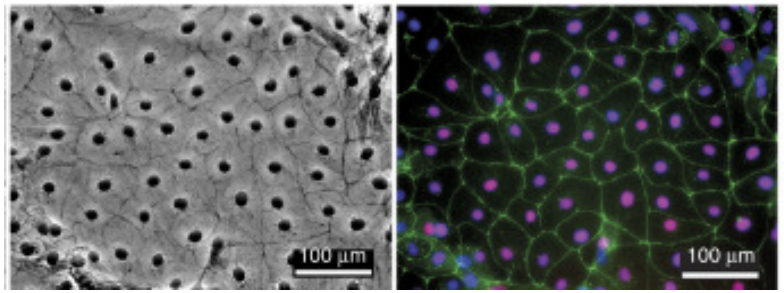
Generation of the epicardial lineage from human pluripotent stem cells

Alec D Witty[1,2], Anton Mihic[1,3–5], Roger Y Tam[6–8], Stephanie A Fisher[6–8], Alexander Mikryukov[1], Molly S Shoichet[1,6–9], Ren-Ke Li[1,3–5], Steven J Kattman[1,11] & Gordon Keller[1,2,10]

The epicardium supports cardiomyocyte proliferation early in development and provides fibroblasts and vascular smooth muscle cells to the developing heart. The epicardium has been shown to play an important role during tissue remodeling after cardiac injury, making access to this cell lineage necessary for the study of regenerative medicine. Here we describe the generation of epicardial lineage cells from human pluripotent stem cells by stage-specific activation of the BMP and WNT signaling pathways. These cells display morphological characteristics and express markers of the epicardial lineage, including the transcription factors WT1 and TBX18 and the retinoic acid–producing enzyme ALDH1A2. When induced to undergo epithelial-to-mesenchymal transition, the cells give rise to populations that display characteristics of the fibroblast and vascular smooth muscle lineages. These findings identify BMP and WNT as key regulators of the epicardial lineage *in vitro* and provide a model for investigating epicardial function in human development and disease.

NATURE BIOTECHNOLOGY VOLUME 32 NUMBER 10 OCTOBER 2014

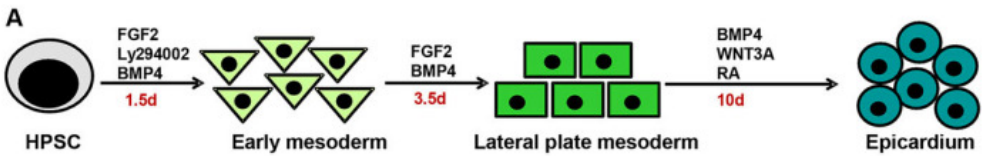


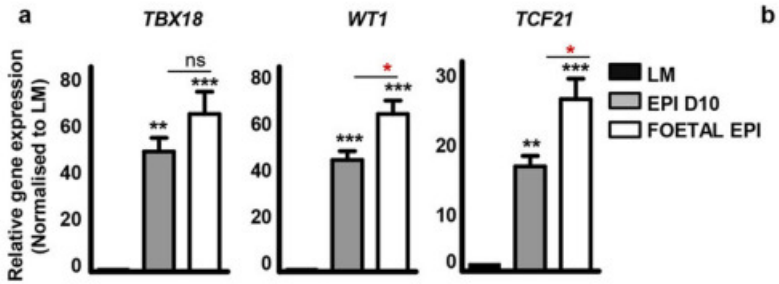


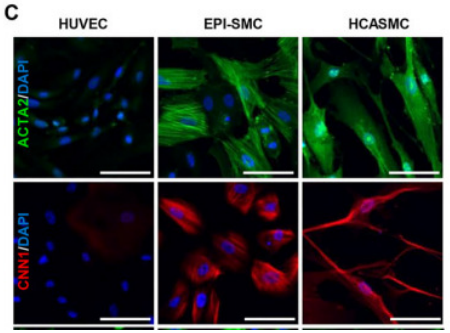
RESEARCH ARTICLE TECHNIQUES AND RESOURCES

Robust derivation of epicardium and its differentiated smooth muscle cell progeny from human pluripotent stem cells

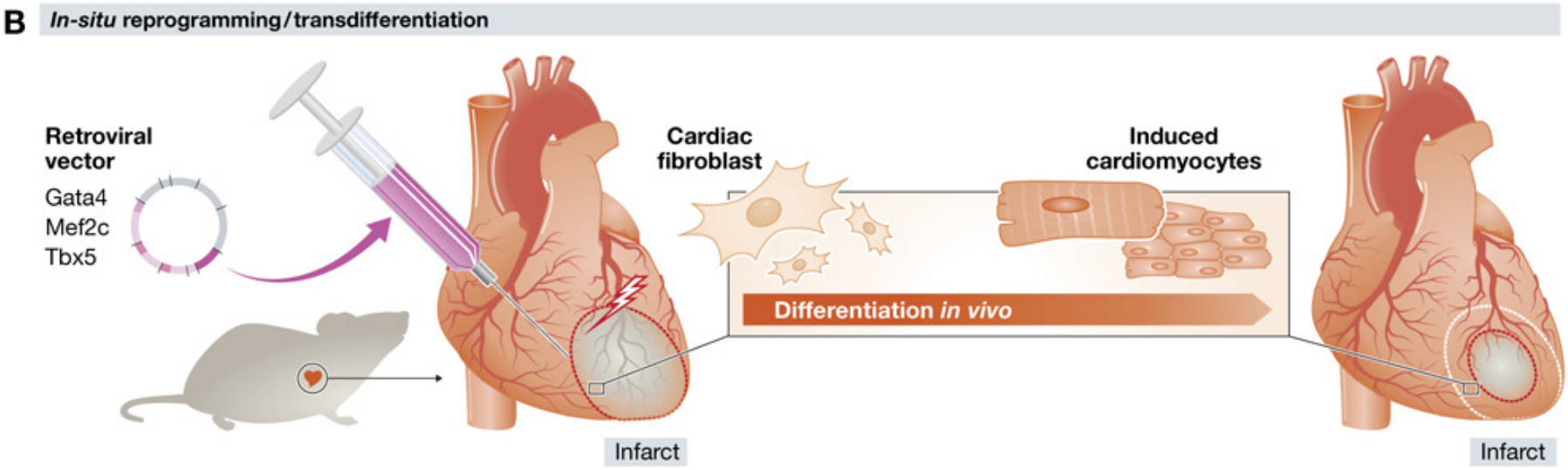
Dharini Iyer, Laure Gambardella, William G. Bernard, Felipe Serrano, Victoria L. Mascetti, Roger A. Pedersen, Amarnath Talasila and Sanjay Sinha*

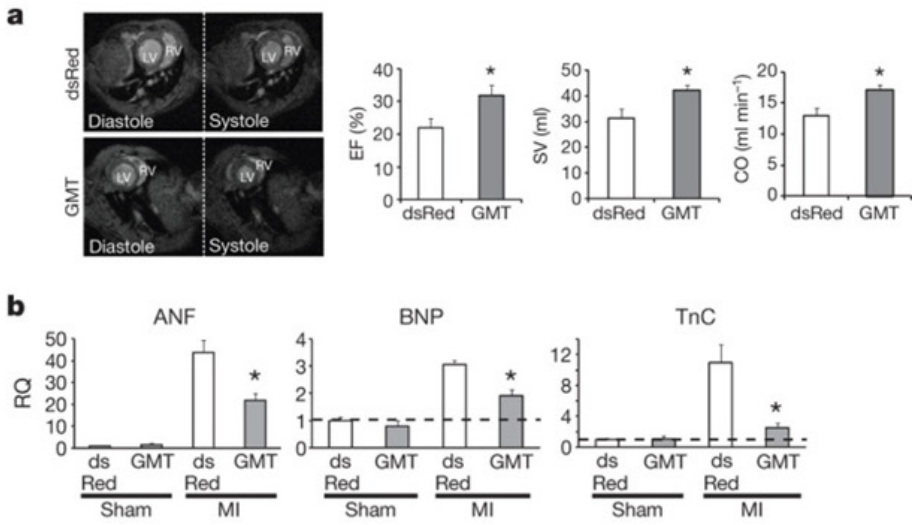


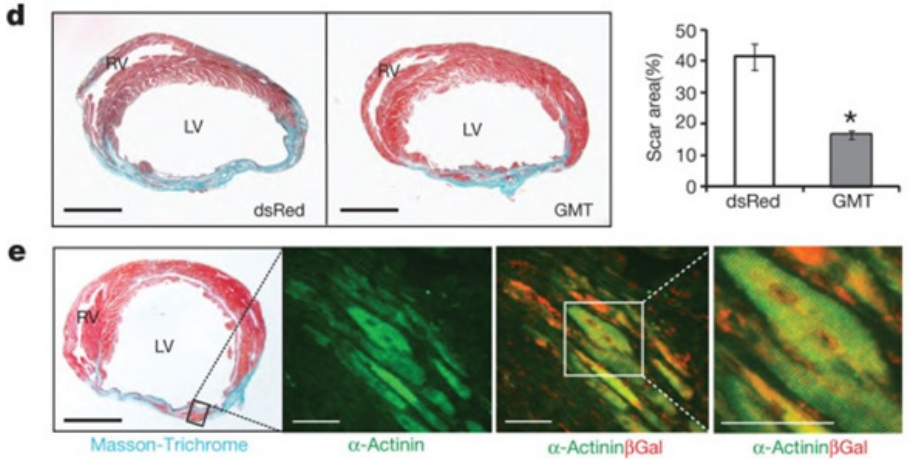




In vivo Cardiac Reprogramming: Improved Cardiomyocyte Maturation and Improved Cardiac Function







nature

L Qian *et al. Nature* **000**, 1-6 (2012) doi:10.1038/nature11044

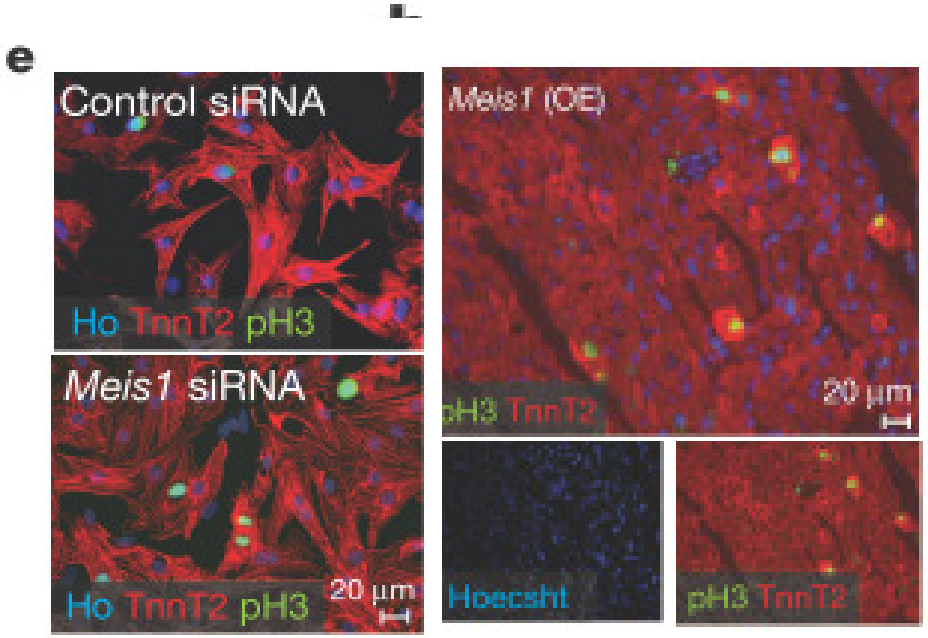
Cell cycle re-entry in adult cardiomyocytes

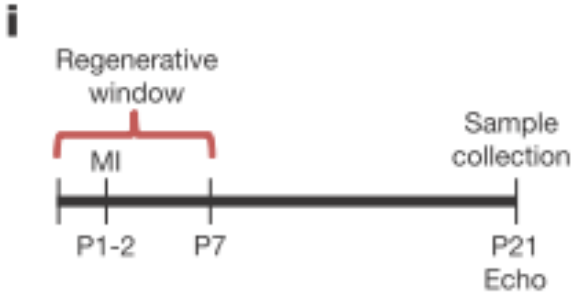
LETTER

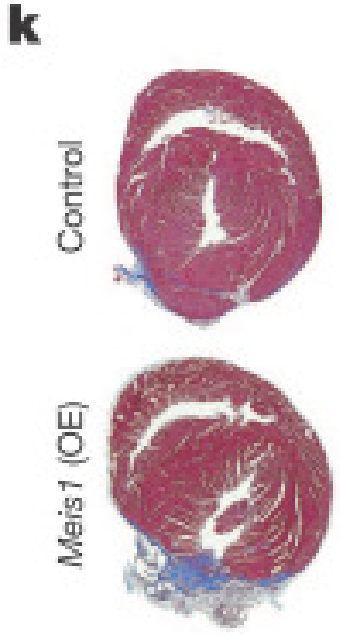
doi:10.1038/nature12054

Meis1 regulates postnatal cardiomyocyte cell cycle arrest

Ahmed I. Mahmoud[1]*, Fatih Kocabas[1]*, Shalini A. Muralidhar[1]*, Wataru Kimura[1], Ahmed S. Koura[2], Suwannee Thet[1], Enzo R. Porrello[3] & Hesham A. Sadek[1]



