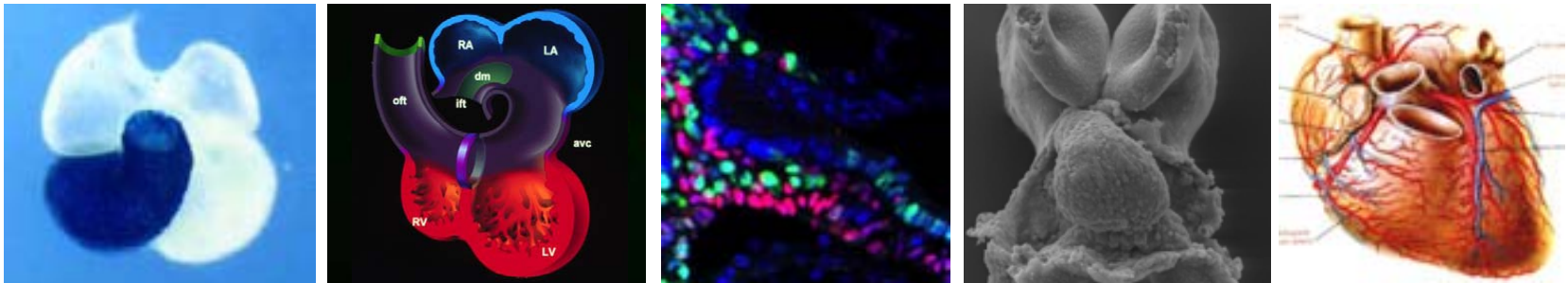


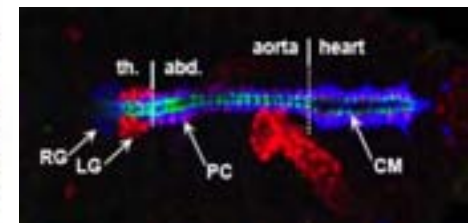
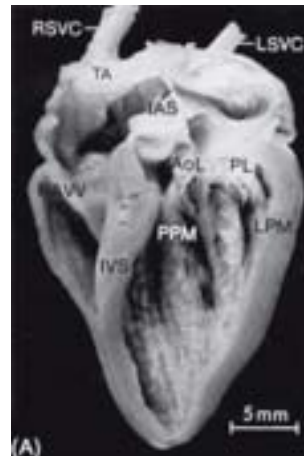
Heart Development



- Origins of congenital heart defects
- Properties of cardiac progenitor cells

Robert G. Kelly

Animal models of heart development



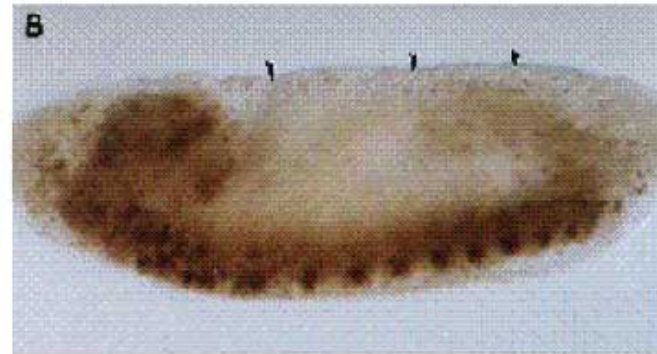
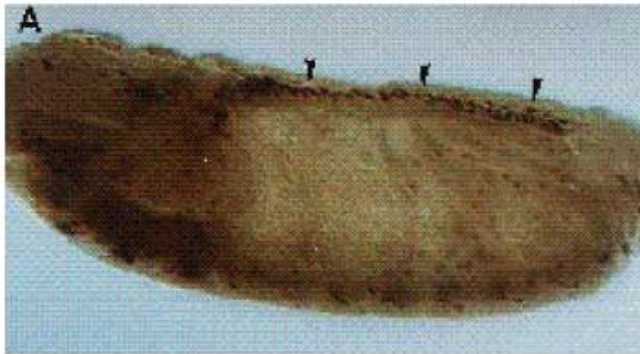


Development 118, 719-729 (1993)

Printed in Great Britain © The Company of Biologists Limited 1993

The gene *tinman* is required for specification of the heart and visceral muscles in *Drosophila*

Rolf Bodmer



Tinman/Nkx2.5 expression in different species



In situ hybridisation

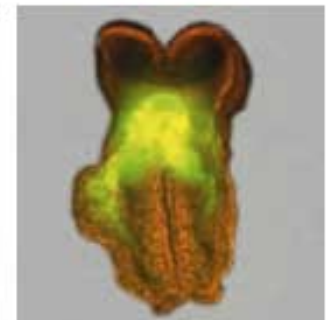
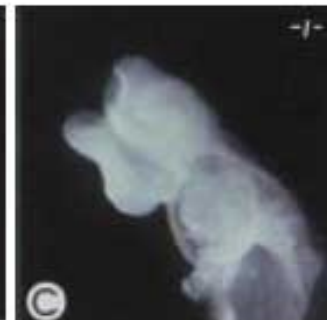
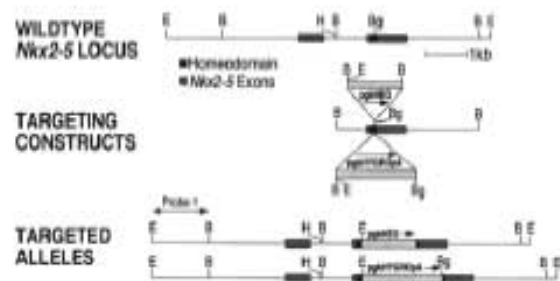
Harvey 1996
Dev Biol 178:203-16



Myogenic and morphogenetic defects in the heart tubes of murine embryos lacking the homeo box gene Nkx2-5.

I Lyons, L M Parsons, L Hartley, et al.

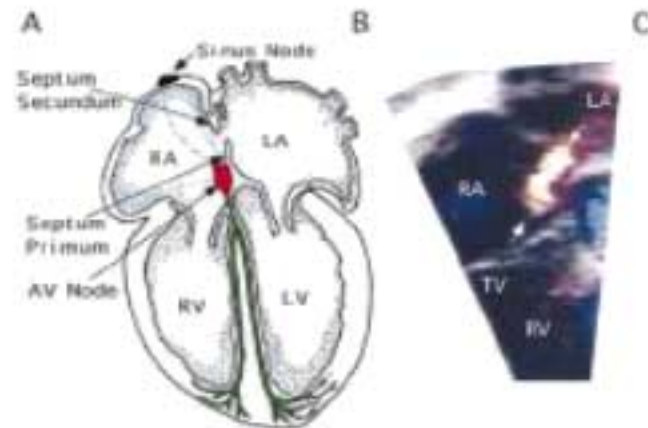
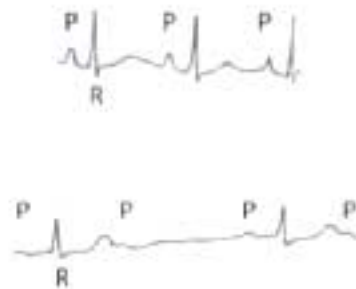
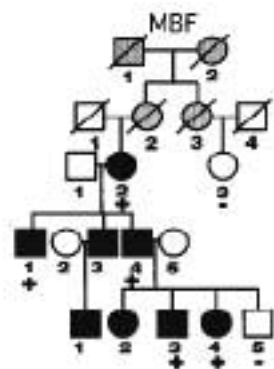
Genes Dev. 1995 9: 1654-1666



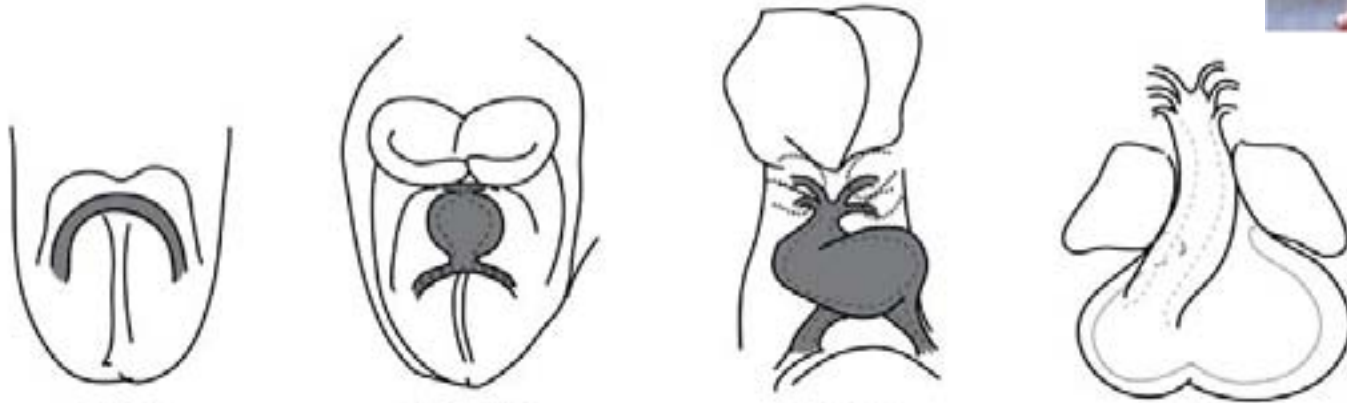


Congenital Heart Disease Caused by Mutations in the Transcription Factor NKX2-5

Jean-Jacques Schott, *et al.*
Science **281**, 108 (1998)

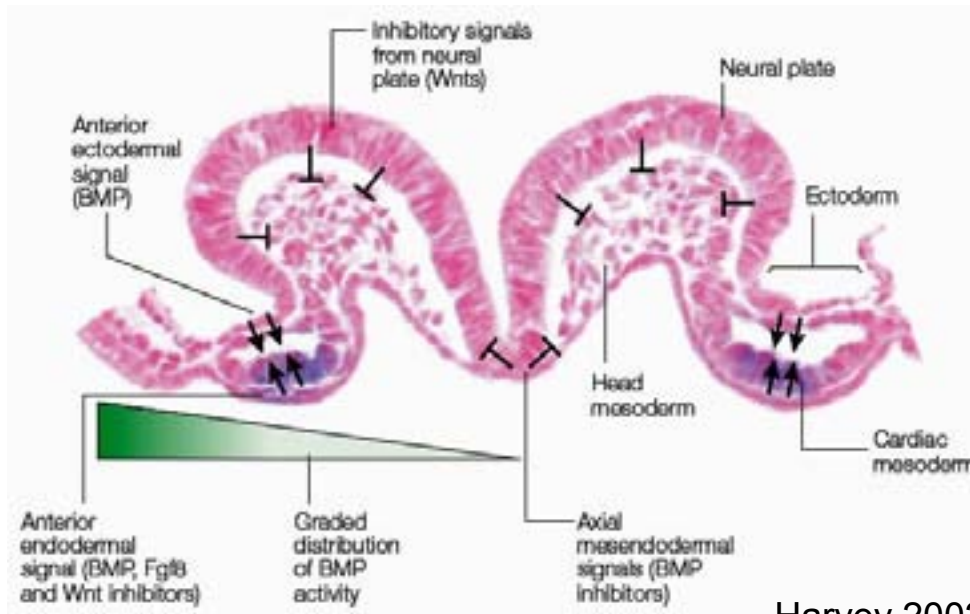
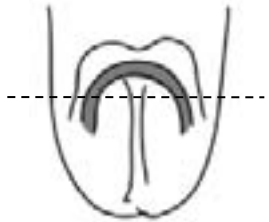


Heart Development



- From the cardiac crescent to the embryonic heart
- Second heart field cardiac progenitor cells
- Cardiac septation and chamber morphogenesis
- Conduction system and epicardial development