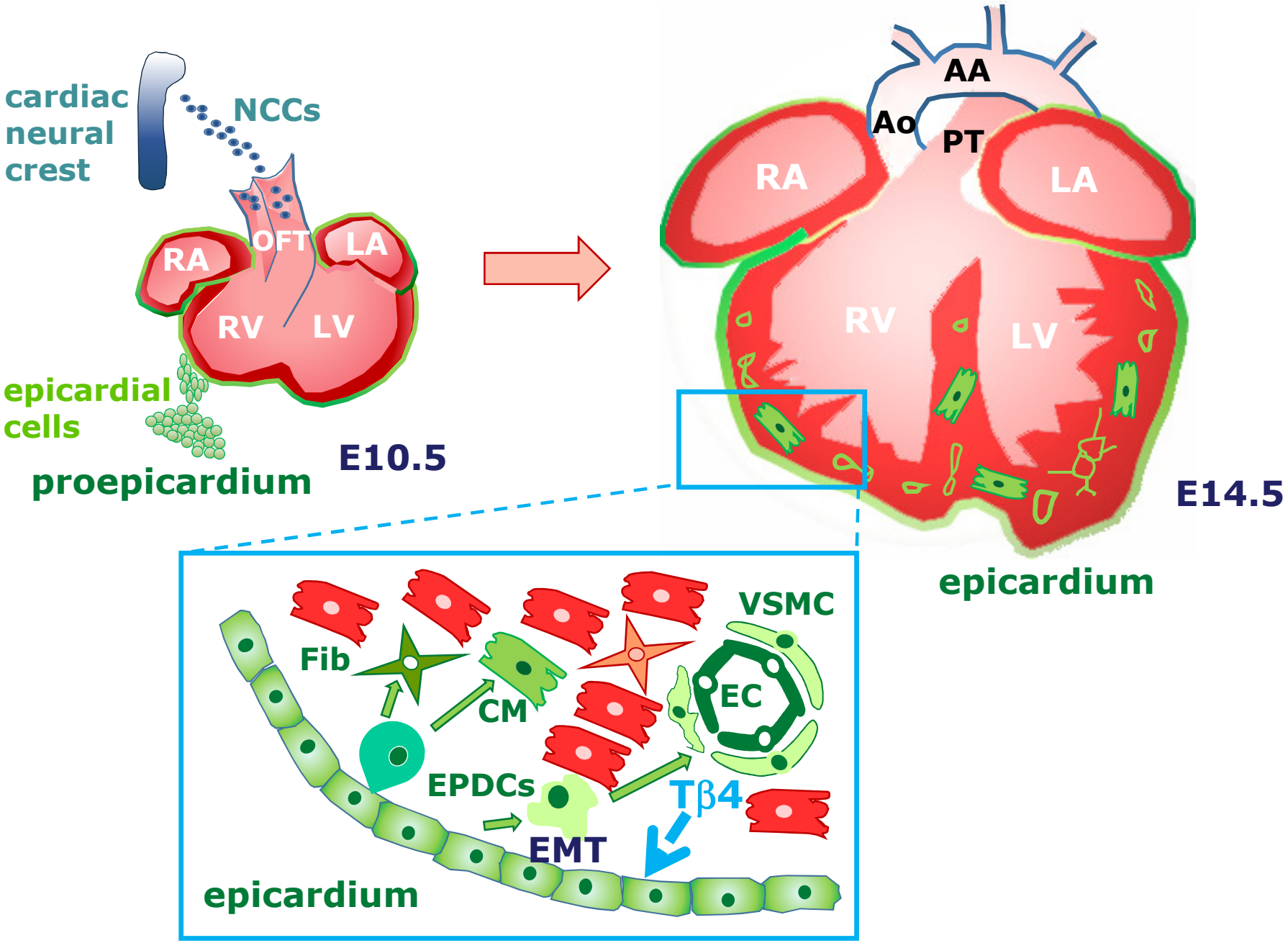




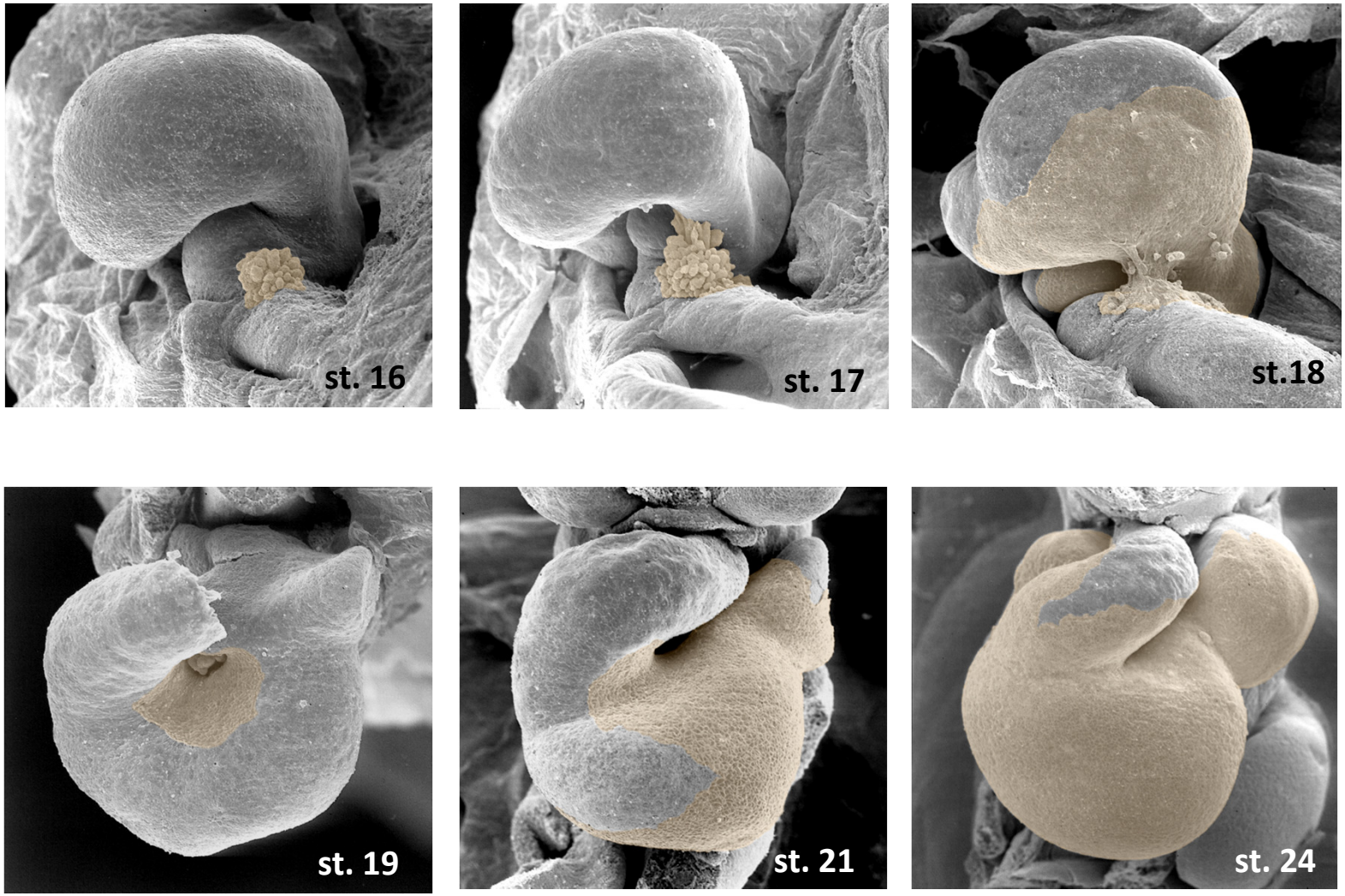
Mahmoud et al (2013) *Nature* 497:249-53

Epicardium-Derived Cells (EPDCs)

Epicardial Contribution to the Developing Heart



The proepicardium: cell transfer and epicardium formation

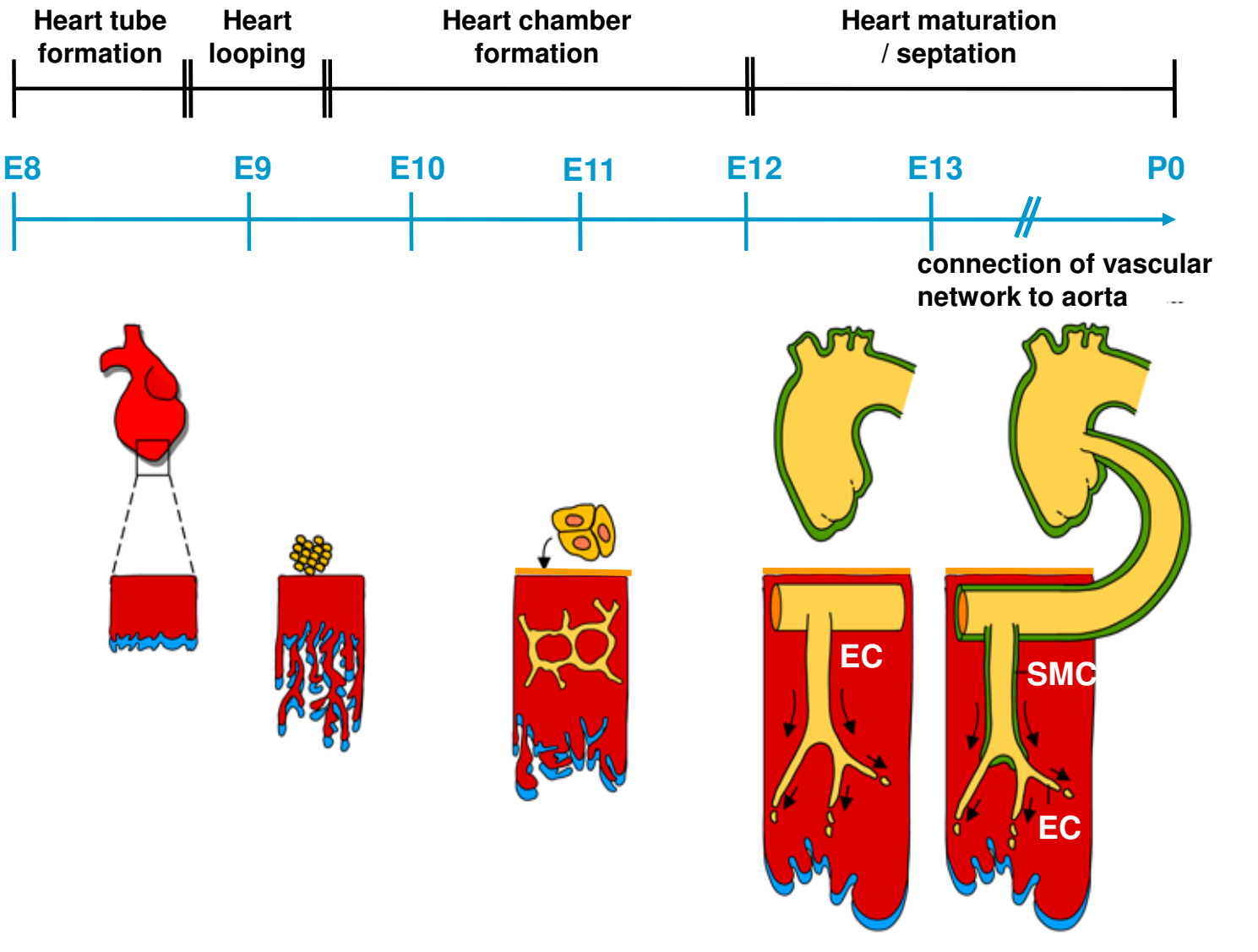


Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

harefield
heartsciencecentre

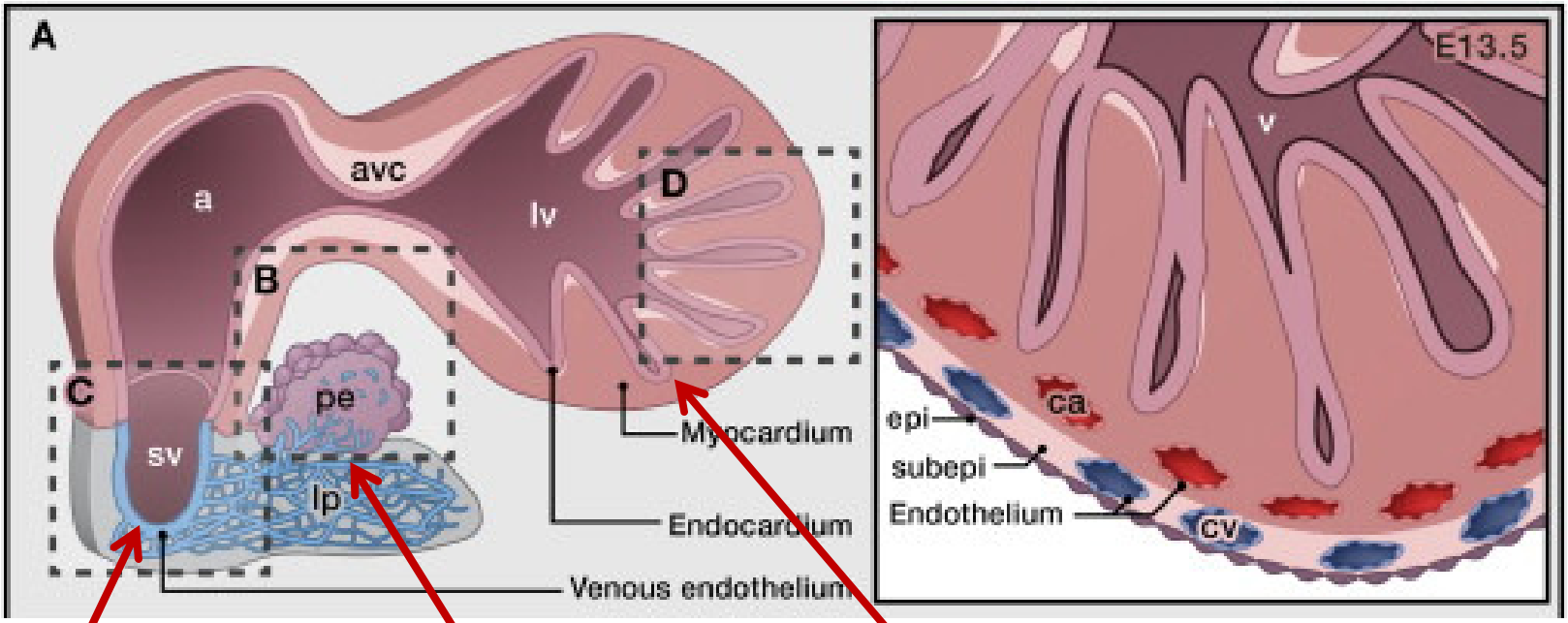
Thomas Brand, Professor and Chair
of Developmental Dynamics

Development of the Coronary Vasculature



Luttun, A & Carmeliet, P. (2003) Cardiovasc. Res. 58: 378-389

Unresolved: Developmental Origin of Coronary Arteries



Sinus venosus (and atrial) endocardium

K Red-Horse *et al.* (2010) *Nature* 464, 549-553

Tian et al (2013) *Cell Res.*:1-16

Proepicardial organ

Katz et al (2012) Dev. Cell 22(3):639-50.

Ventricular endocardium

Wu et al (2012) Cell 151: 1083-1096

Del Monte and Harvey (2012) Cell 151; 932-4

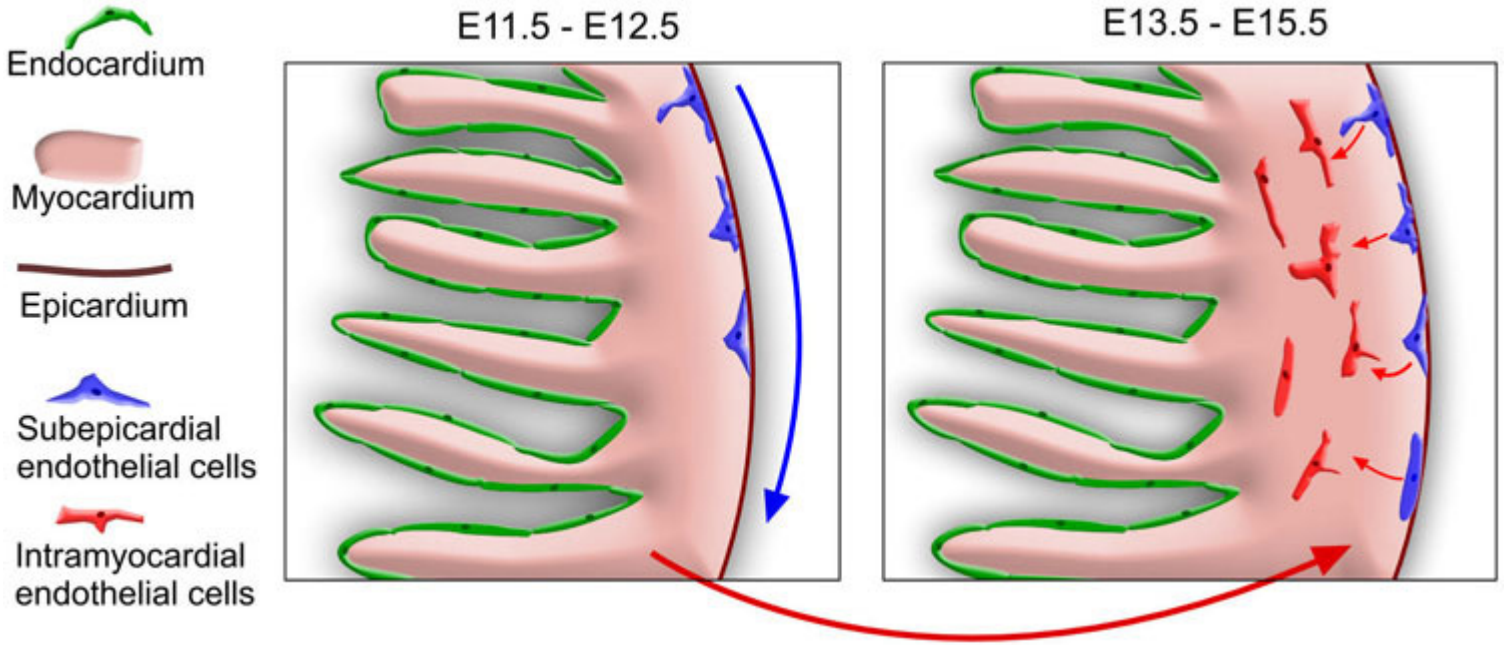
Open
ORIGINAL ARTICLE

Cell Research (2013) :1-16.

www.nature.com/cr

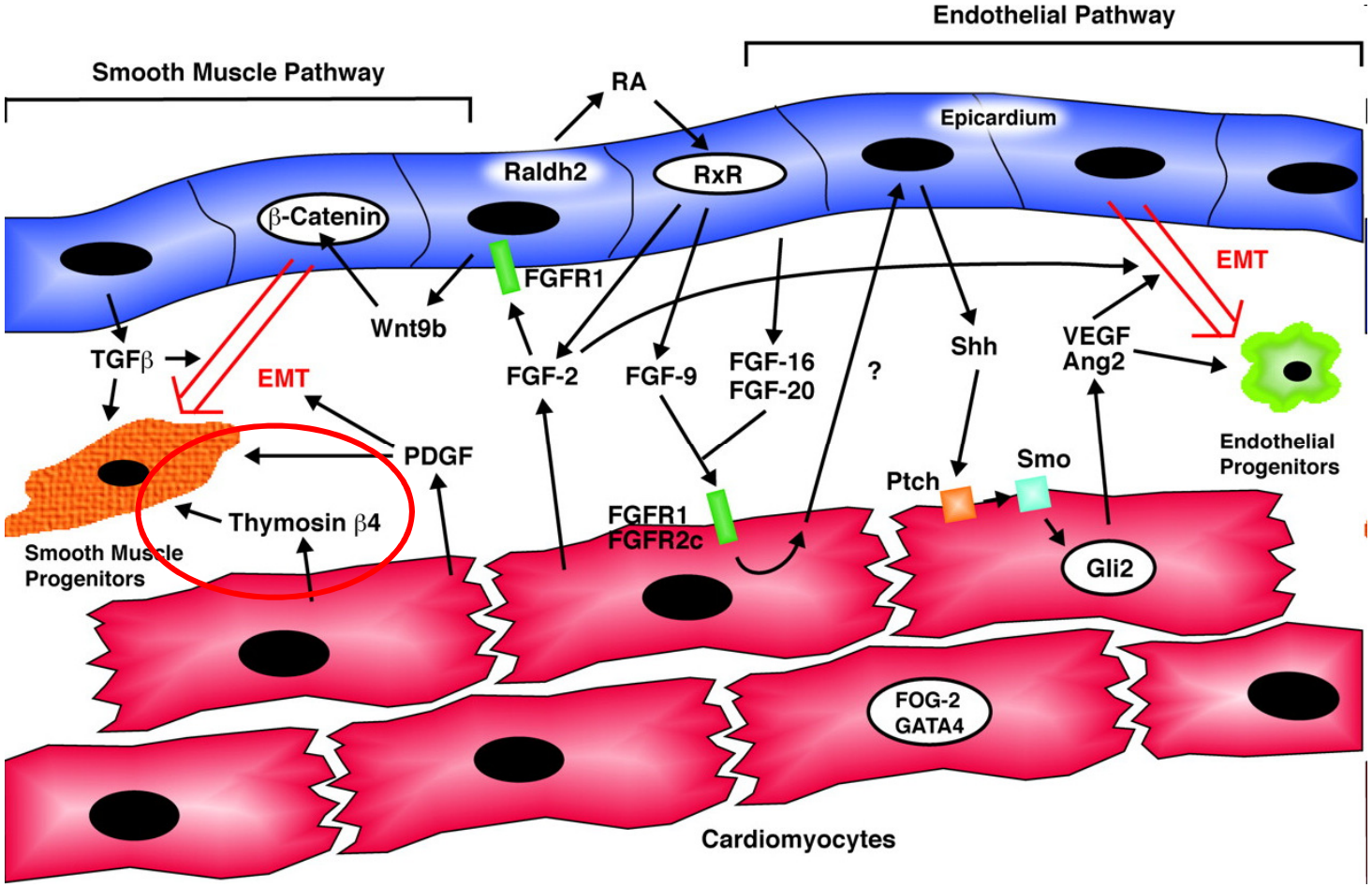
Subepicardial endothelial cells invade the embryonic ventricle wall to form coronary arteries

Xueying Tian[1,*], Tianyuan Hu[1,*], Hui Zhang[1,*], Lingjuan He[1], Xiuzhen Huang[1], Qiaozhen Liu[1], Wei Yu[1], Liang He[1], Zhongzhou Yang[2], Zhen Zhang[3], Tao P Zhong[4], Xiao Yang[5], Zhen Yang[6], Yan Yan[6], Antonio Baldini[7], Yunfu Sun[8], Jie Lu[9], Robert J Schwartz[10], Sylvia M Evans[11], Adriana C Gittenberger-de Groot[12], Kristy Red-Horse[13], Bin Zhou[1]



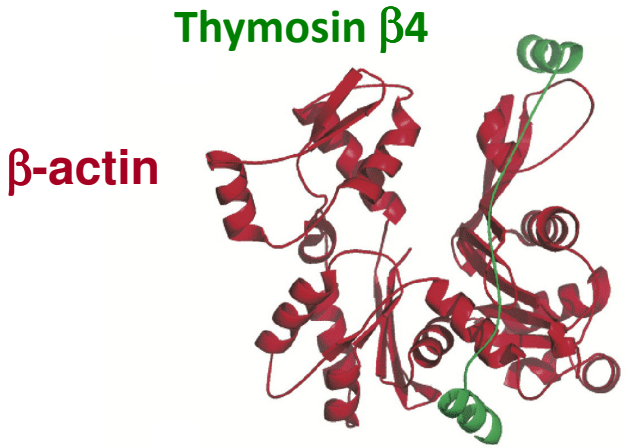
Tian et al (2013) *Cell Res*.:1-16

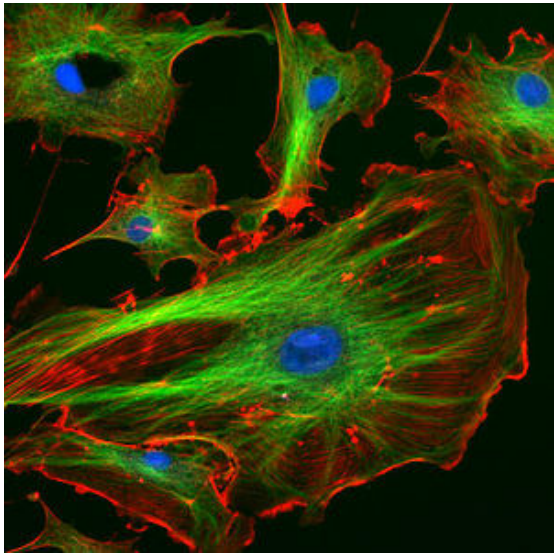
Epicardial–myocardial signaling pathways in coronary vascular development

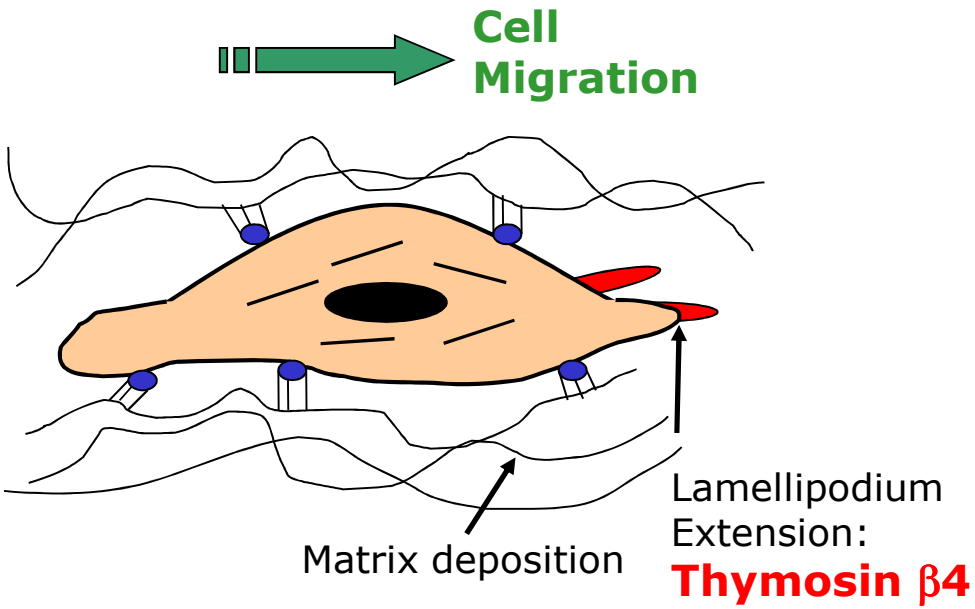


Olivey & Svensson (2010) Circ. Res. 106, 818-832

Thymosin β4 (Tβ4)

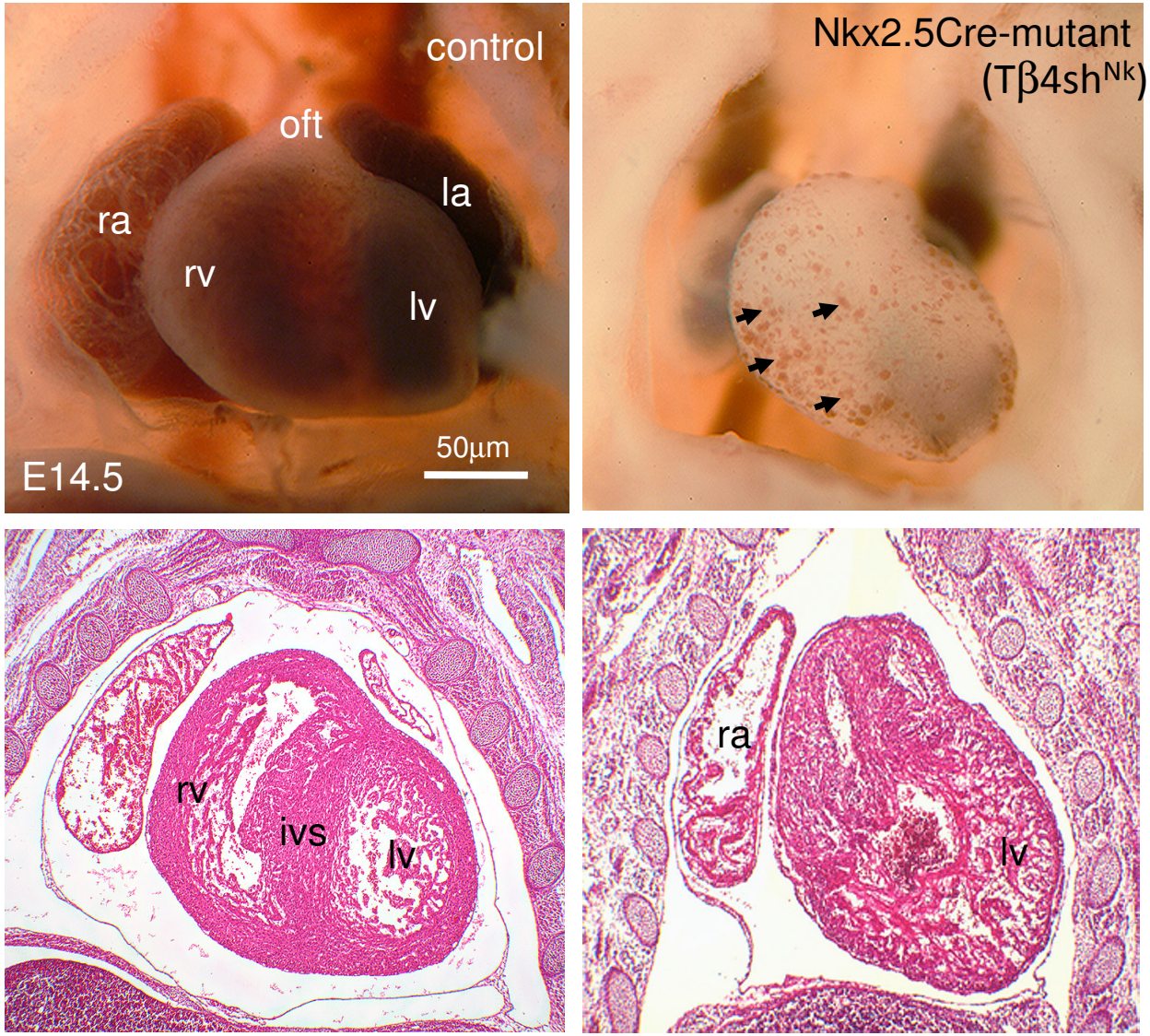






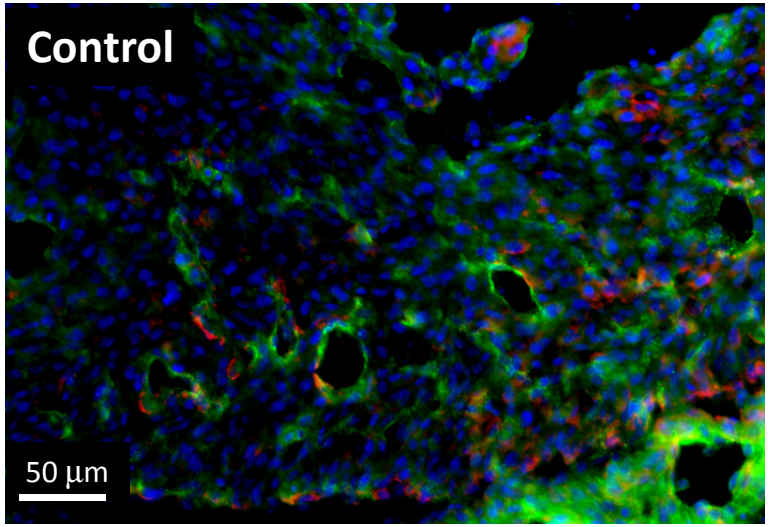
Adapted from: Ridley, A (2000) *Nature* 406, 466-467

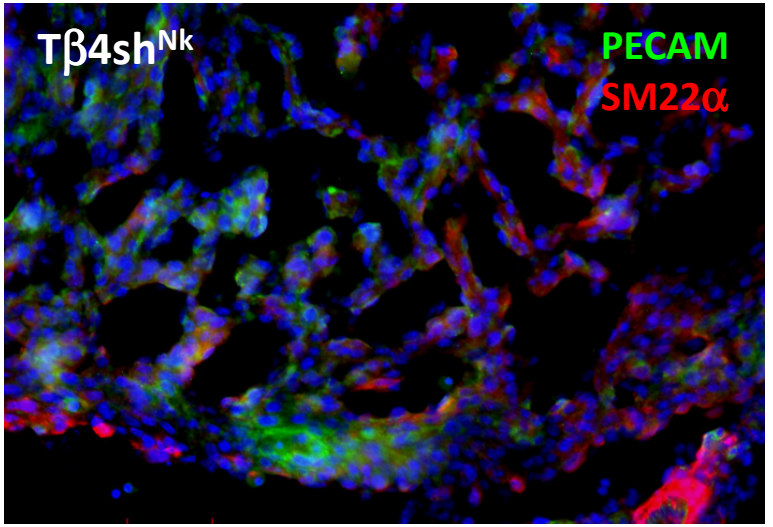
Cardiac-specific knockdown of Tβ4

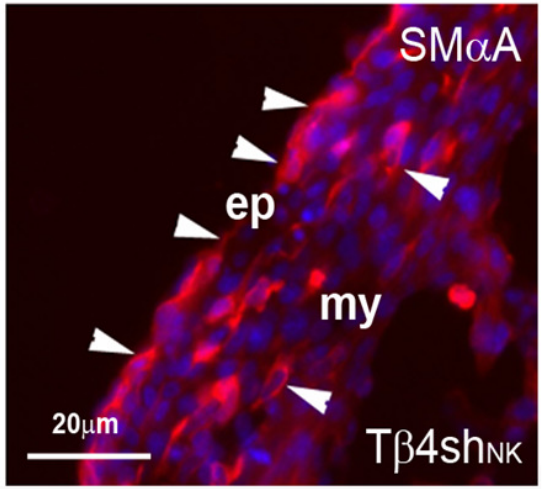


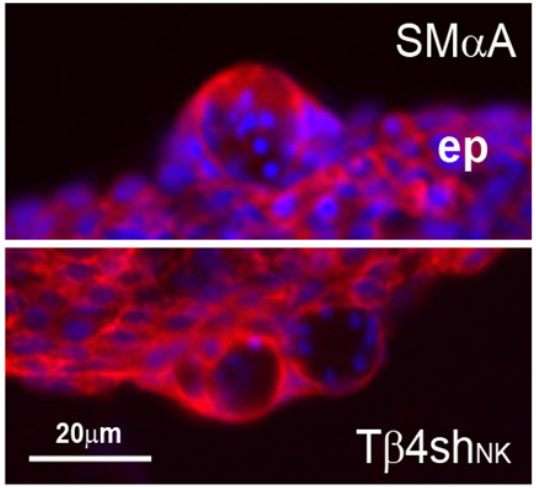
Smart et al. (2007) *Nature* 445, 177-182.