Specifying cardiac fate in the early embryo



Harvey 2002
Nat Rev Genet 3:544-56

Inductive signals



Baf60c-**Gata4**
Tbx5



Mef2c, Nkx2.5, Hand, Isl1



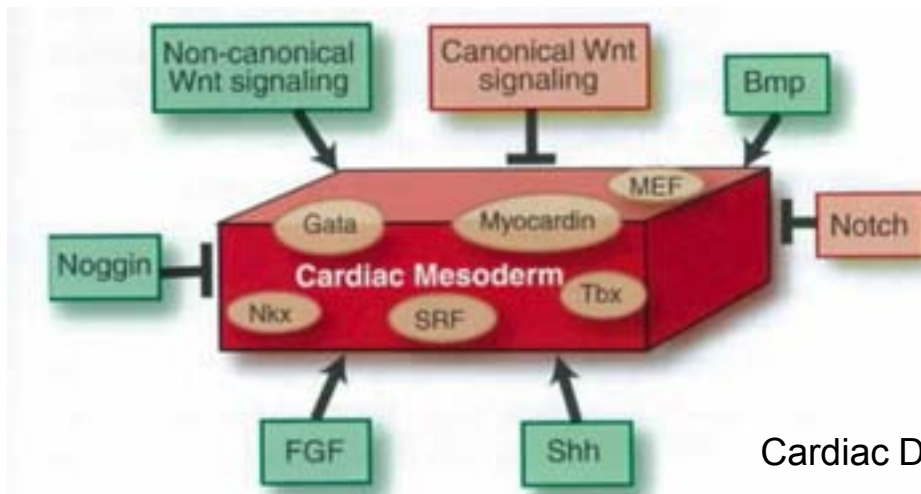
Muscle gene activation



Beating heart muscle

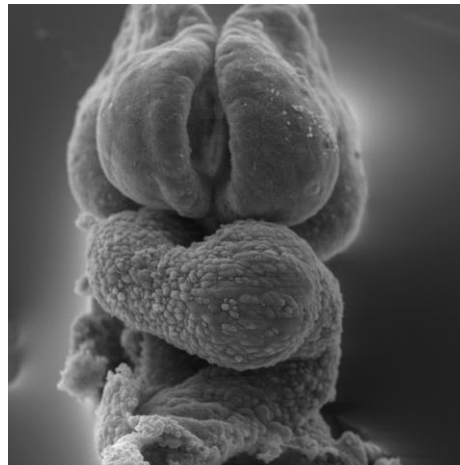
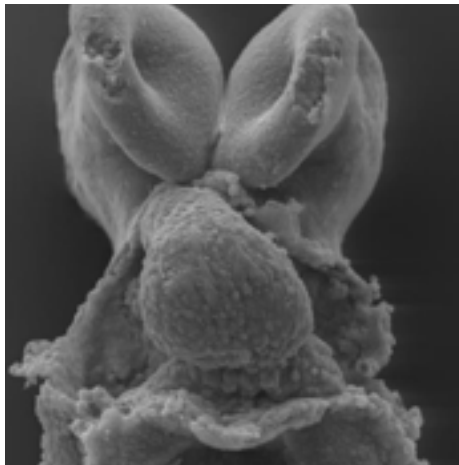
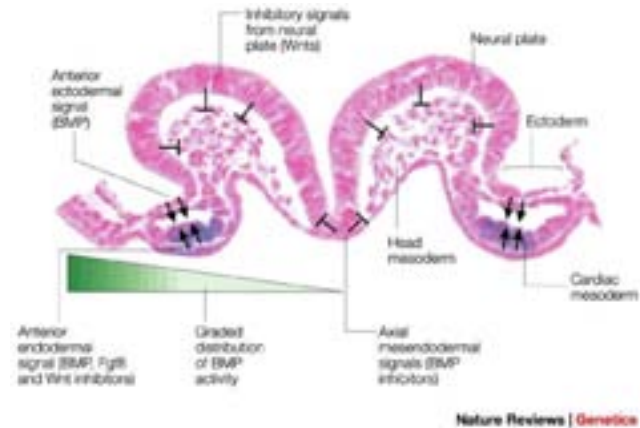
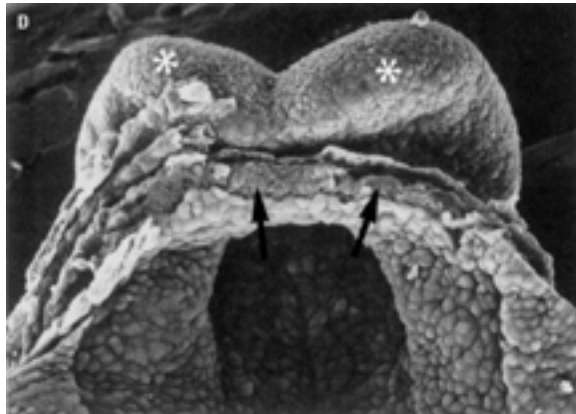
Takeuchi and Bruneau 2009
Nature 459:708-11

Ieda et al 2010
Cell 142:375-86

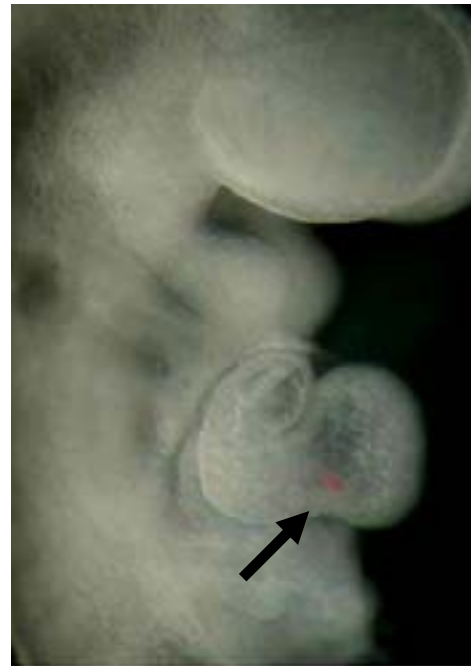


Kirby 2007
Cardiac Development

From the cardiac crescent to the embryonic heart

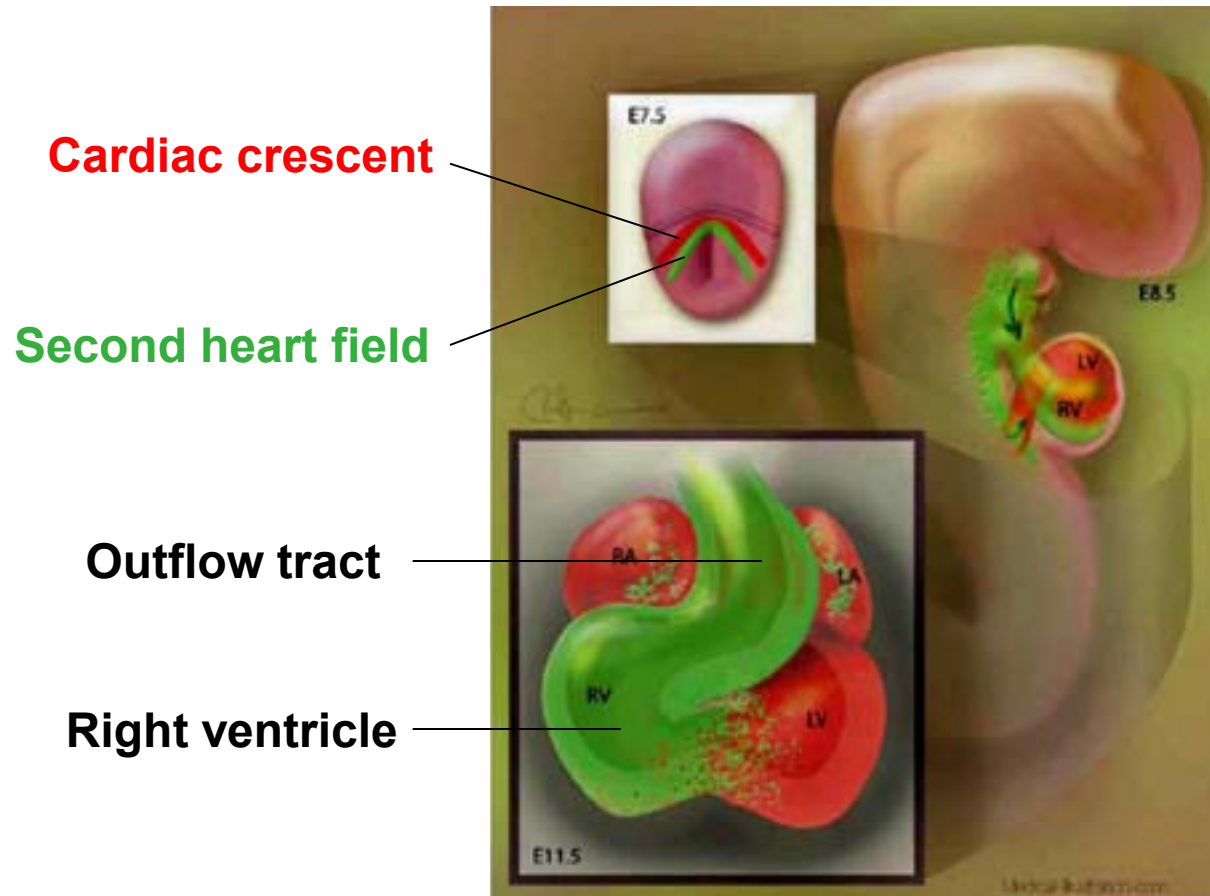


The right ventricle and outflow tract are added progressively to the elongating heart tube



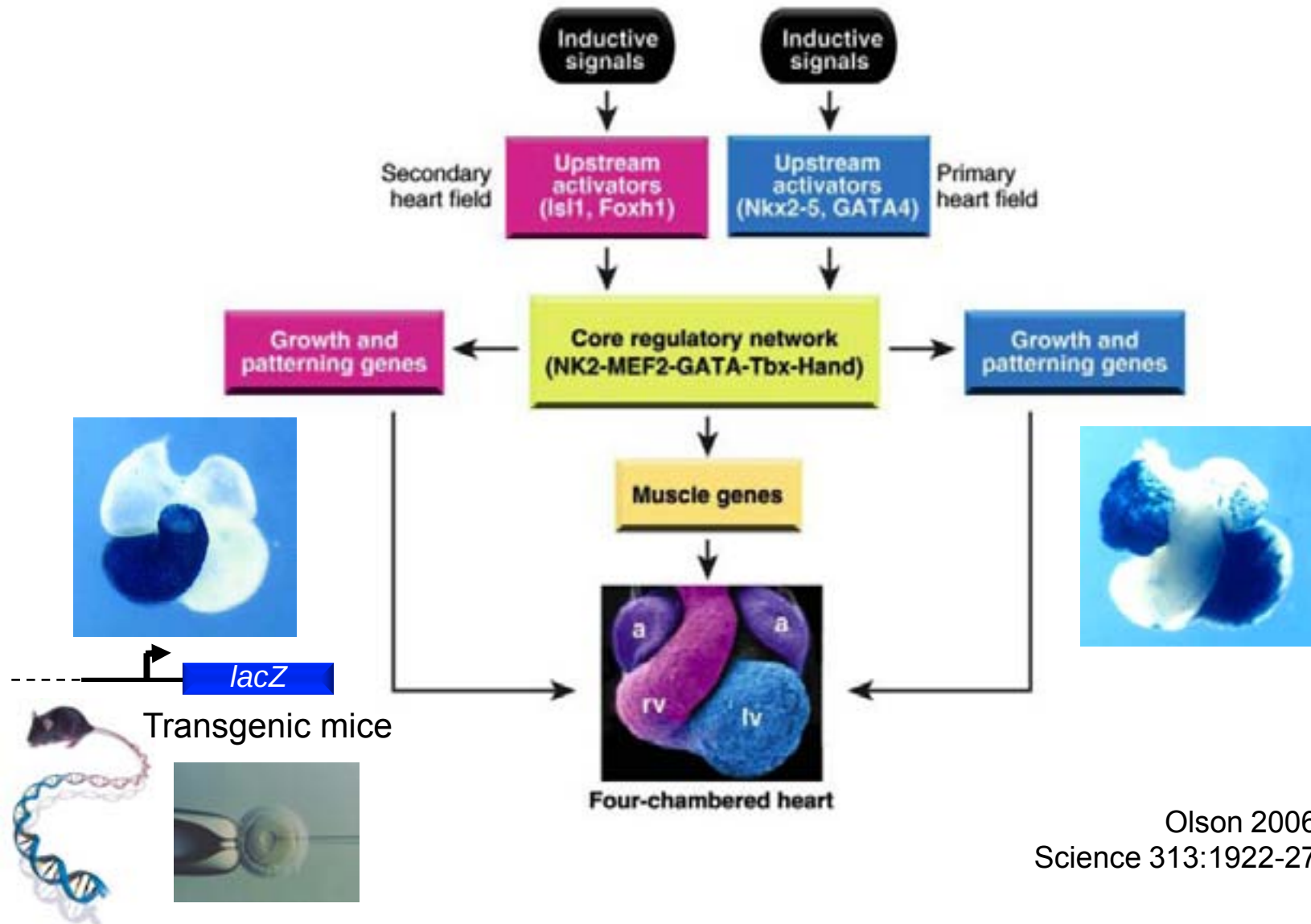
Dil labeling, 24hr embryo culture

The second heart field



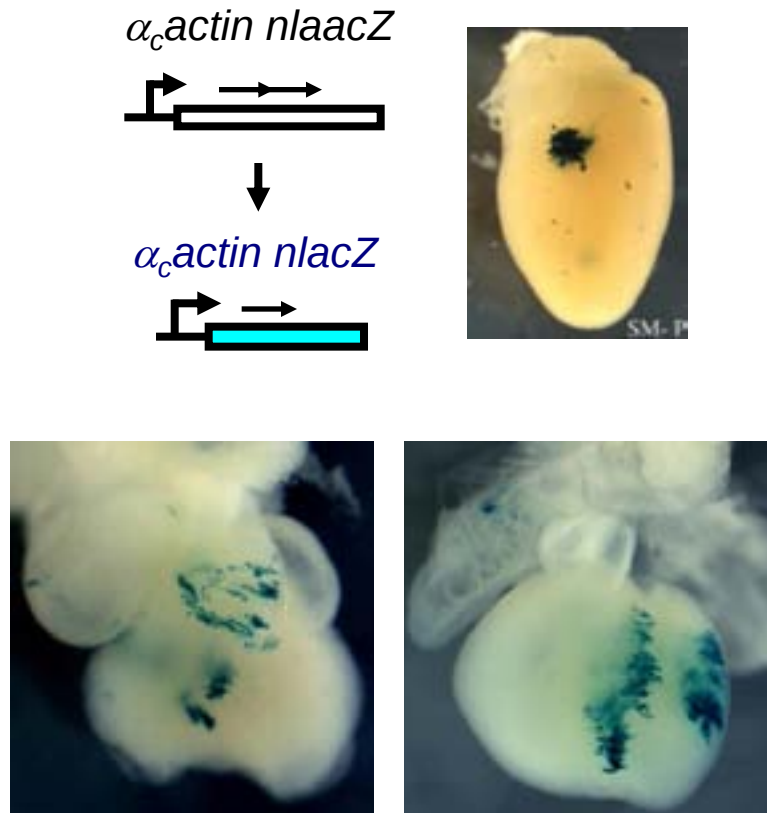
Parmacek and Epstein 2005
Cell 120:295-298

Transcriptional programs in the first and second heart field



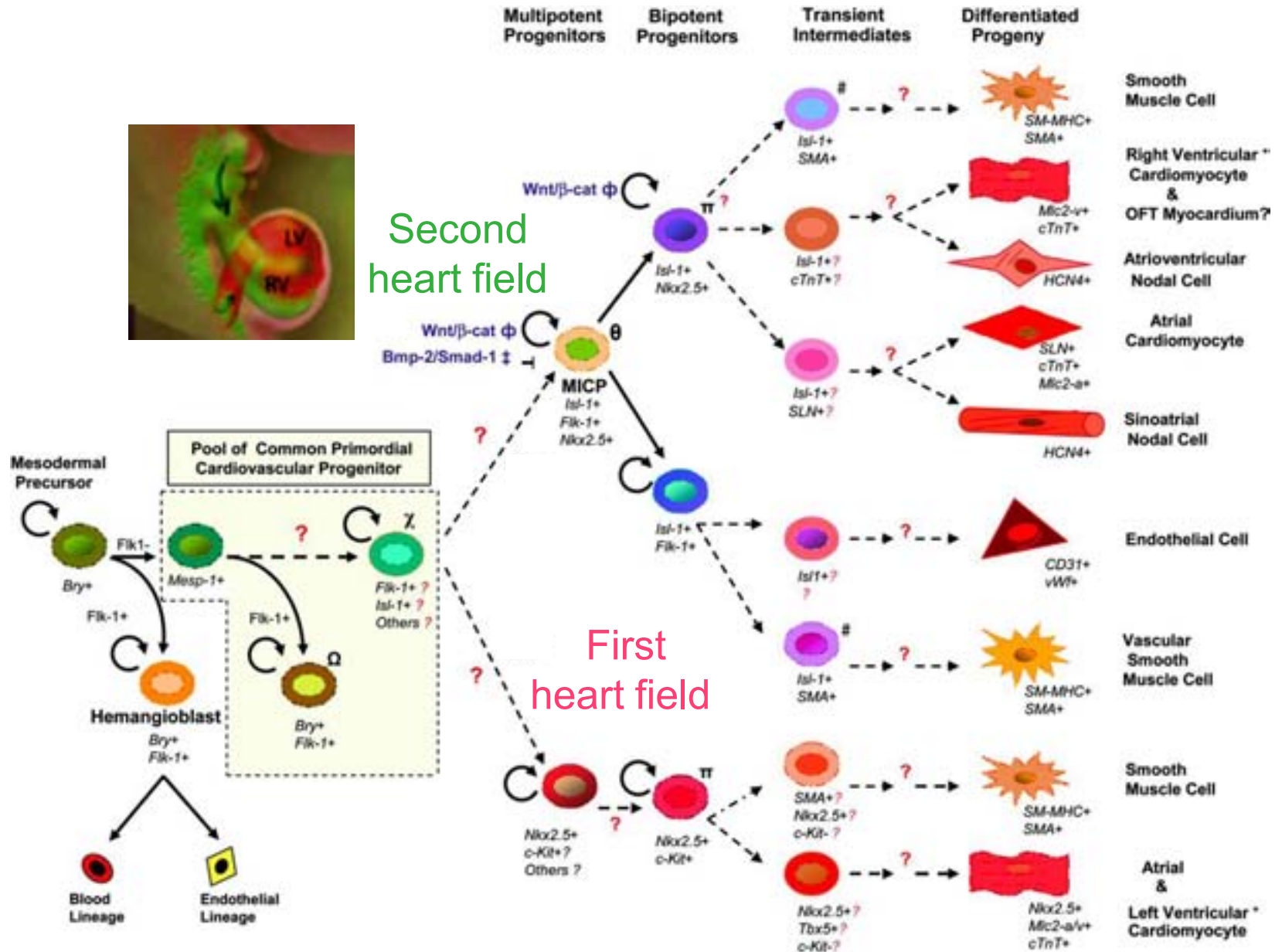
Olson 2006
Science 313:1922-27

Clonal analysis in the embryonic heart: evidence for the existence of two myocardial lineages

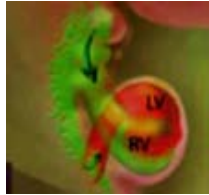


Meilhac et al., 2004
Dev Cell 6:685-98

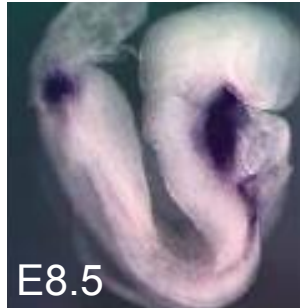
Cardiac progenitor cell lineages



Gene expression in the second heart field



Isl1



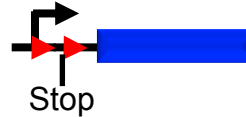
Wildtype

Isl1^{-/-}



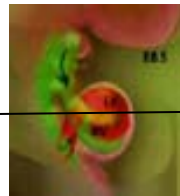
Isl1-Cre

Rosa26-Stop-lacZ



Cai et al. 2003
Dev Cell 5:877-89

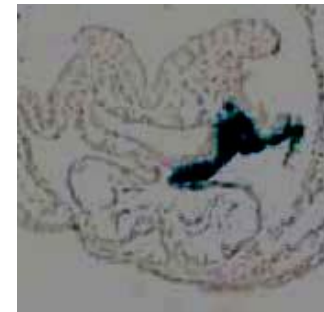
Fgf10



E8.5



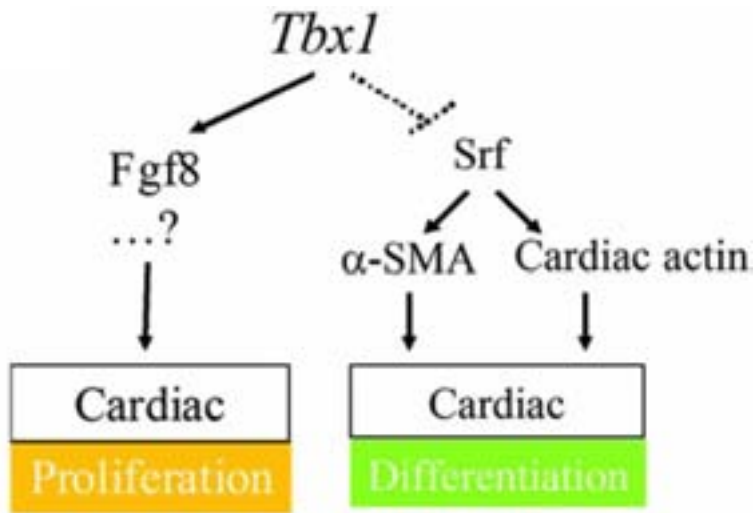
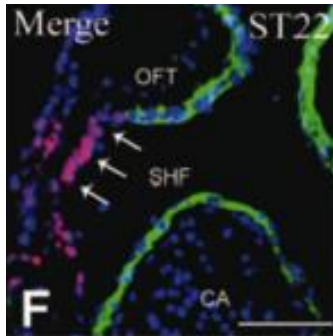
Fgf10 lacZ



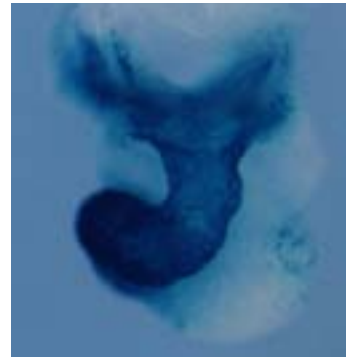
Pitx2c

Tbx1: DiGeorge Syndrome candidate gene expressed in the second heart field

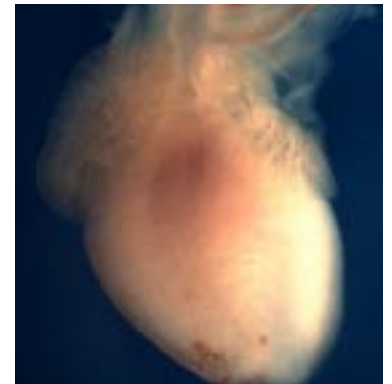
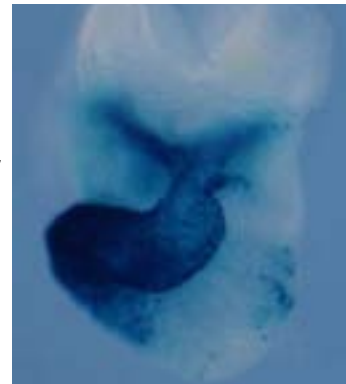
Tbx1