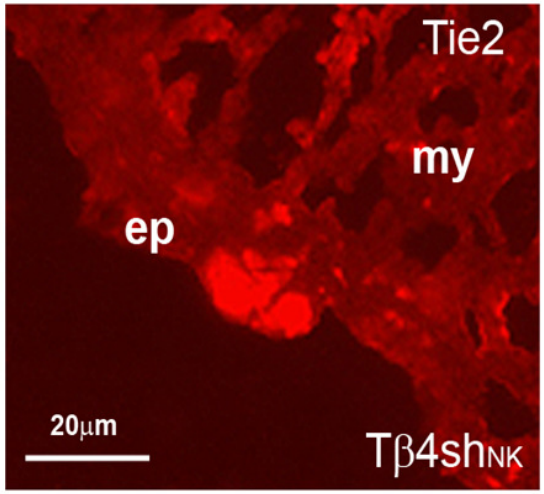
Coronary vascular precursors fail to migrate into the myocardium in Tβ4 knockdown hearts





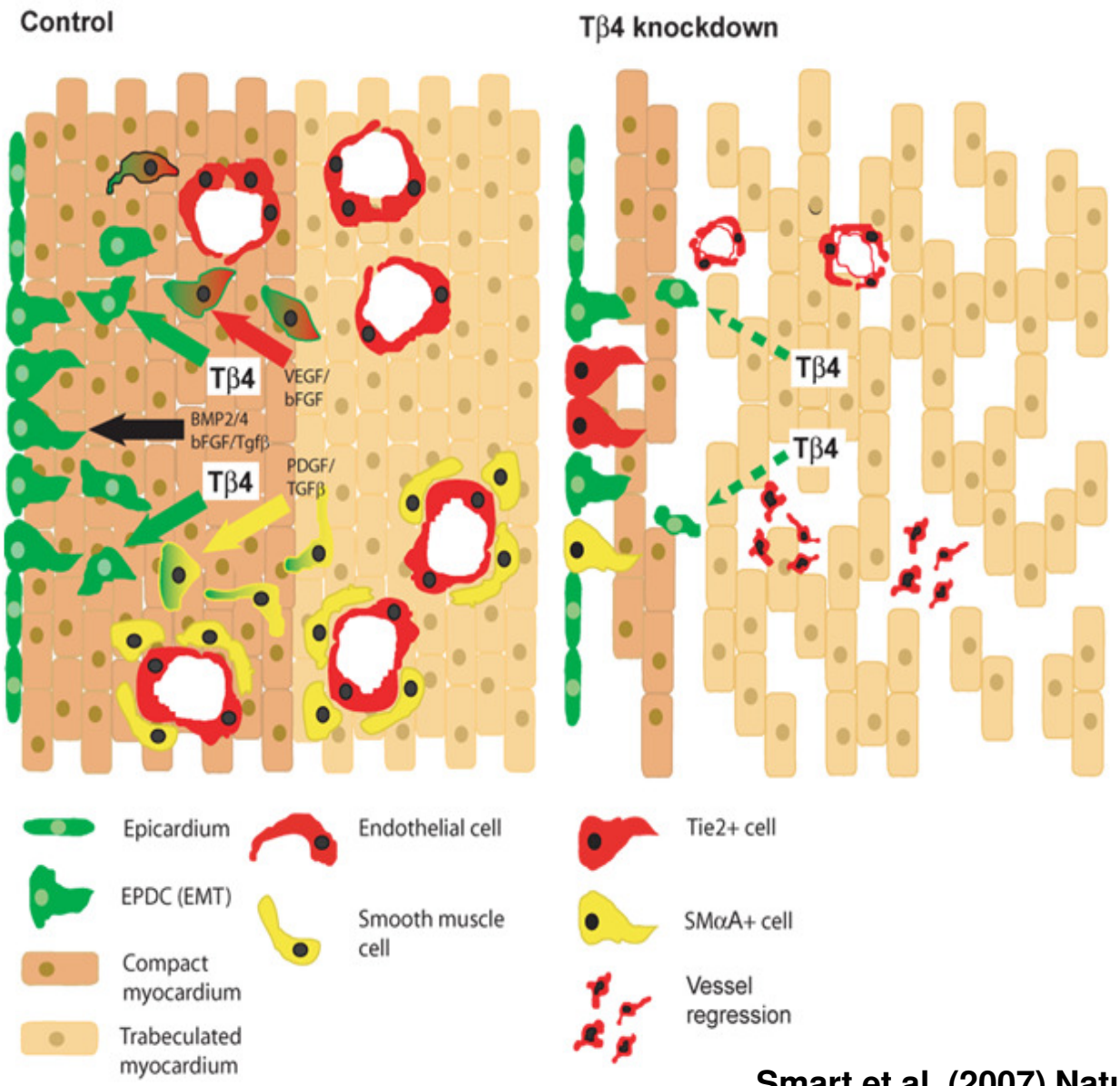






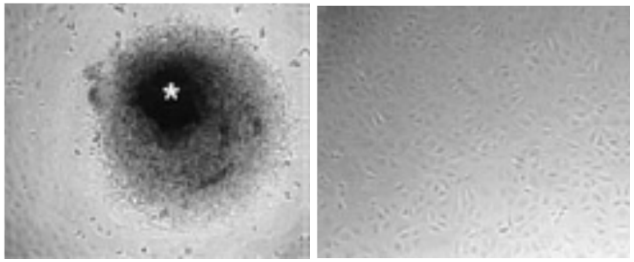
Smart et al. (2007) Nature 445, 177-182

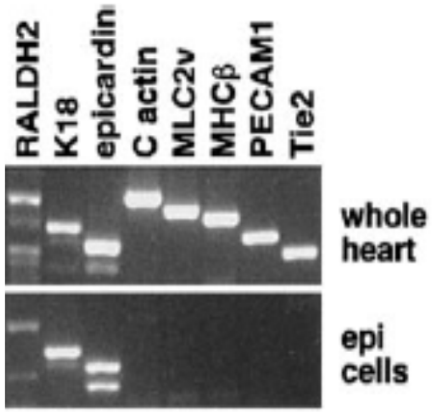
The role of Tβ4 in coronary vessel development

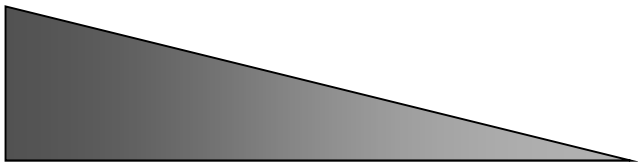


Smart et al. (2007) Nature 445, 177-182.

The Stimulation of Resident Cardiac Progenitor Cells



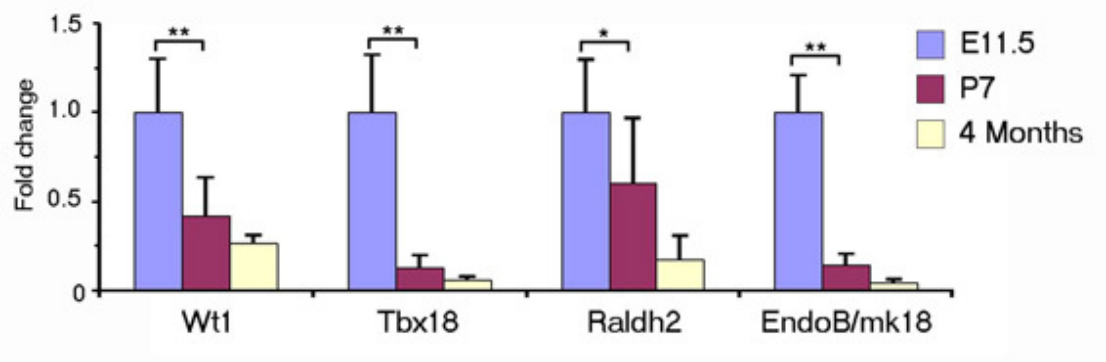


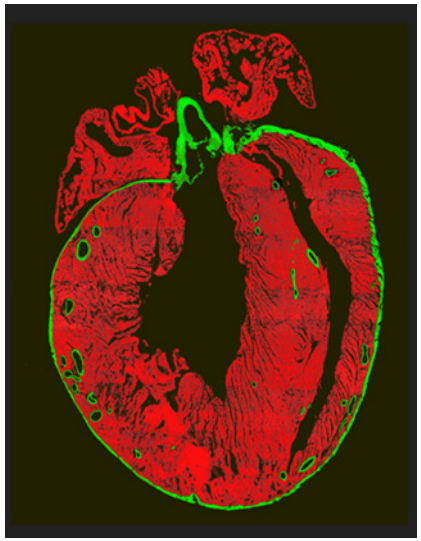


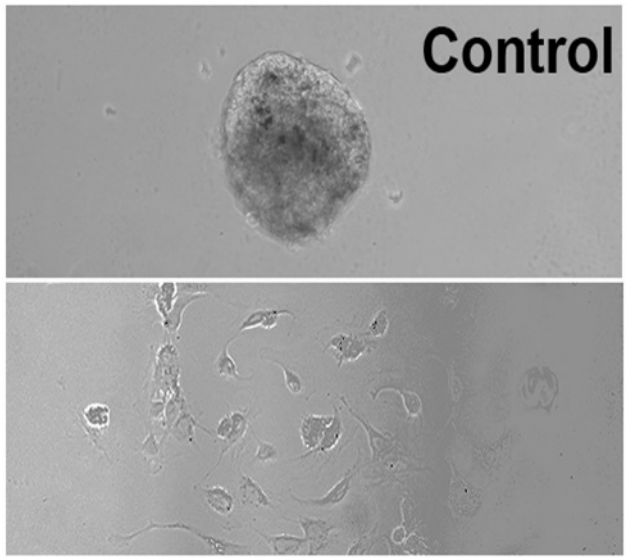
E10.5 **P4**

Outgrowth of EPDCs

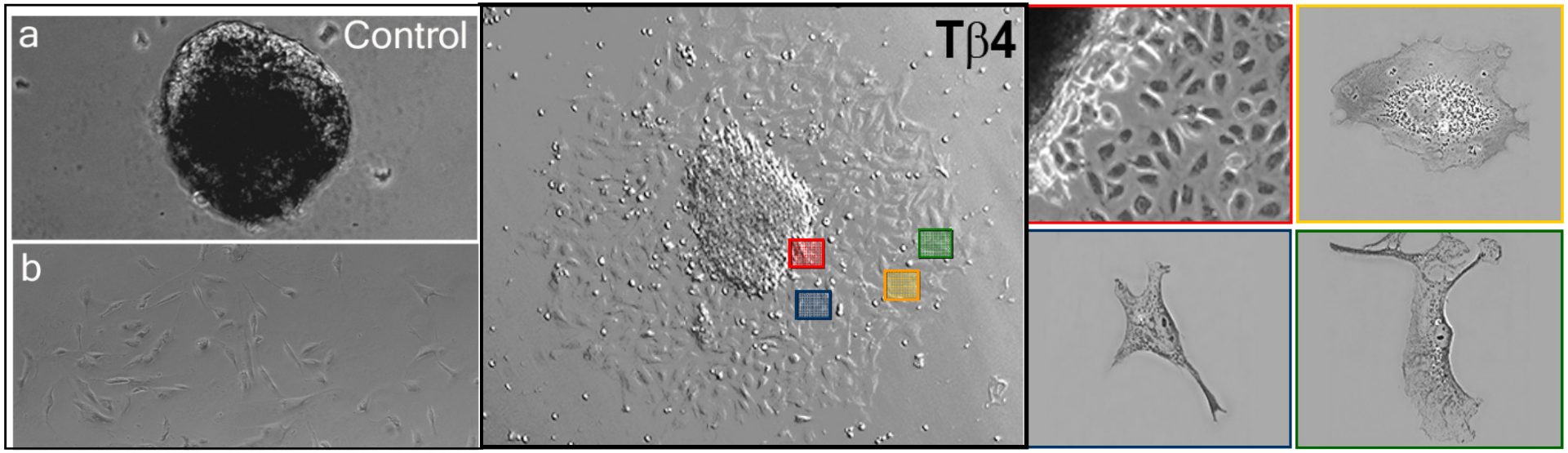
Chen et al (2002) Dev Biol. 250: 198-207.

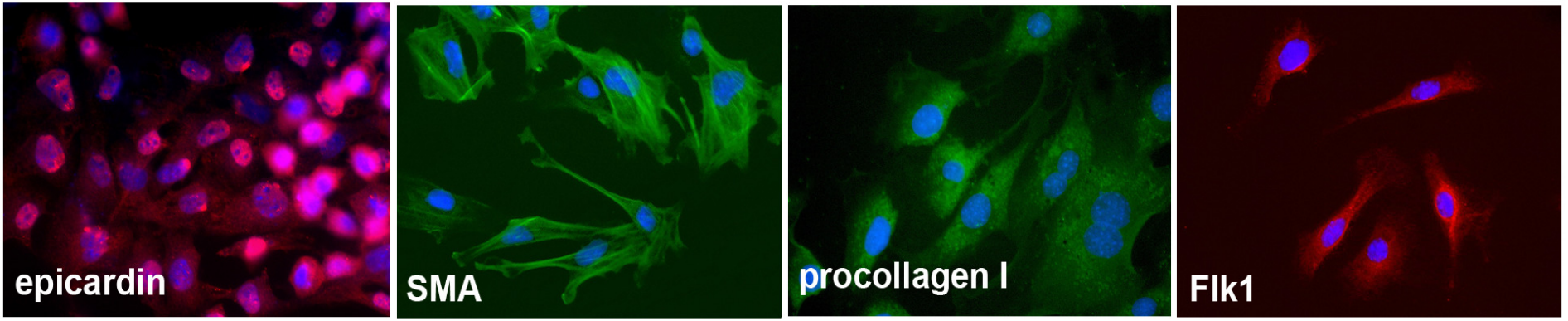






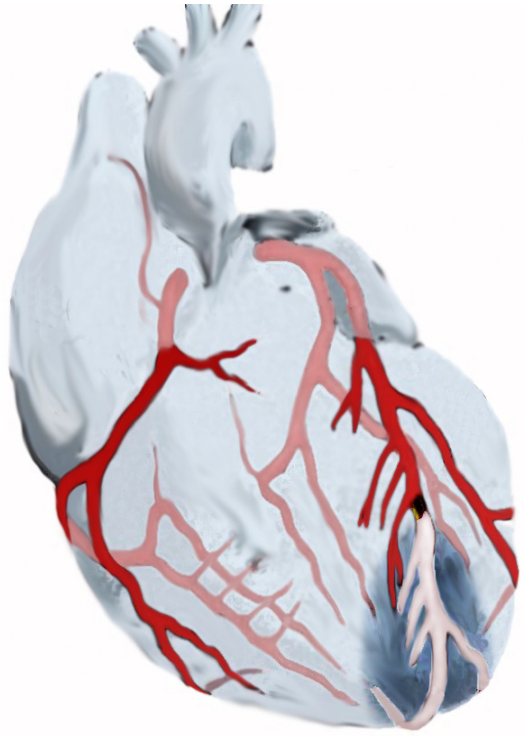
Tβ4 promotes migration of EPDCs from adult heart





Smart et al. (2007) *Nature* 445, 177-182.