Tbx1^{+/-}



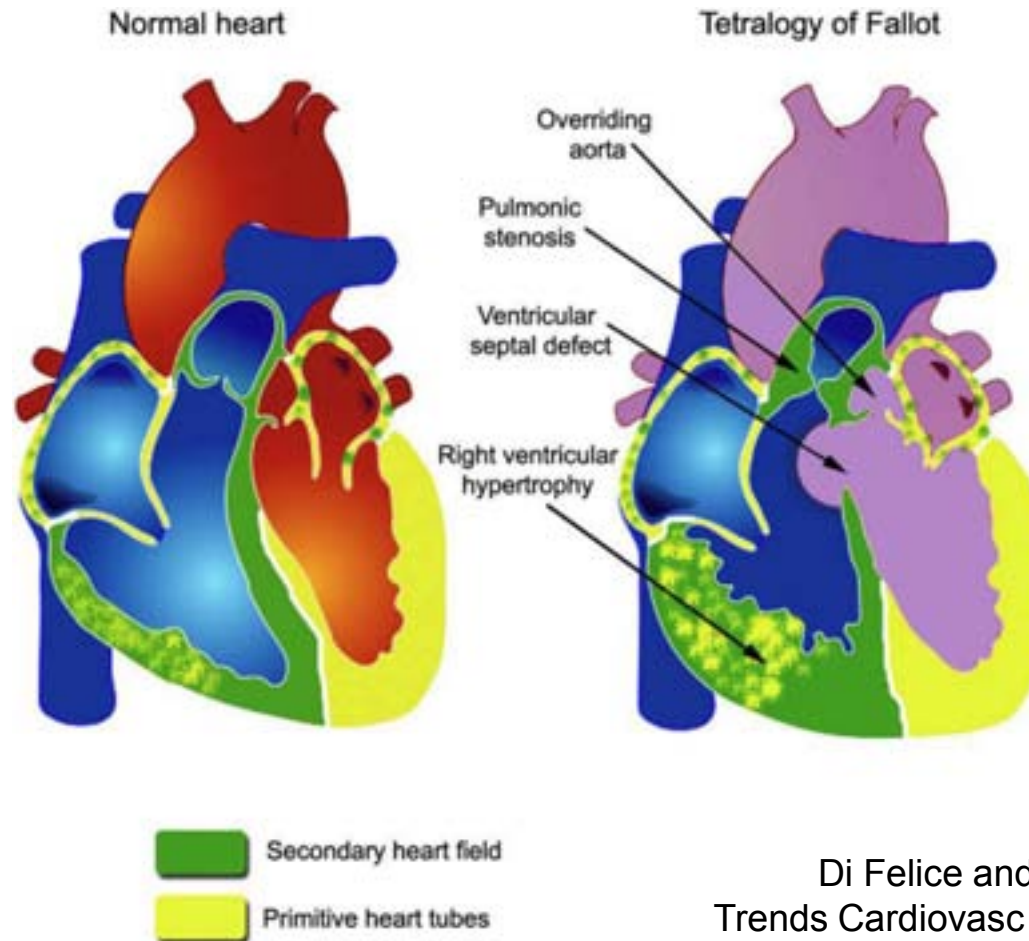
Tbx1^{-/-}



Fgf10 lacZ

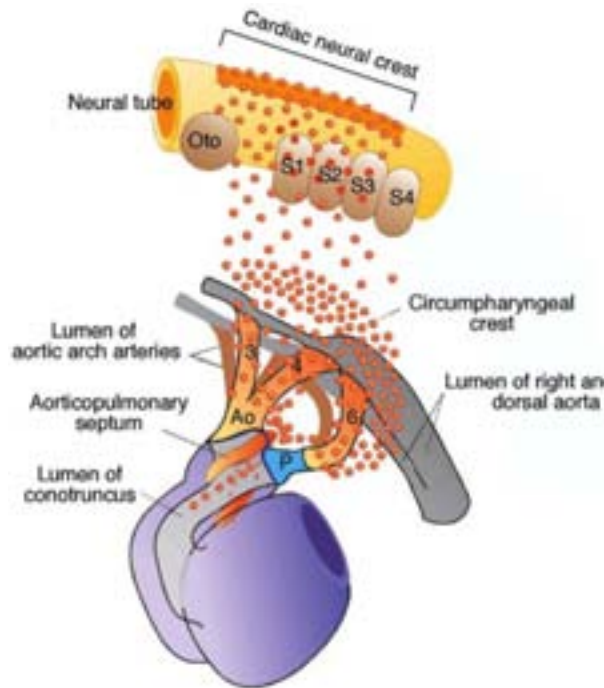
Chen et al. 2009
Circ Res 105:842-51

The second heart field and conotruncal congenital heart defects



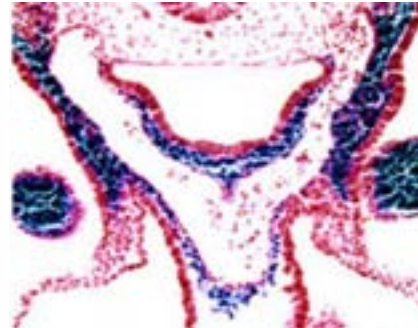
Di Felice and Zummo 2009
Trends Cardiovasc Med 19:130-5

The second heart field and cardiac neural crest cells

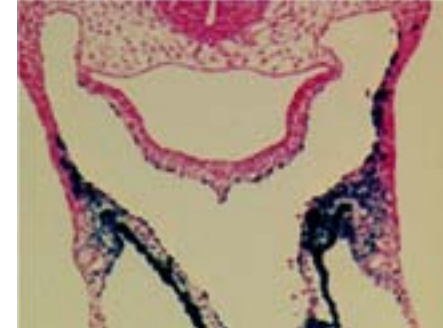


Hutson and Kirby, 2007
Sem Cell Dev Biol

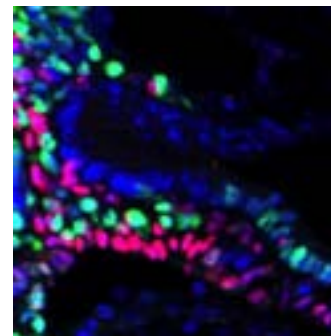
Wnt1-Cre R26R



Fgf10 lacZ

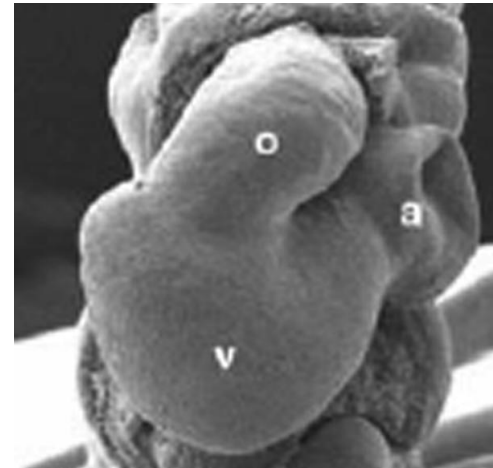
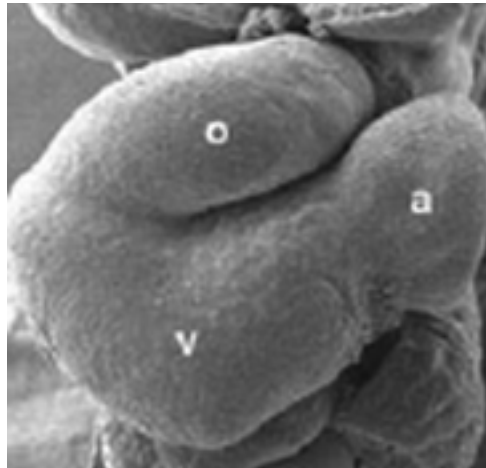


Jiang *et al.* 2000
Development 127:1607-16

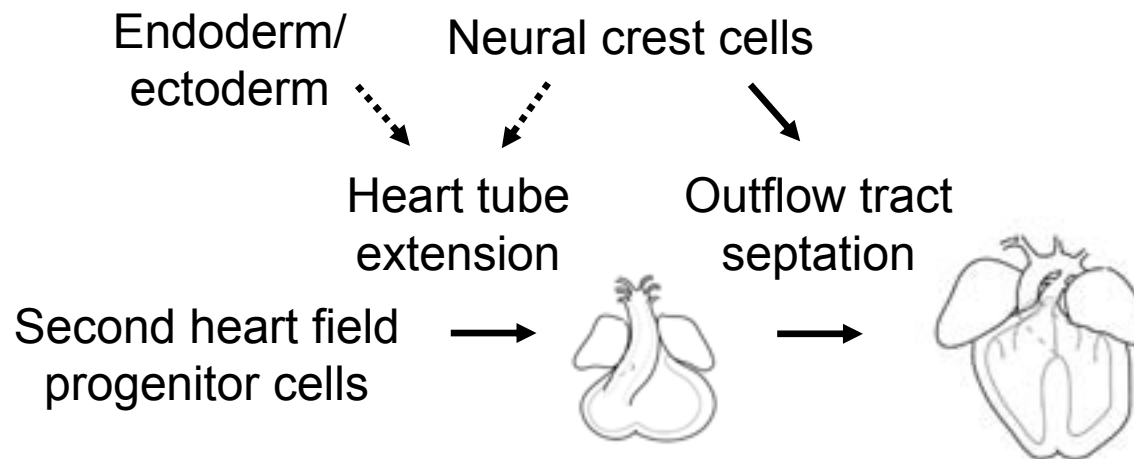


Neural crest
Mesoderm

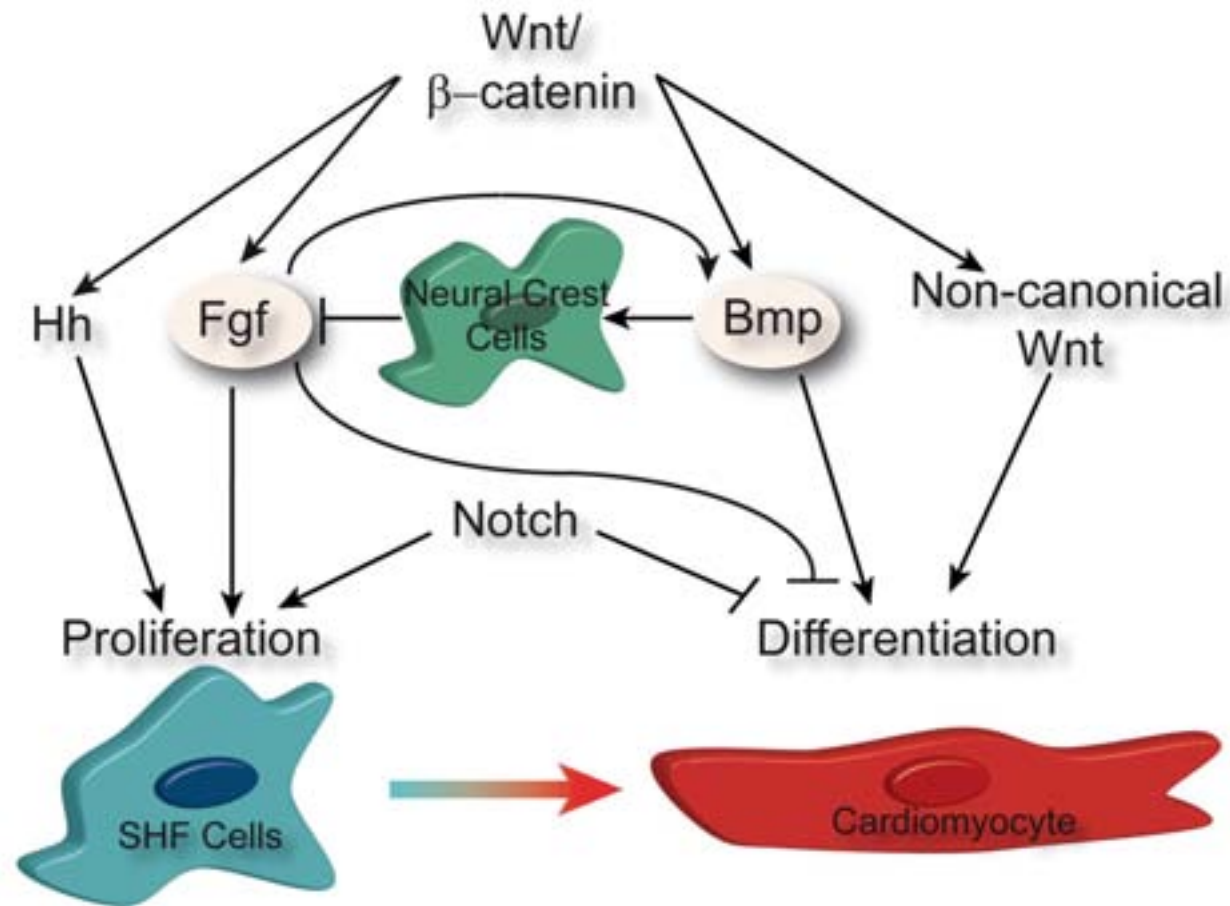
Ablation of the cardiac neural crest impairs second heart field development



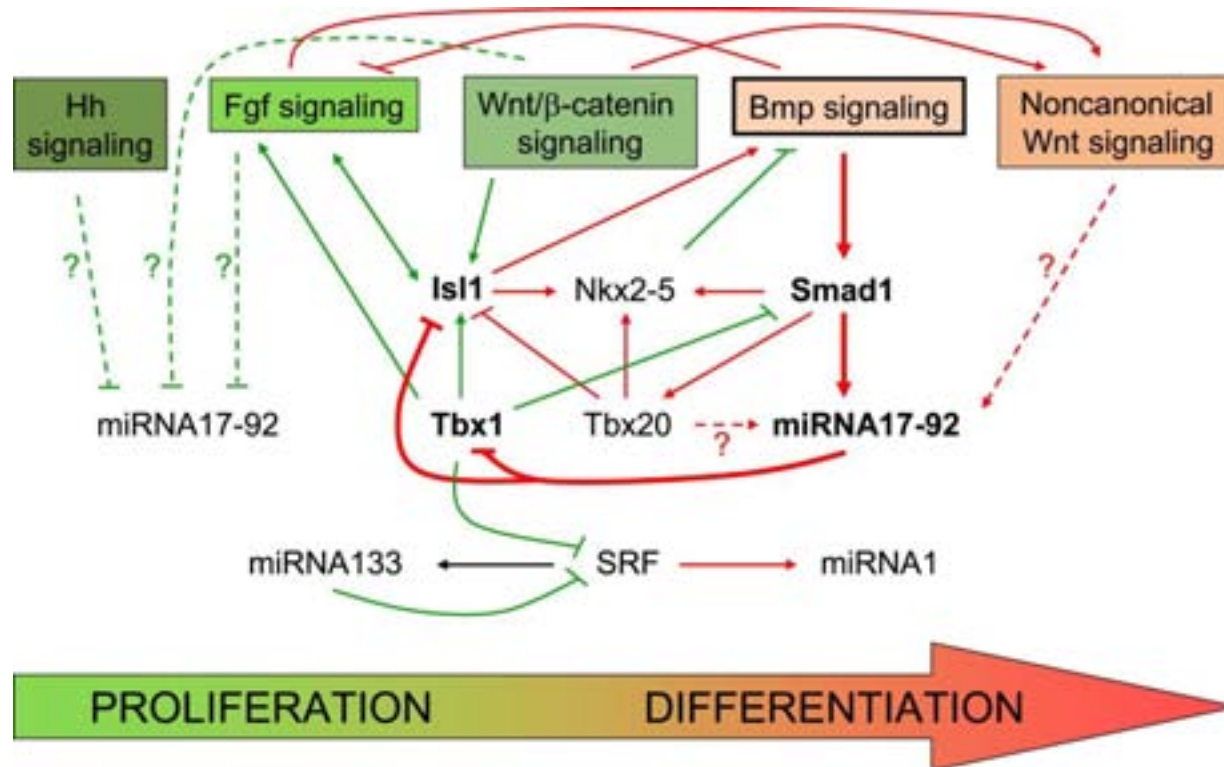
Yelbuz et al, 2002
Circulation 106:504-10



Signaling pathways controlling second heart field development

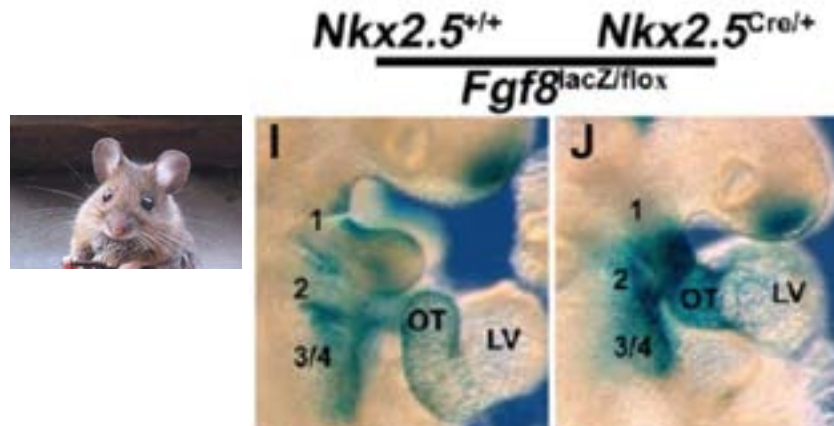


Regulation of second heart field differentiation by microRNAs

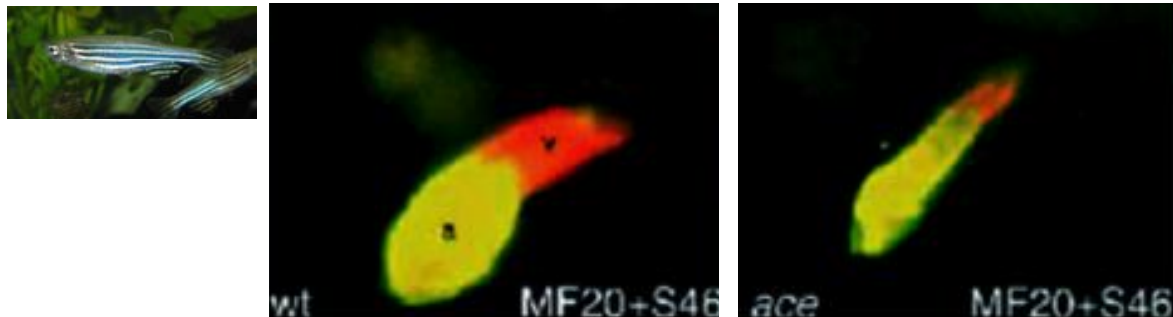


Wang et al 2010
Dev Cell 19:903-12

Fgf8 is required for second heart field and outflow tract development



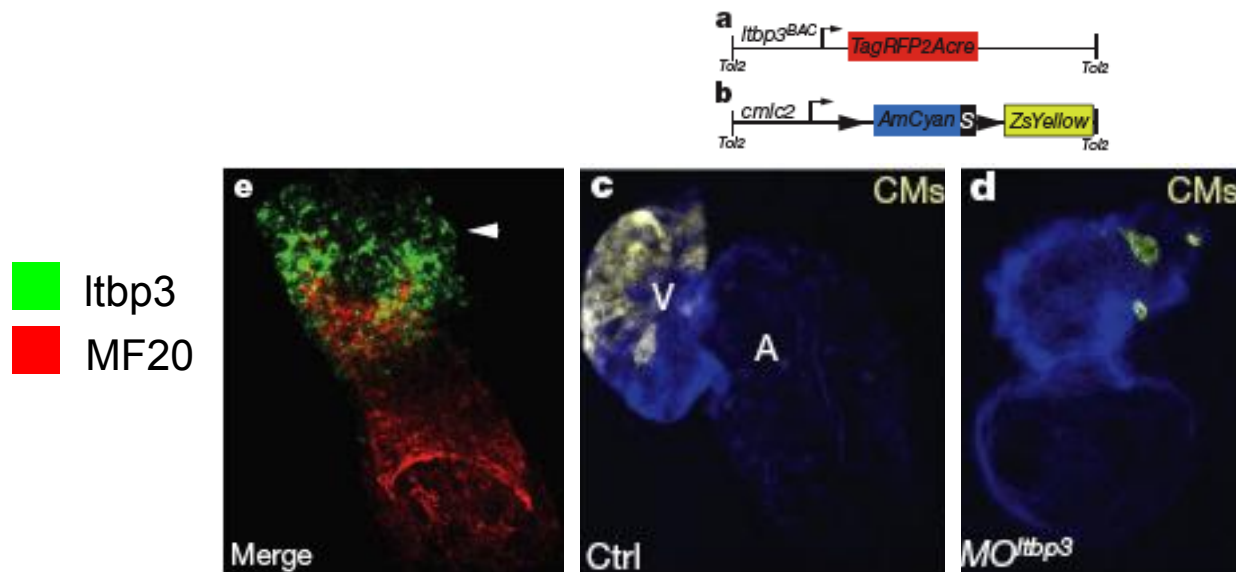
Ilagan *et al.* 2006
Development 133:2435-45



Reifers *et al.* 2001
Development 126:225-35

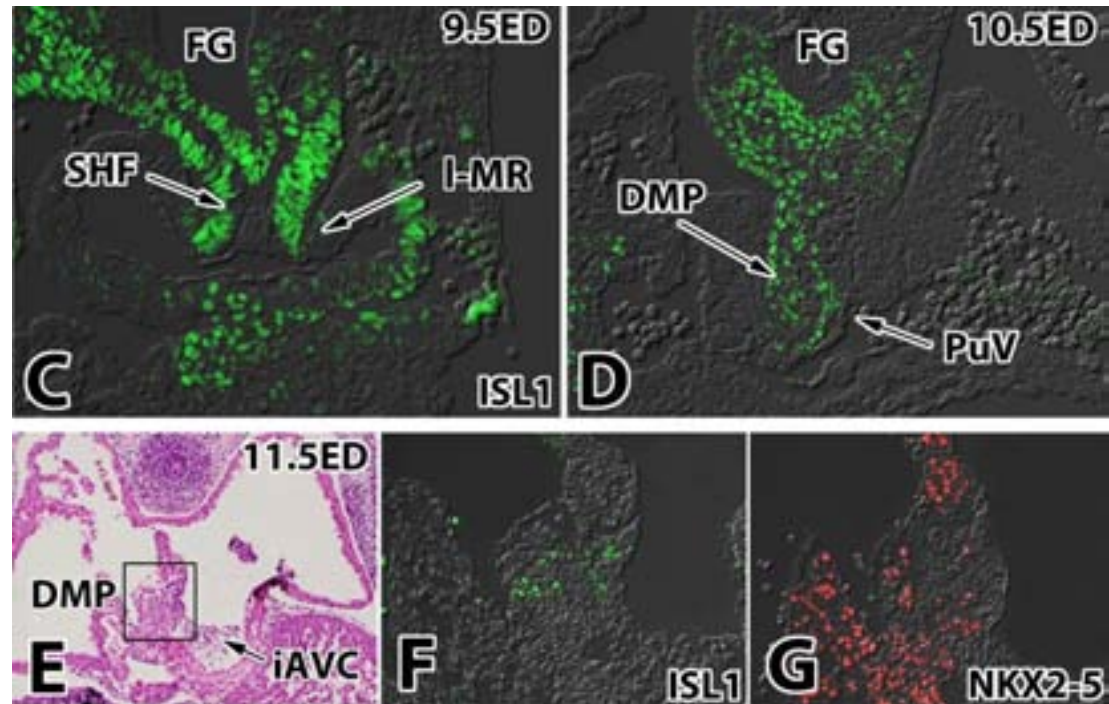
Latent TGF- β binding protein 3 identifies a second heart field in zebrafish