Tβ4

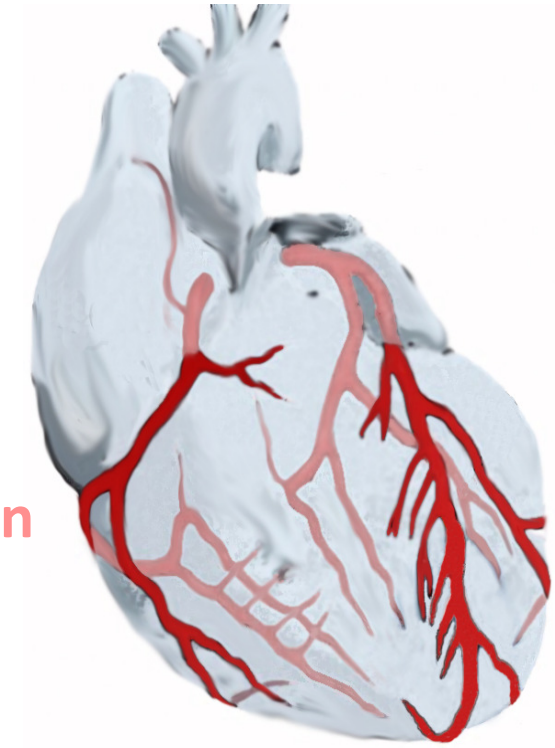


REPAIR

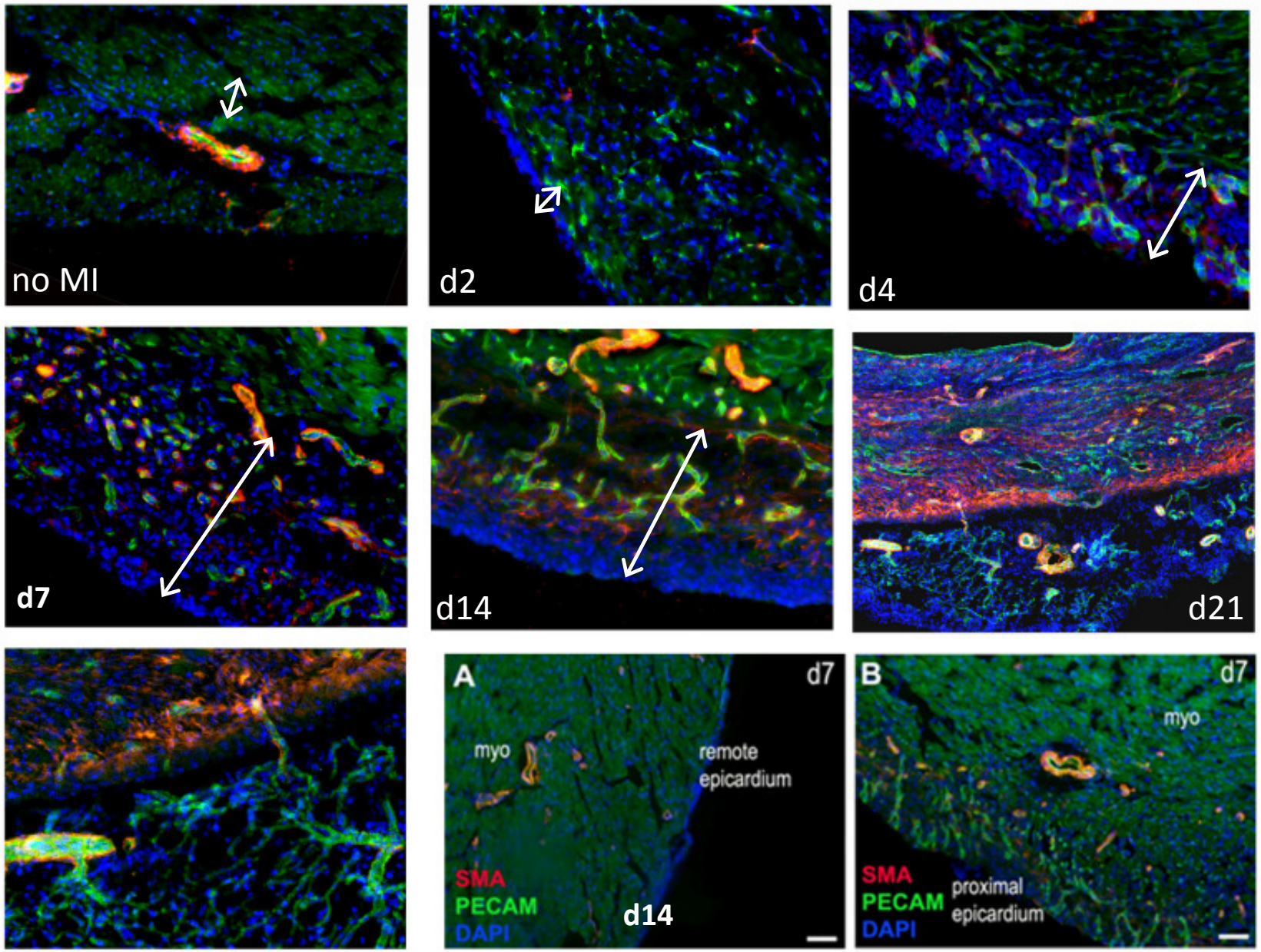
Neovascularisation

Myocardial Regeneration

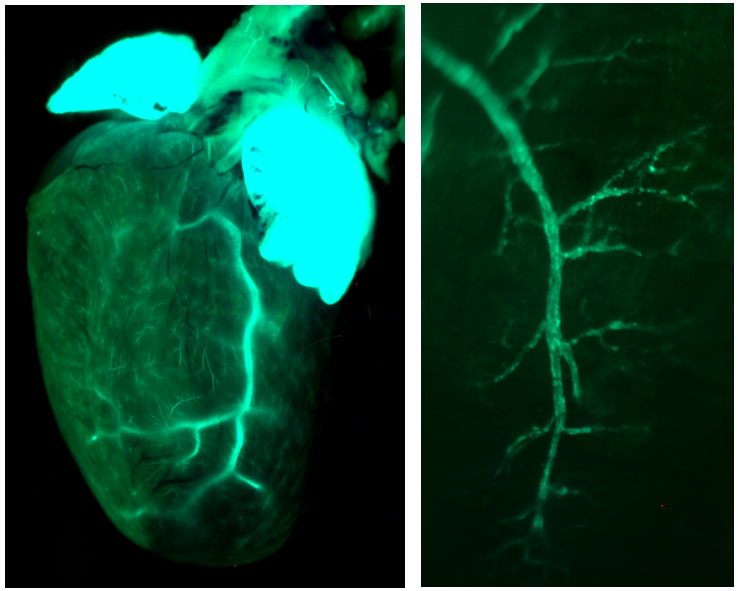
Inflammation

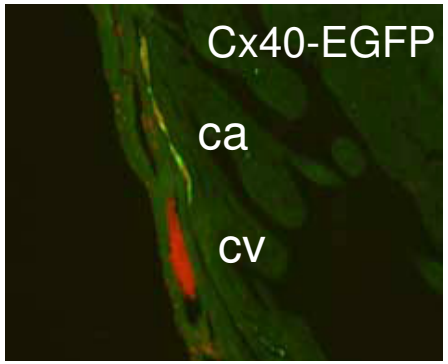


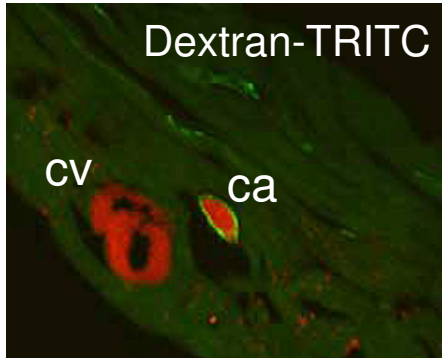
Tβ4 and the Epicardium: Neovascularisation

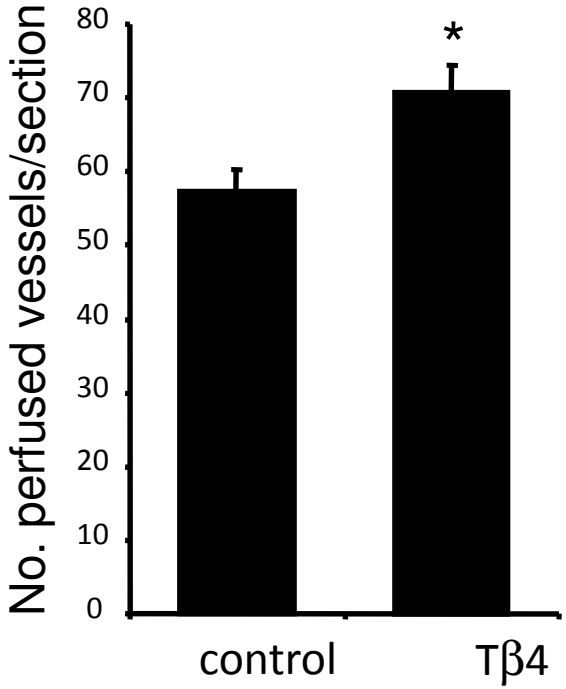


Tβ4 promotes formation of durable, perfused vessels





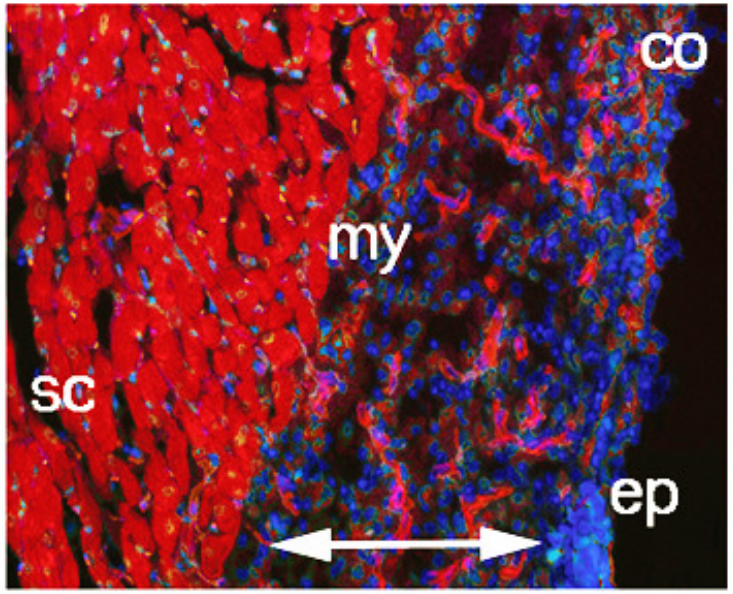


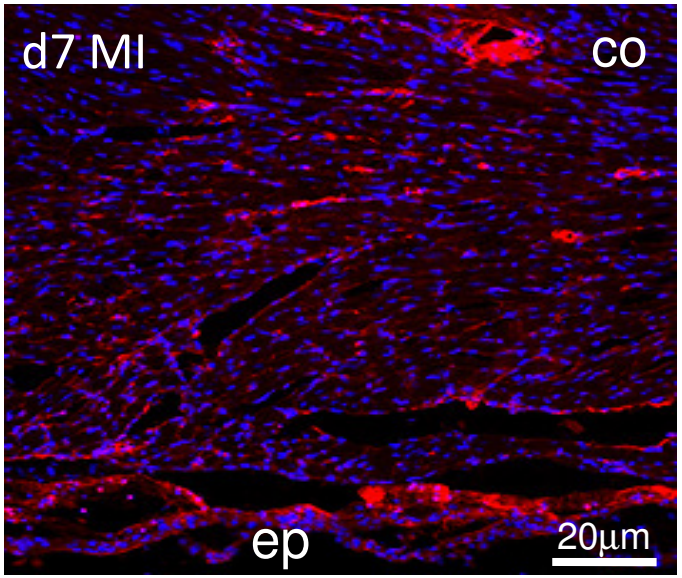


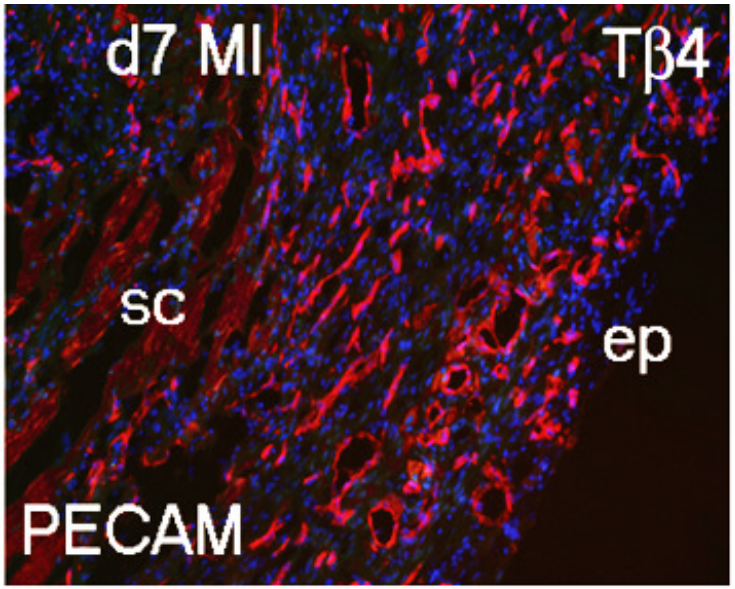
Smart et al. (2010) *Annals New York Acad Sci*, 1194:97-104

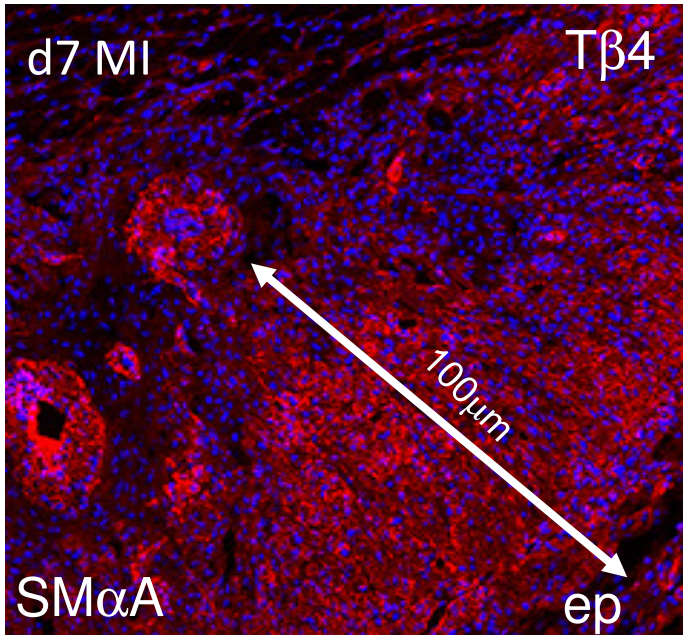
Cx40-EGFP: Miquerol et al., (2004) Cardiovascular Research 63, 77-86