Yong Zhou^{1,2}, Timothy J. Cashman^{1,2}, Kathleen R. Nevis^{1,2}, Pablo Obregon^{1,2}, Sara A. Carney³, Yan Liu^{2,4}, Aihua Gu^{1,2,5}, Christian Mosimann^{2,6}, Samuel Sondalle^{1,2,7}, Richard E. Peterson³, Warren Heideman³, Caroline E. Burns^{1,2,7} & C. Geoffrey Burns^{1,2}



Zhou et al 2011
Nature 474:645-8

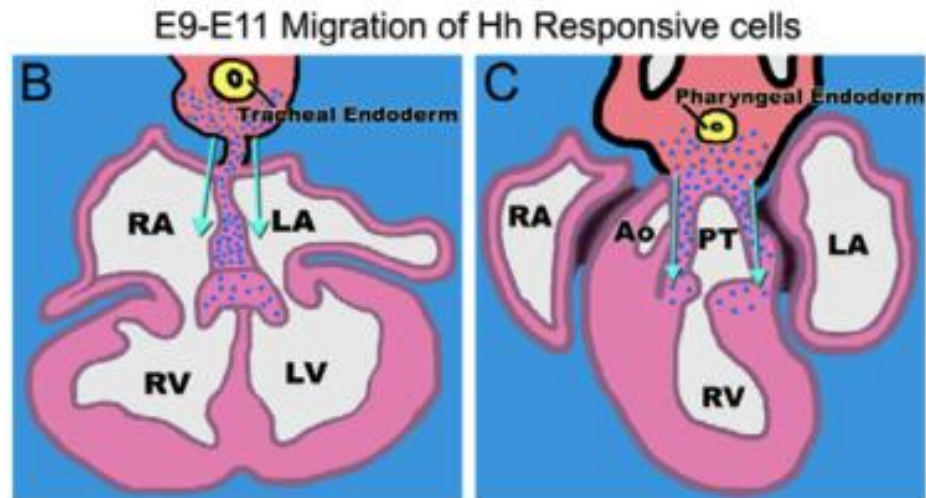
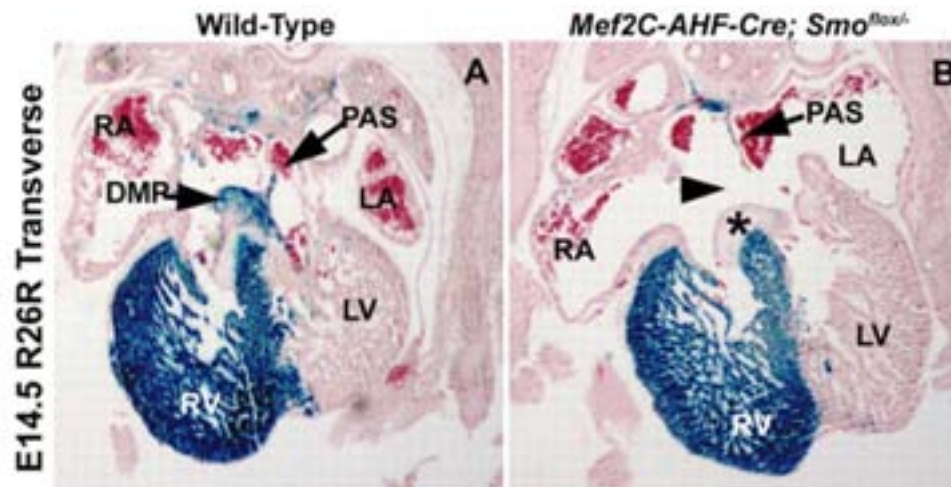
Second heart field contribution at the venous pole of the heart



■ ISL1
■ NKX2.5

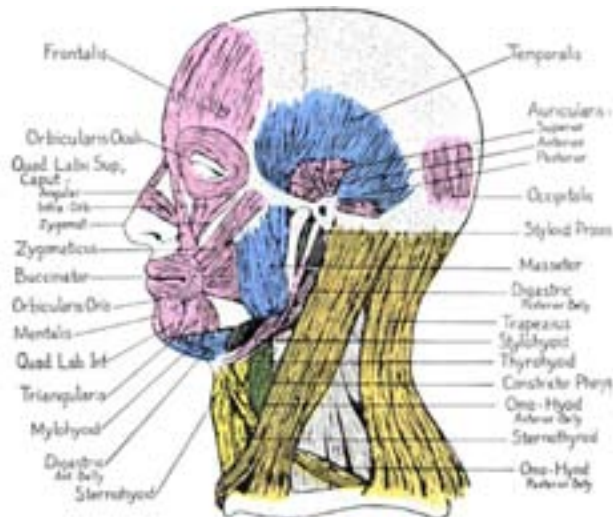
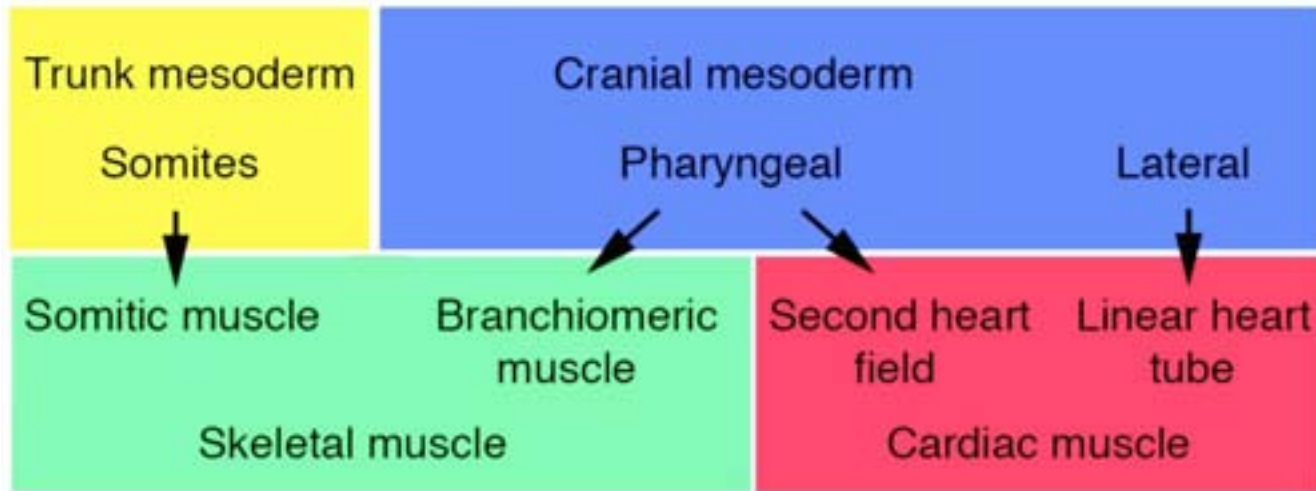
Briggs et al 2012
Differentiation 84:117-30

Second heart field contribution to atrial and AV septation



Hoffman et al 2009
Development 136:1761-70

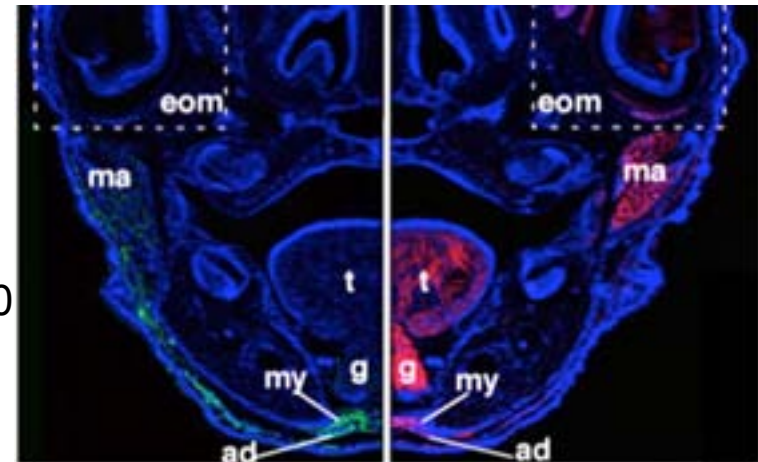
The second heart field is part of a cardiocraniofacial developmental field



Isl1-Cre
R26R

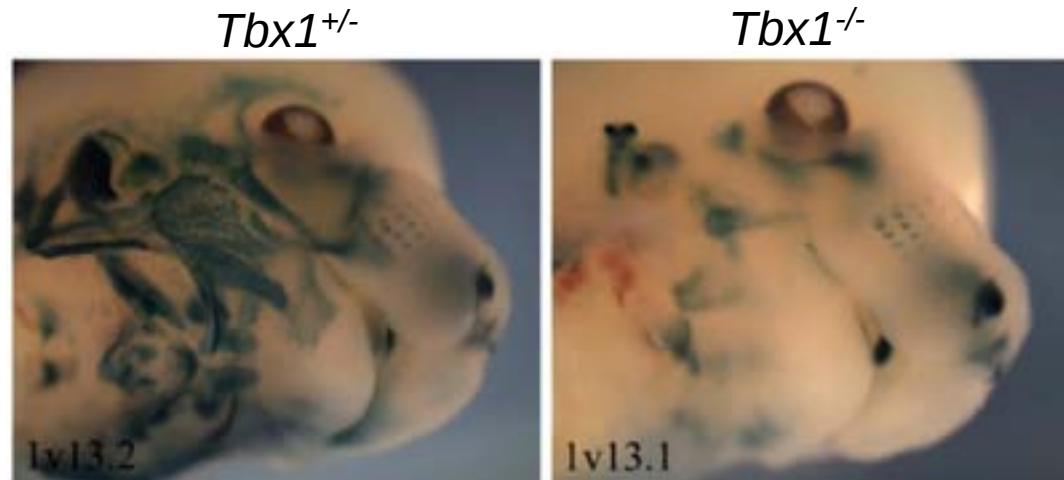
β-gal

MF20

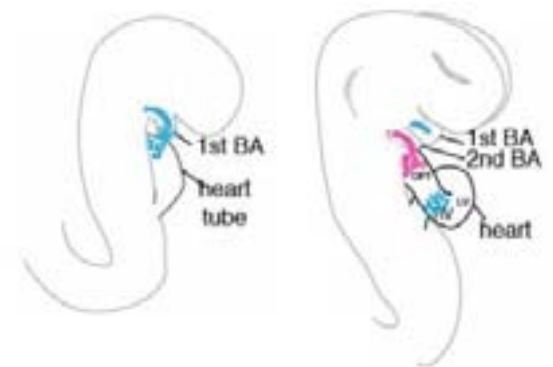
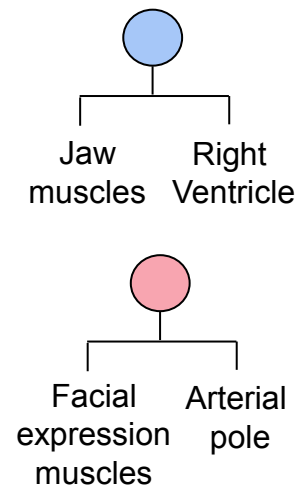
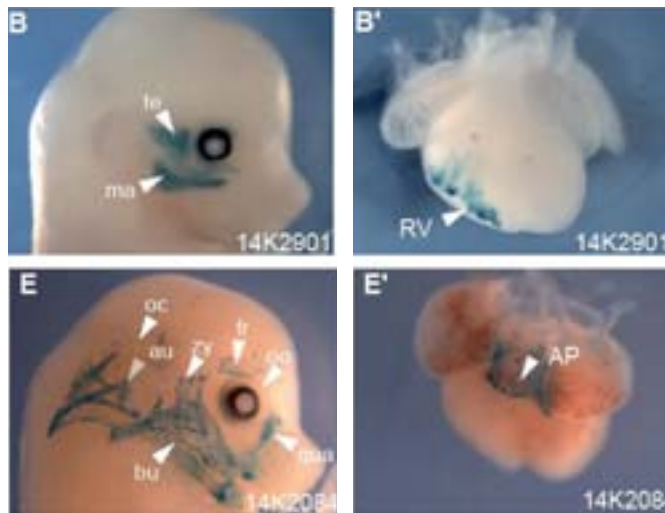
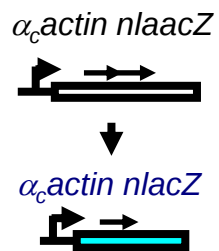


Nathan et al. 2008
Development 135:647-657

A common lineage relationship between head muscles and SHF-derived myocardium



Kelly et al. 2004
Hum Mol Genet
13:2829-40



Lescroart et al 2010
Development 137:3269-79

Heart Development

- From the cardiac crescent to the embryonic heart
- Second heart field cardiac progenitor cells
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- Conduction system and epicardial development



E12.5

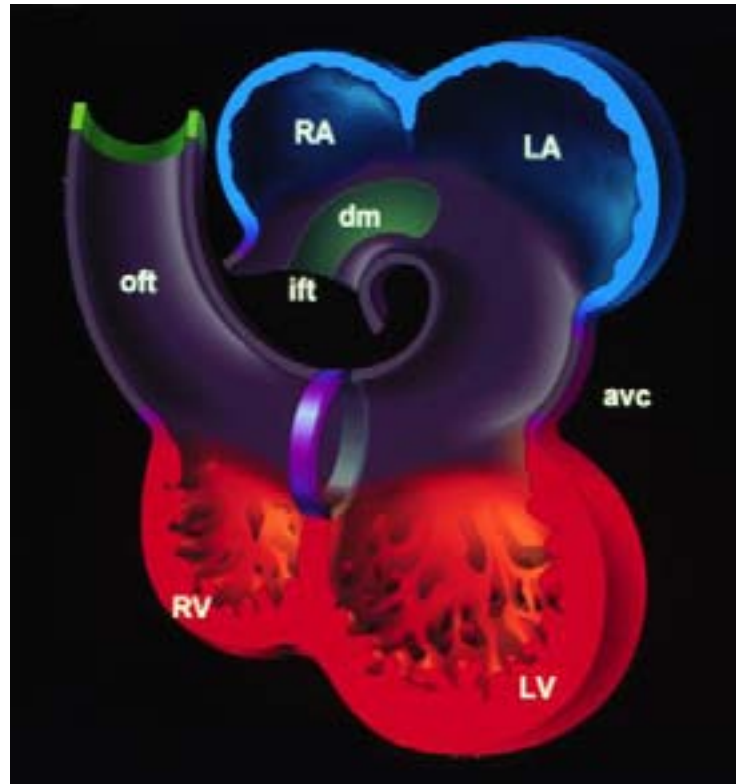


E14.5



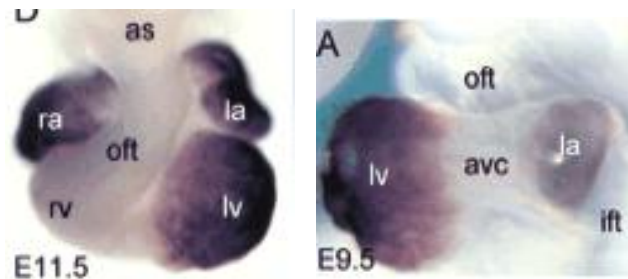
Adult

Cardiac chamber formation: the ballooning model

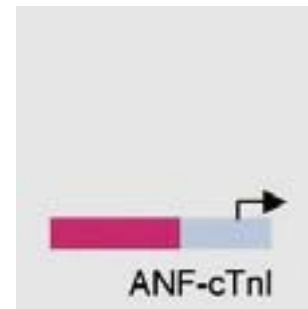
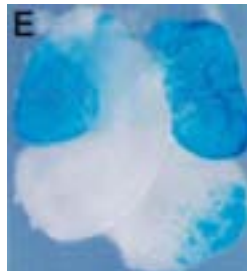
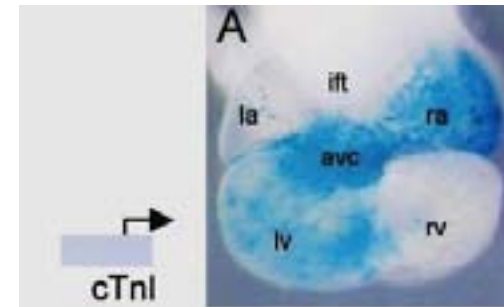


Moorman and Christoffels. 2003
Physiol Rev 84:1223-67

Differential gene expression during chamber formation

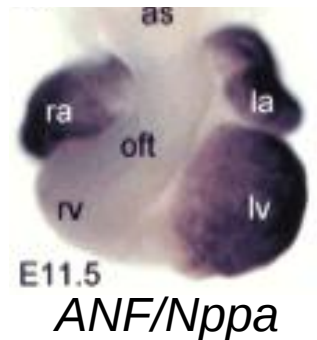


ANF/Nppa

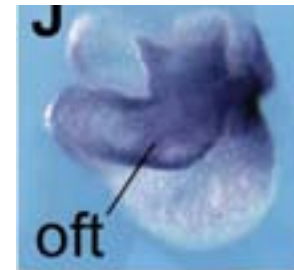


Habets et al. 2002
Genes Dev 16:1234-46

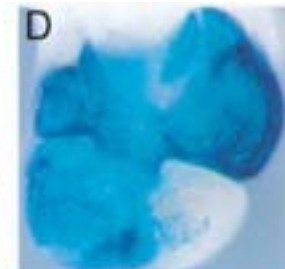
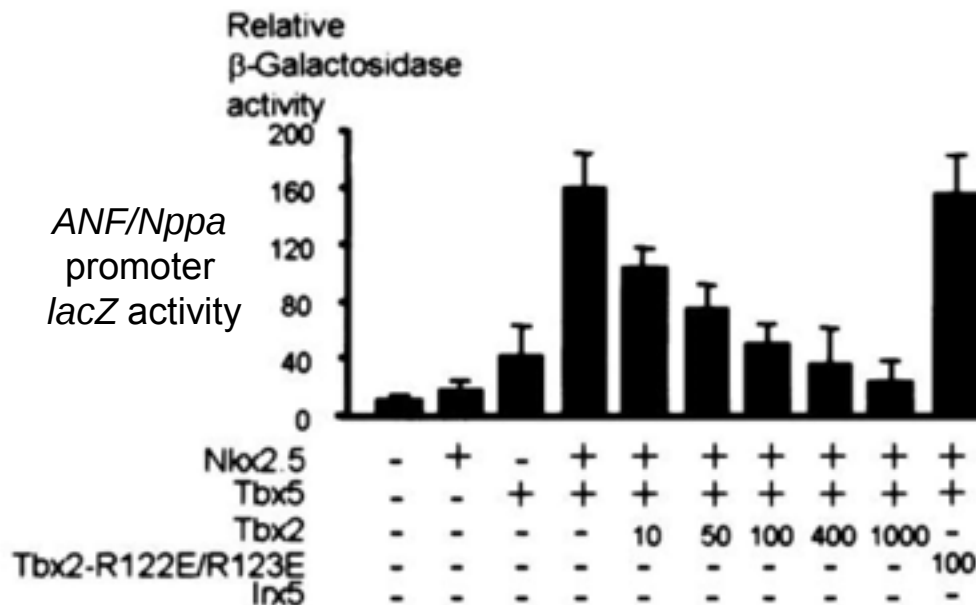
A T-box gene network regulates chamber formation