Tβ4 promotes vasculogenesis and arteriogenesis in the ischaemic heart

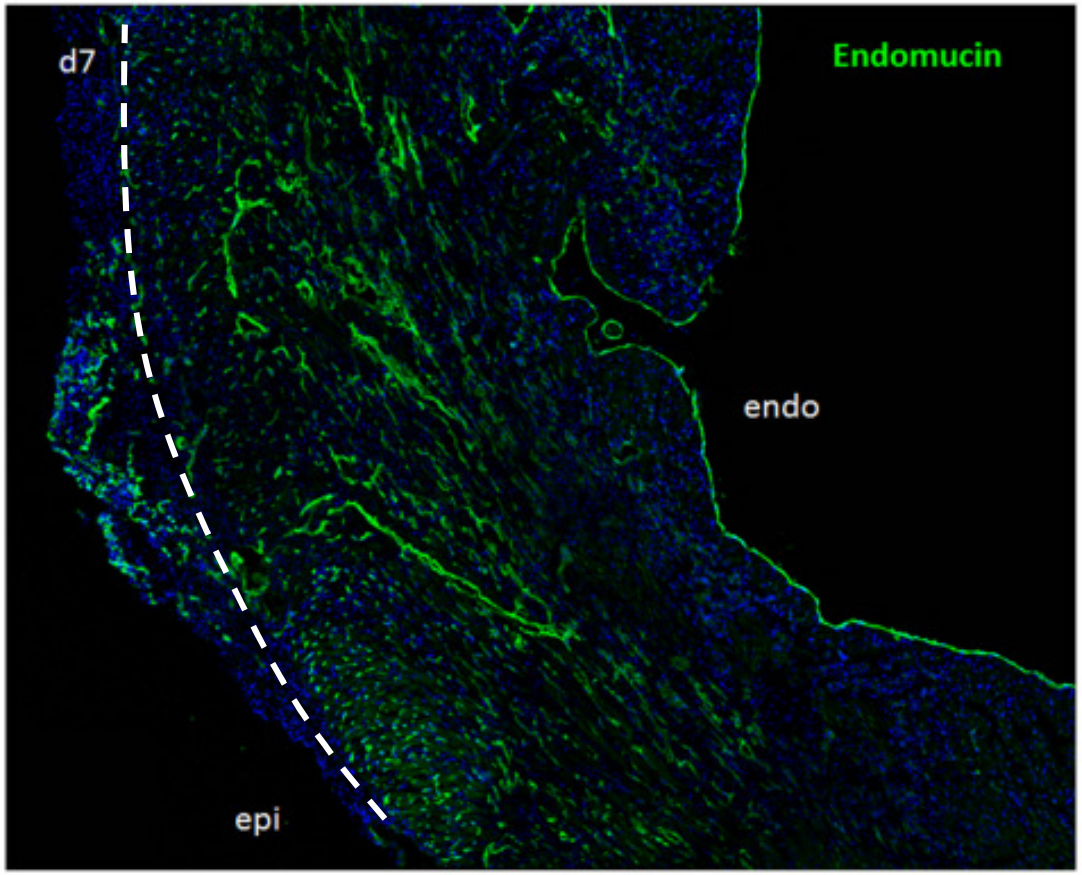


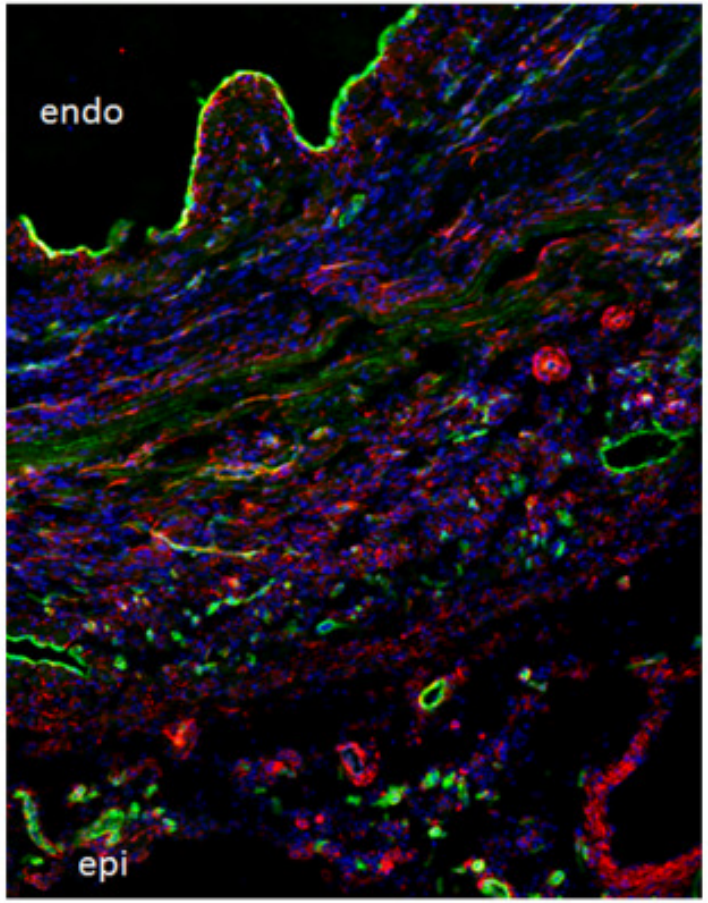






Neovascularisation of the heart post-MI

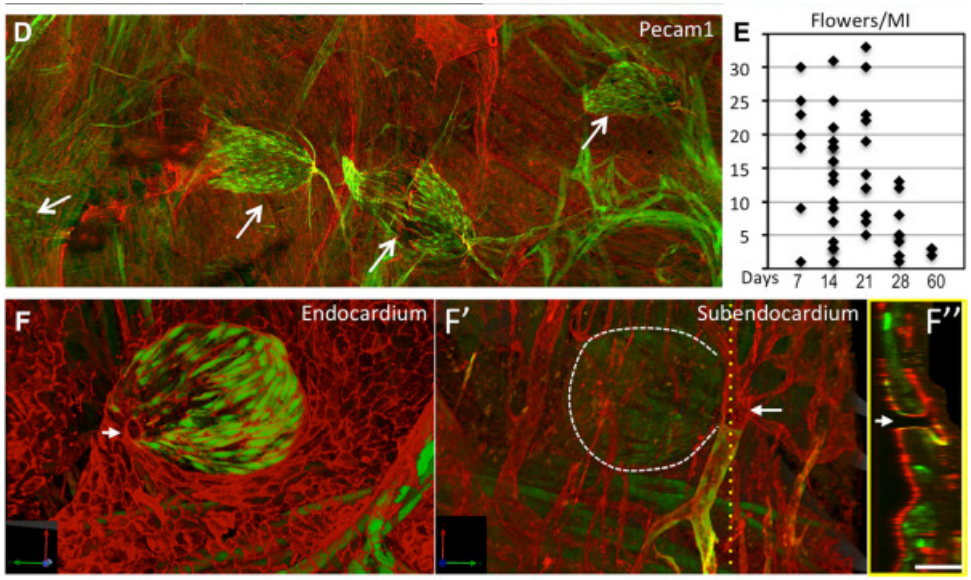


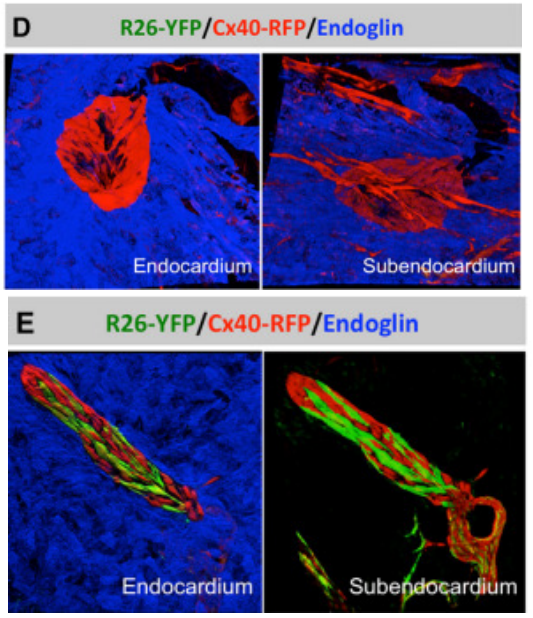


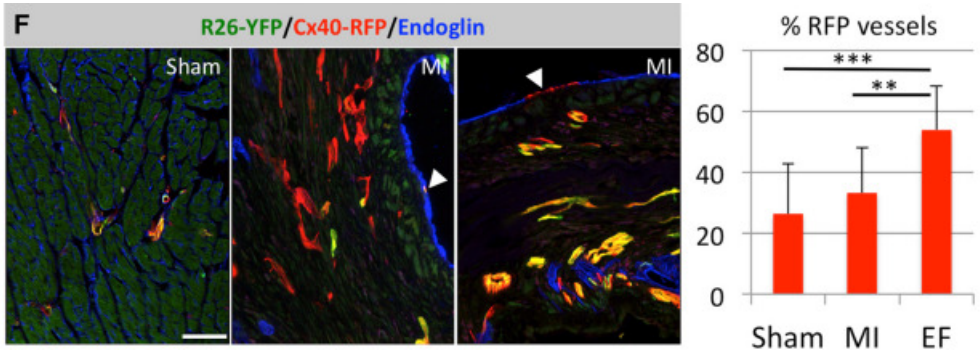
Endothelial Plasticity Drives Arterial Remodeling Within the Endocardium After Myocardial Infarction

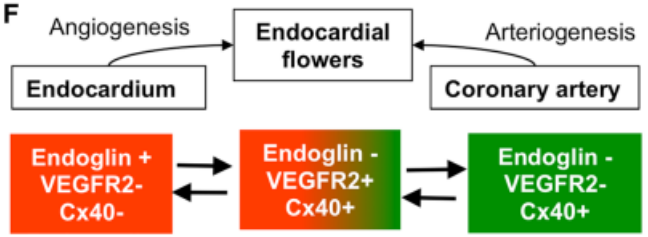
Short Communication

Lucile Miquerol, Jérome Thireau, Patrice Bideaux, Rachel Sturny, Sylvain Richard, Robert G. Kelly



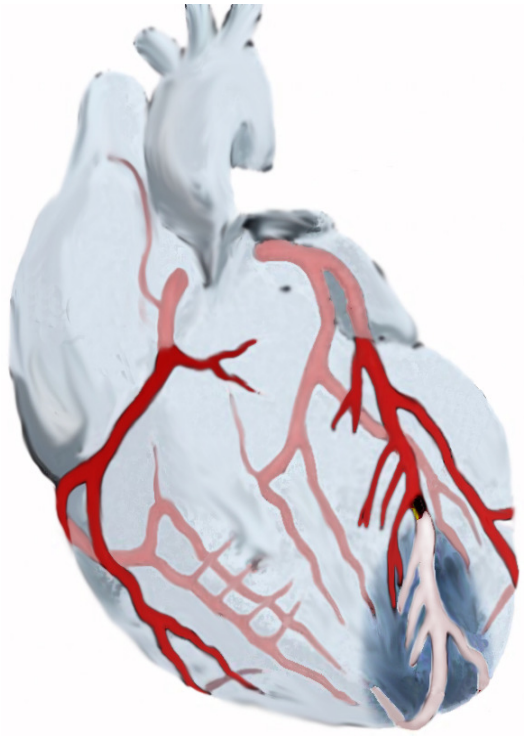






Circ Res. 2015;116:1765-1771

Tβ4

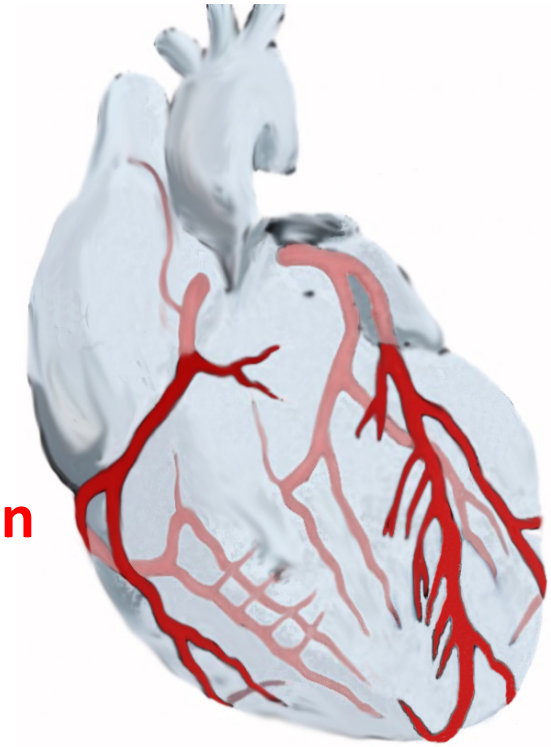


REPAIR

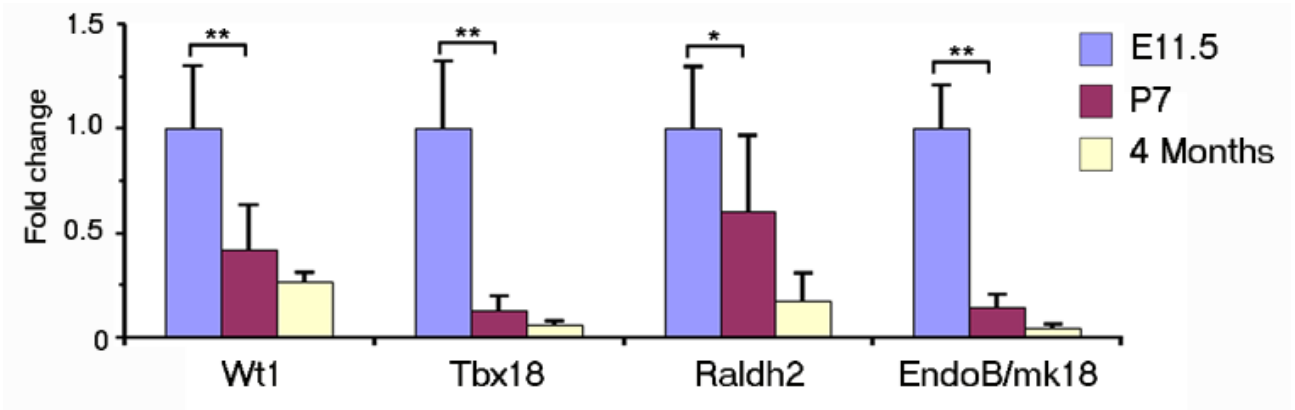
Neovascularisation

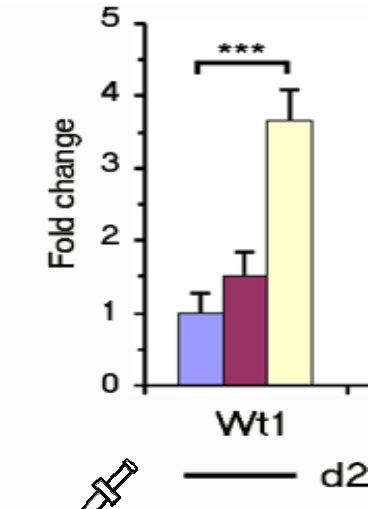
Myocardial Regeneration

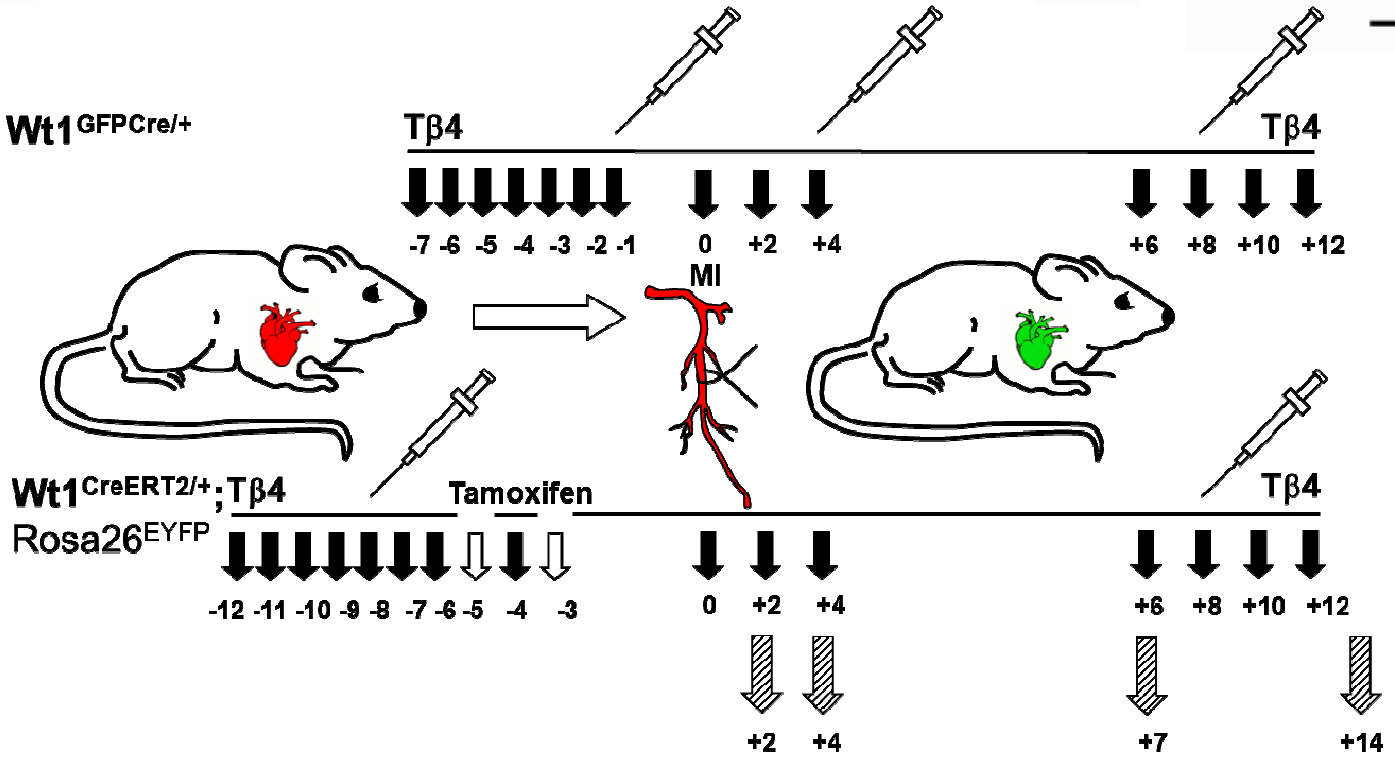
Inflammation



Reactivation of embryonic *Wt1* gene expression in the adult epicardium by Tβ4 priming and injury

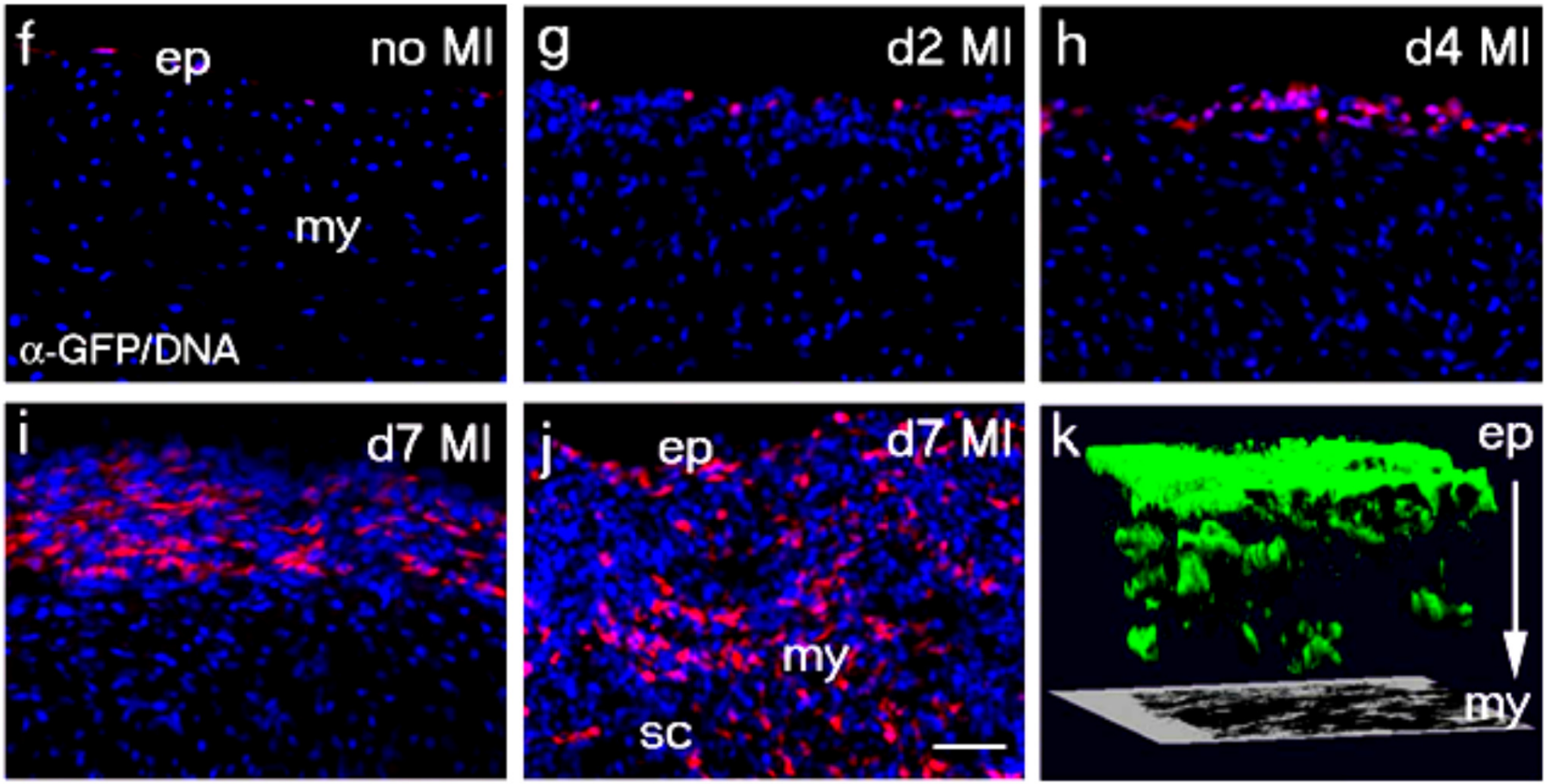




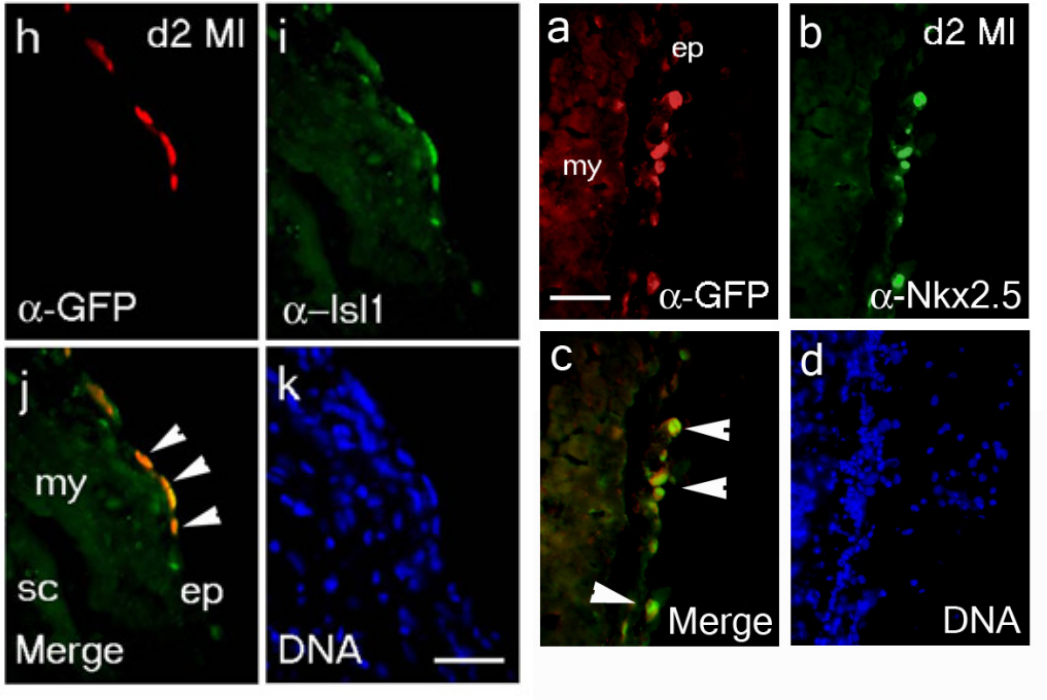


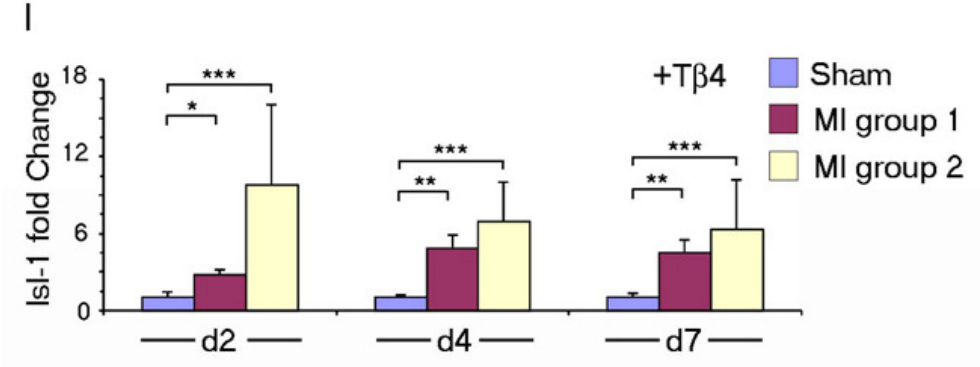
Smart et al (2011). *Nature* 474, 640-644

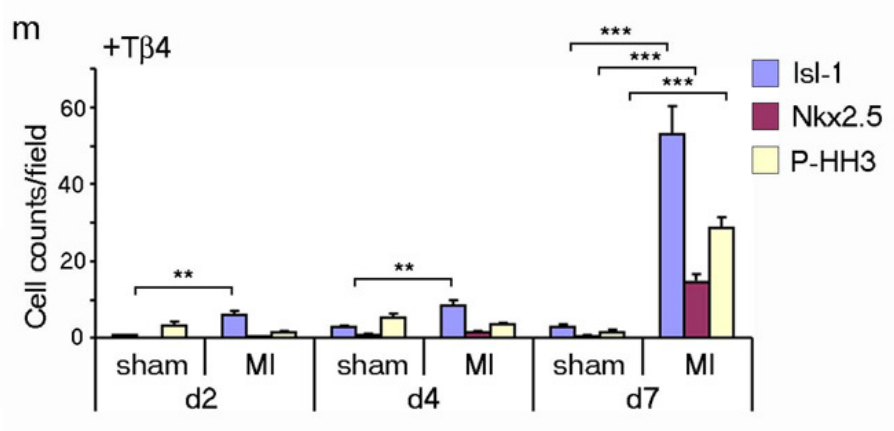
Expansion of GFP+ and YFP+ cells within the epicardium and sub-epicardial regions following Tβ4 priming/injury



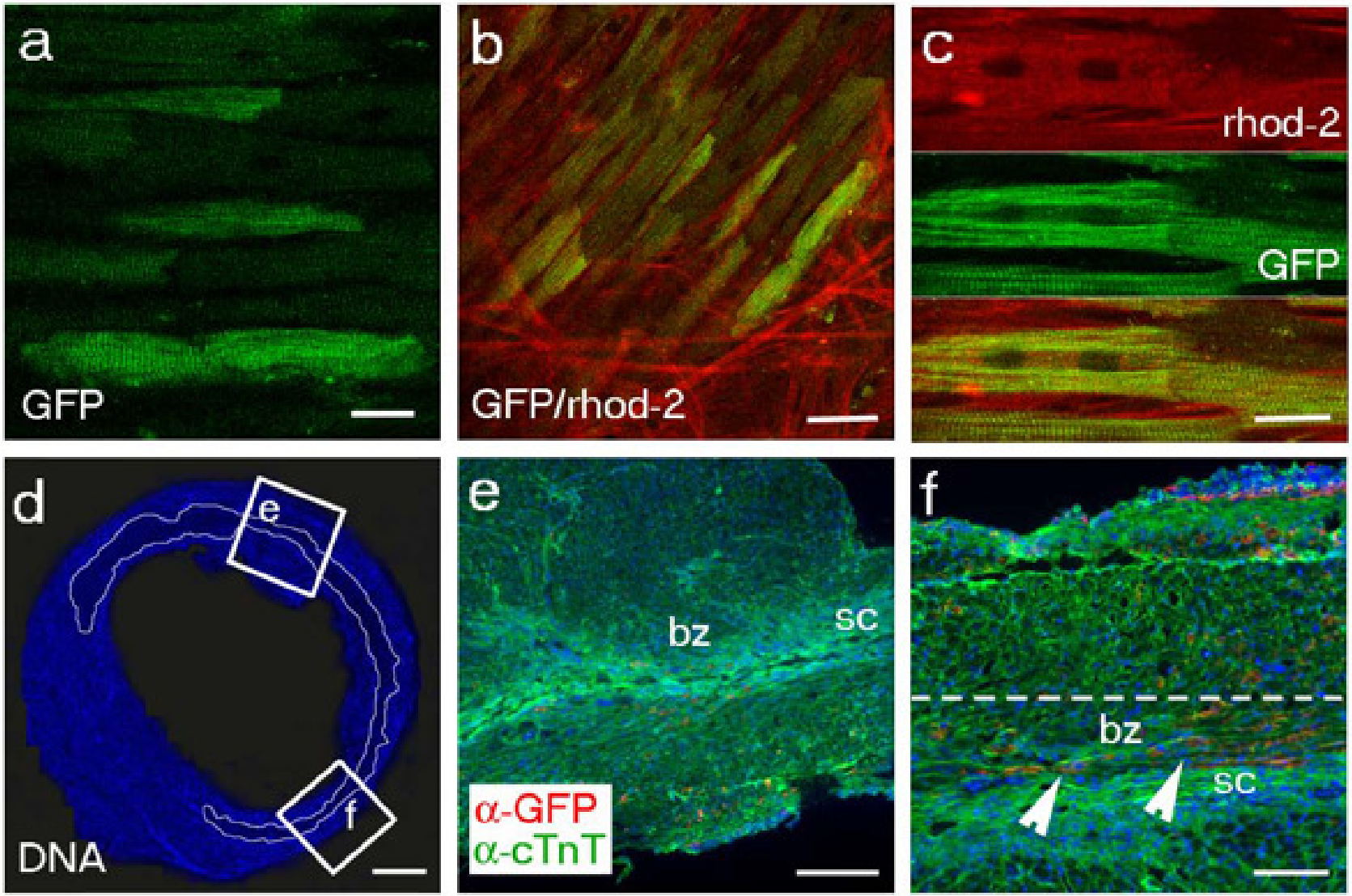
Activated Wt1+ EPDCs give rise to cardiac progenitors in the injured adult heart





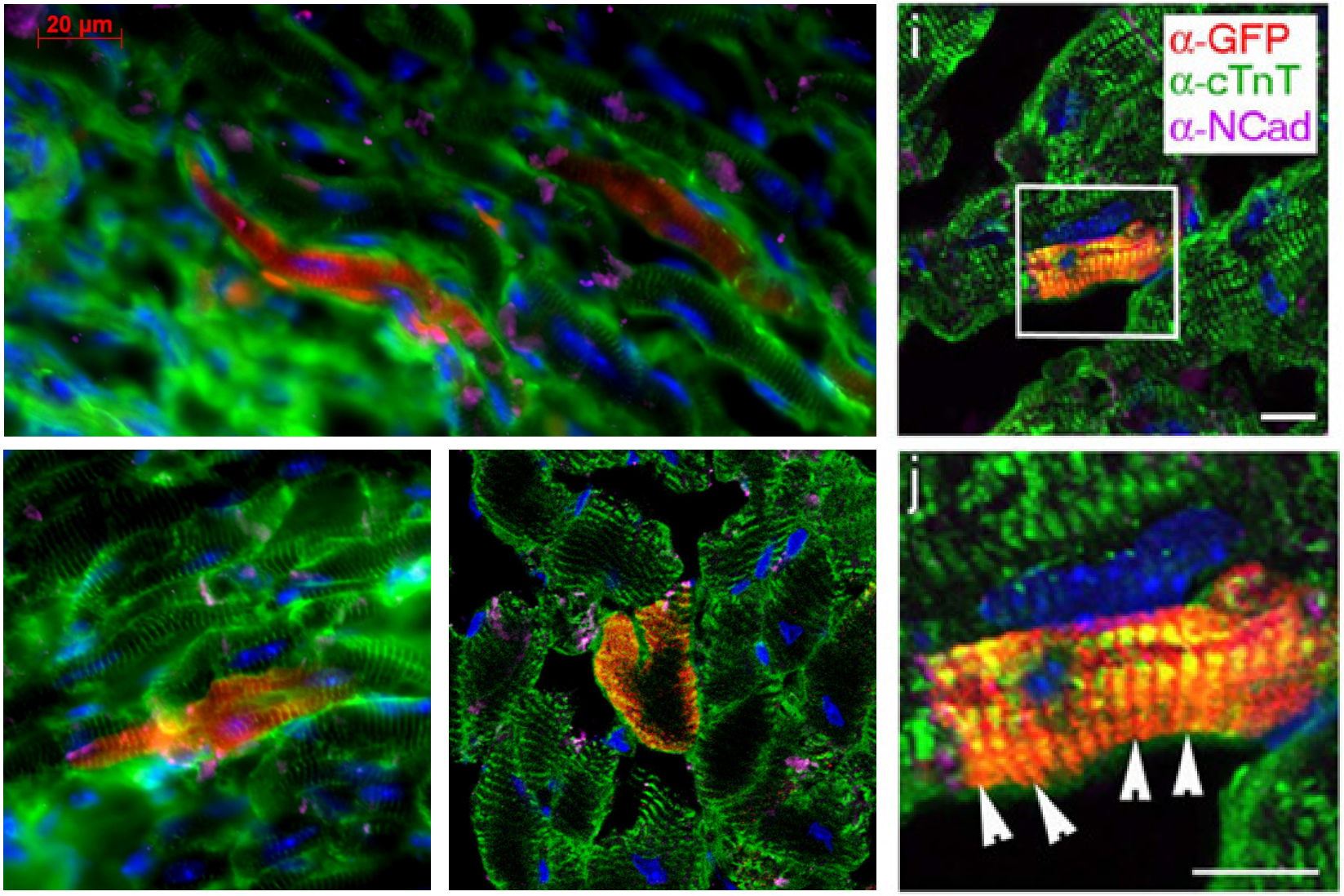


Activated adult Wt1+ EPDCs differentiate into cardiomyocytes



day 14 post-MI

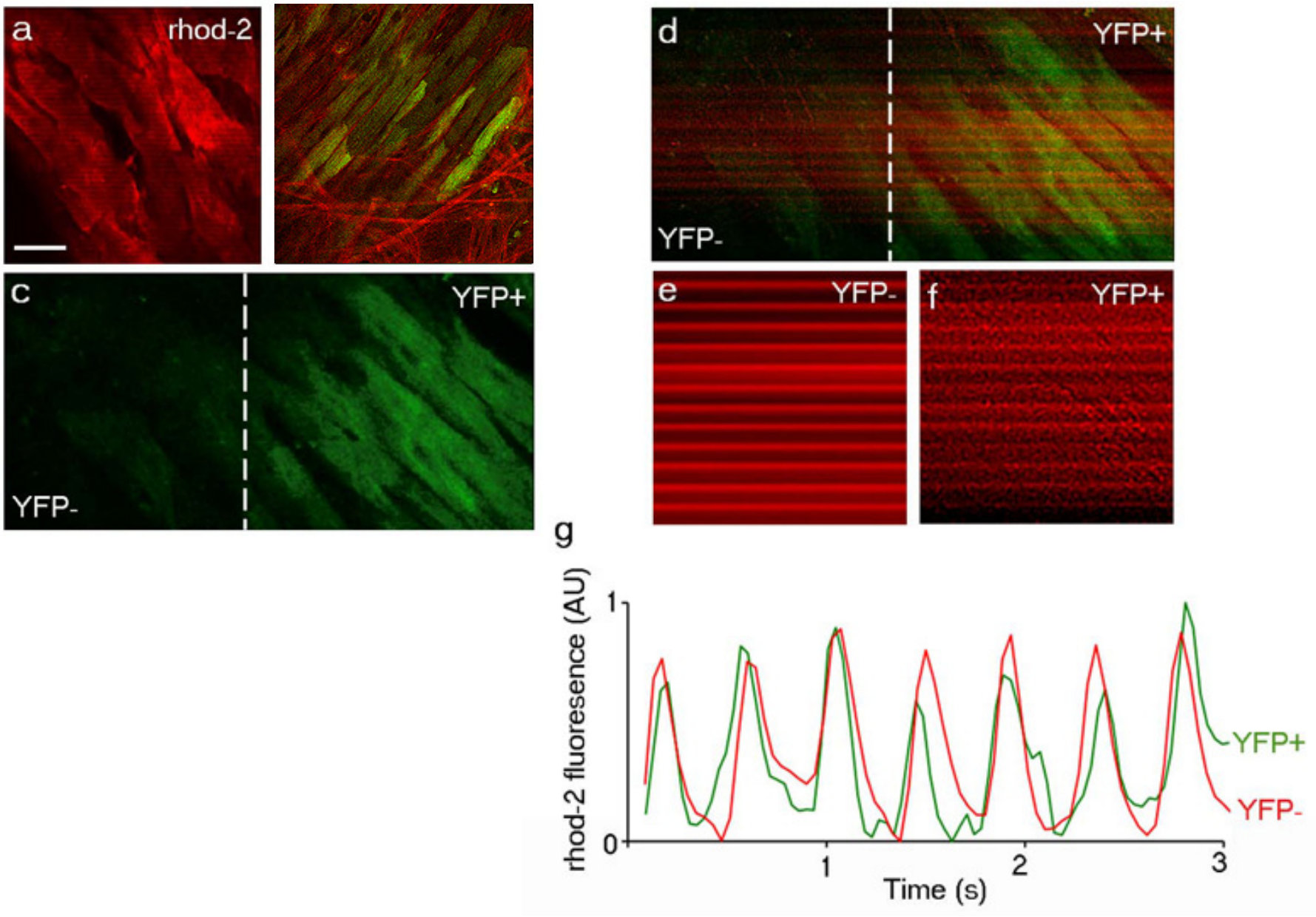
Activated adult EPDCs contribute *de novo* cardiomyocytes to the ischaemic heart



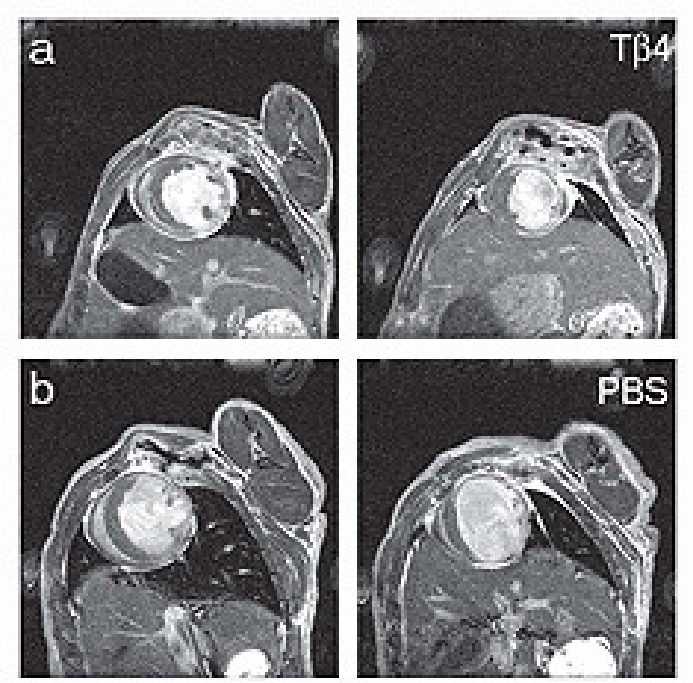
Day 14 post-MI

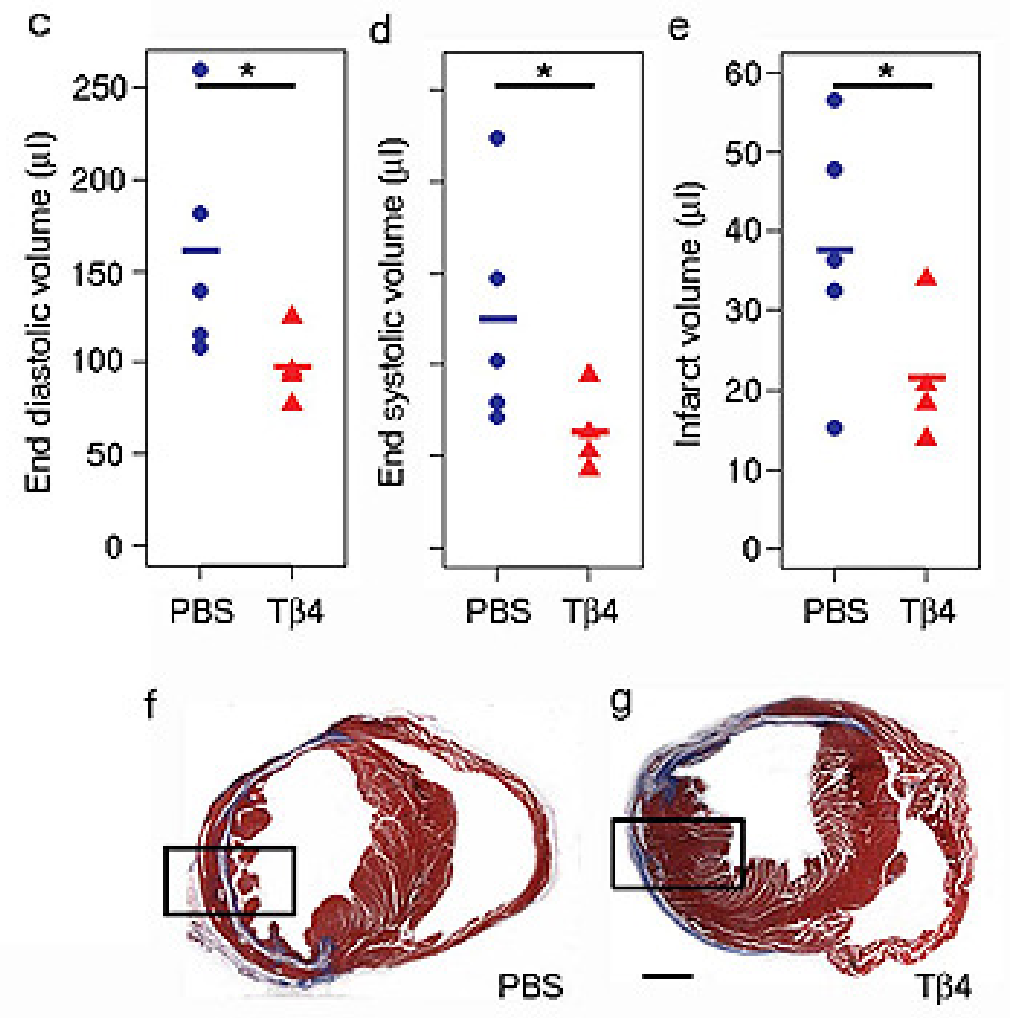
Smart et al (2011) *Nature* 474(7353):640-4

Wt1+ EPDC-derived cardiomyocytes are functional



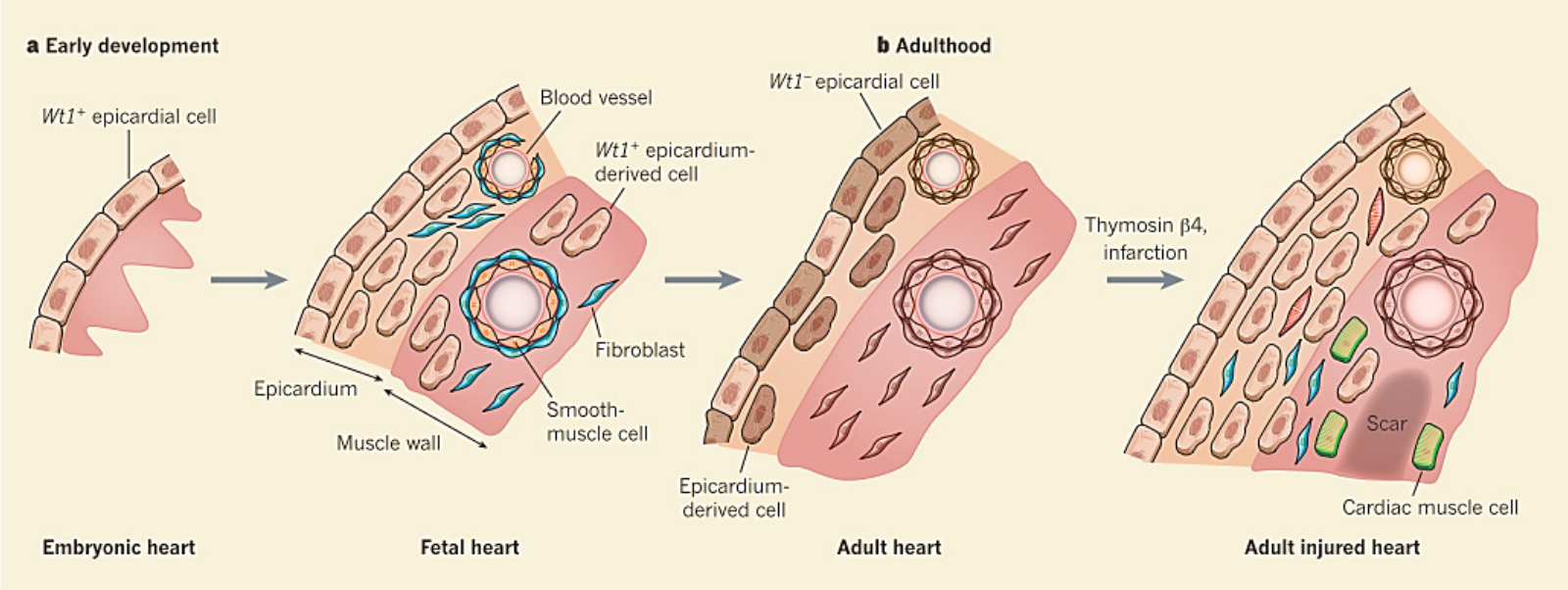
EPDC-derived cardiomyocytes and neovascularisation contribute to Improved cardiac function and reduced scarring



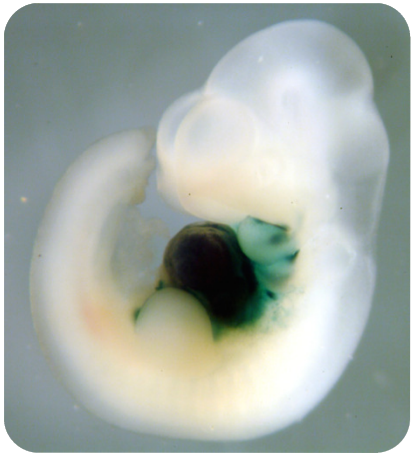


Smart et al (2011) *Nature* 474(7353):640-4

Recapitulating Heart Development in the Adult with Thymosin β4

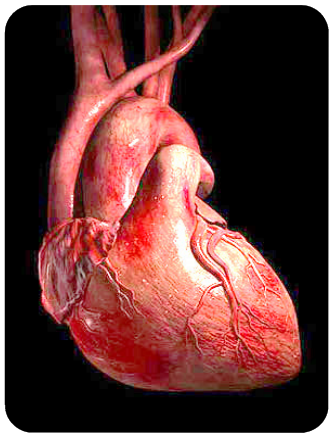


Christoffels (2011) *Nature* 474: 585-586



how to make a heart ?

how to repair a heart ?



Acknowledgements

Physiology, Anatomy & Genetics

Paul Riley

Sonali Munshaw
Joanna Klaptocz
Sophie McManus

UCL-Institute of Child Health
Karina Dubé
Alex Rossdeutsch
Sveva Bollini
Joaquim Vieira

BHF Ian Fleming Senior Basic Science Research Fellowship

John Fell Oxford University Press Research Fund

Collaborators

Sean Davidson
Derek Yellon
Johannes Riegler
Anthony Price
Mark Lythgoe
UCL

James Clark
Mike Marber
Elisabeth Ehler
King's College London

Martin Turner
The Babraham Institute

Bin Zhou
Bill Pu
Children's Hospital Boston

Pilar Ruiz-Lozano
Institute of Molecular Medicine, UCSD

Lucile Miquerol
Developmental Biology Institute of Marseilles

Robert J. Schwartz
Texas A&M Health Science Centre