Tbx5
Activator

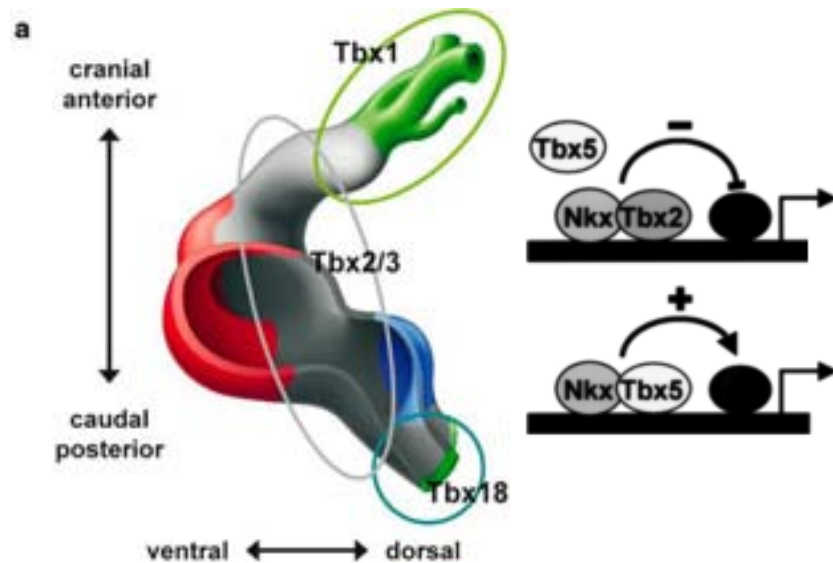


Tbx2
Repressor

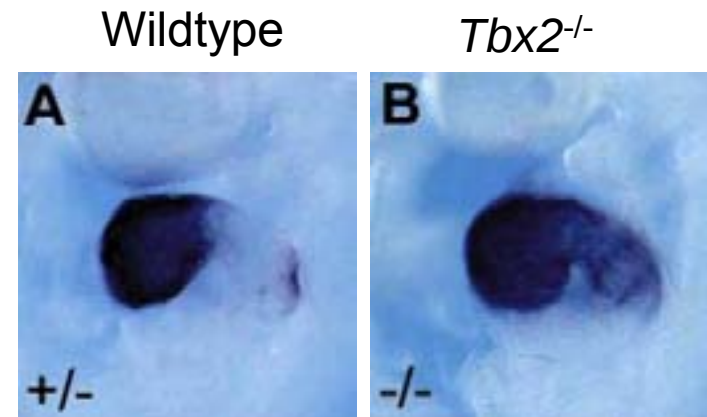


Habets et al. 2002
Genes Dev 16:1234-46

A T-box gene network regulates chamber formation



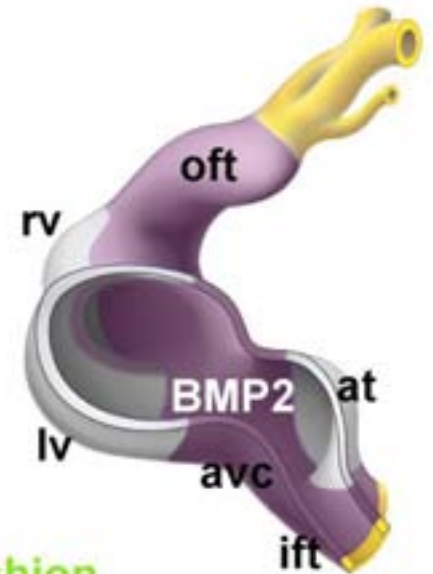
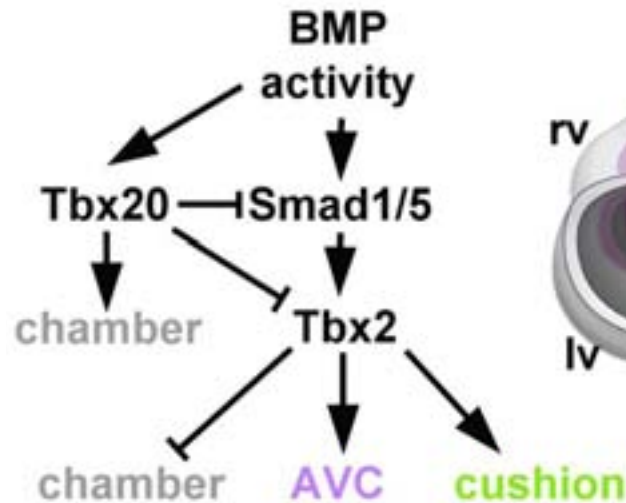
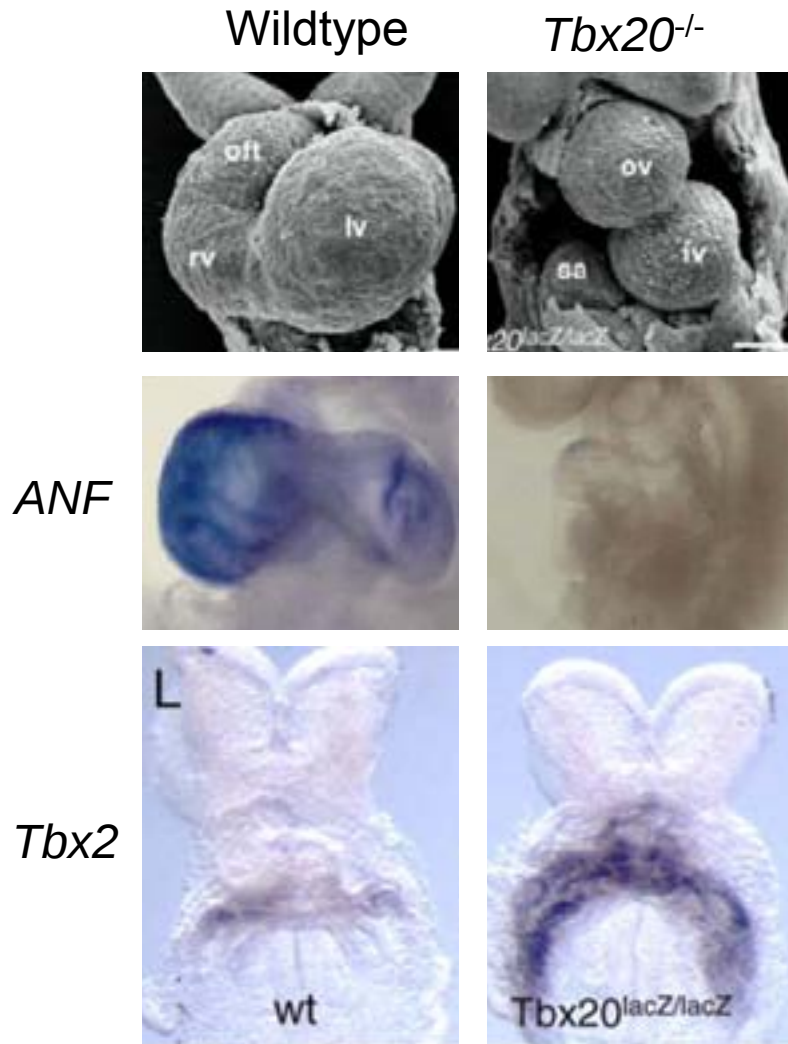
Hoogaars et al. 2007
Cell Mol Life Sci 64:646-660



ANF/Nppa

Harrelson et al. 2004
Development 131, 5041-5052

A T-box gene network regulates chamber formation

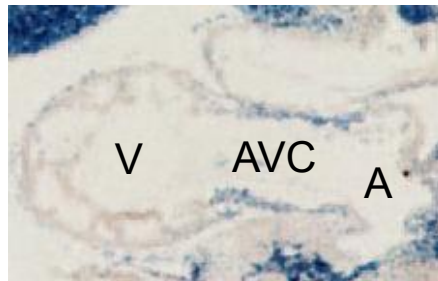


Singh et al. 2009
Circ Res 105:442-52

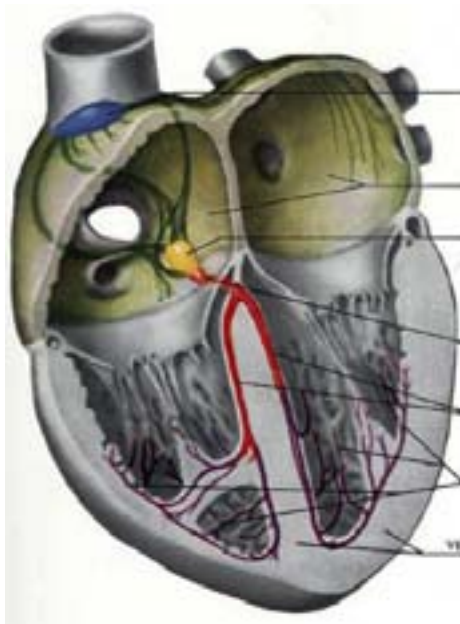
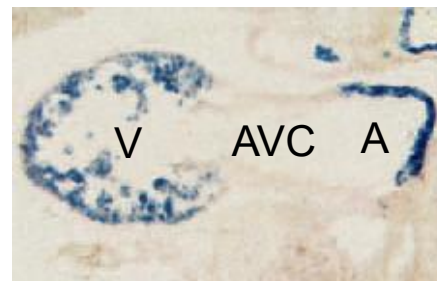
Conduction system development



Tbx3



Cx40

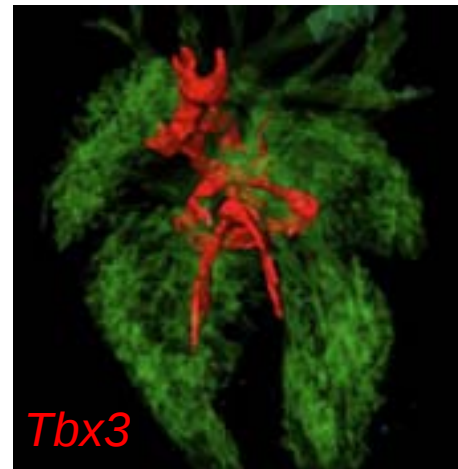


SA node

AV node

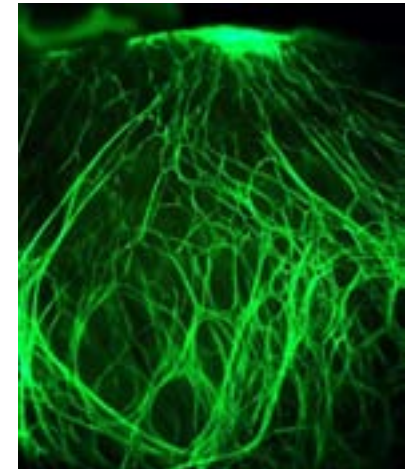
Bundle
branches

Purkinje
fibres



Tbx3

Central conduction
system: AV node

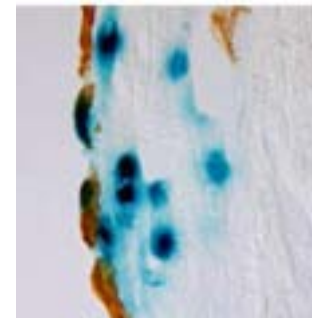
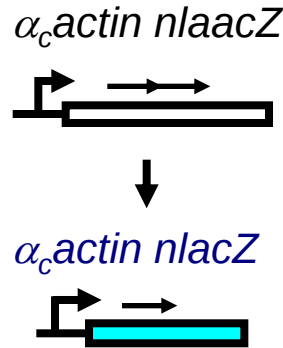
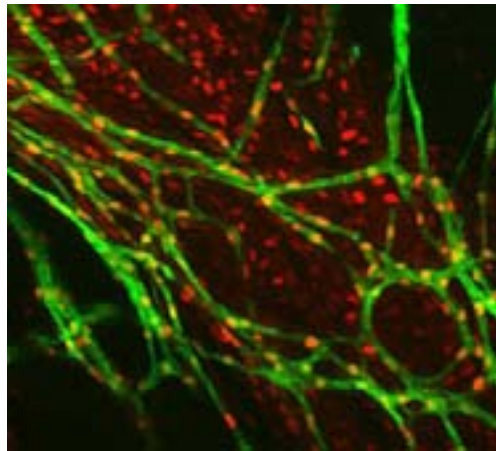


Cx40 GFP

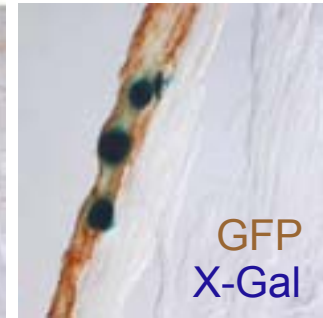


Purkinje fibre network

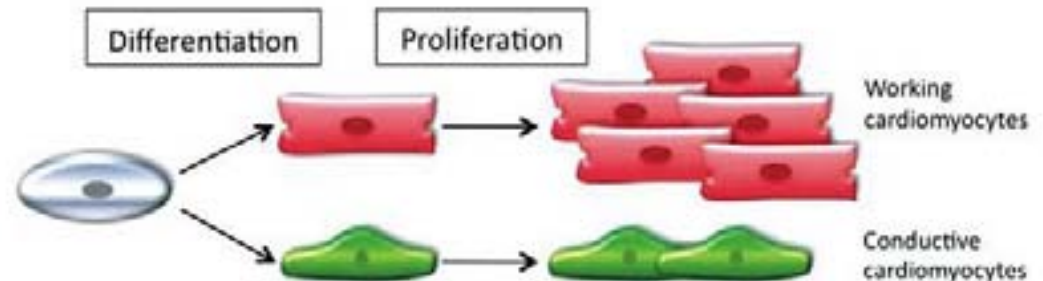
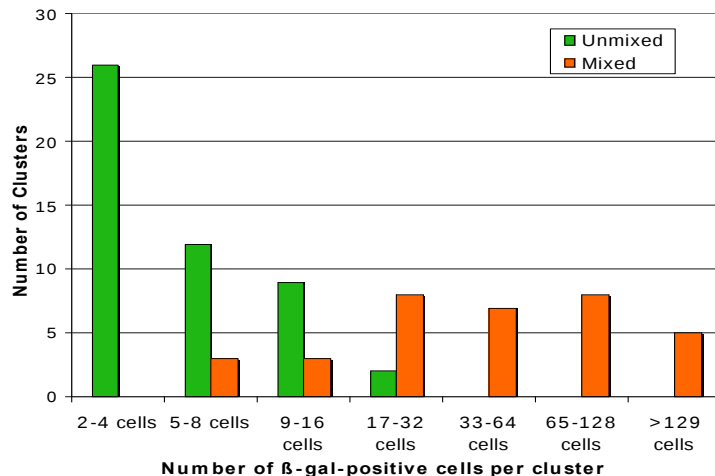
Clonal analysis of the origin of the ventricular conduction system



Mixed clone



Unmixed clone

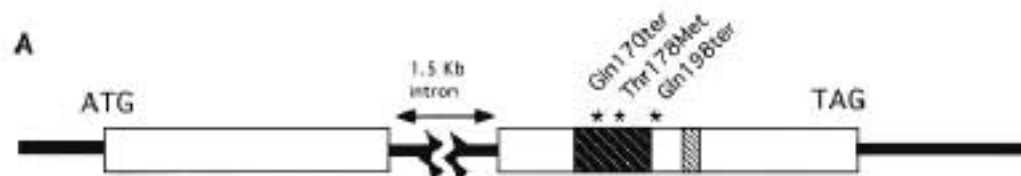
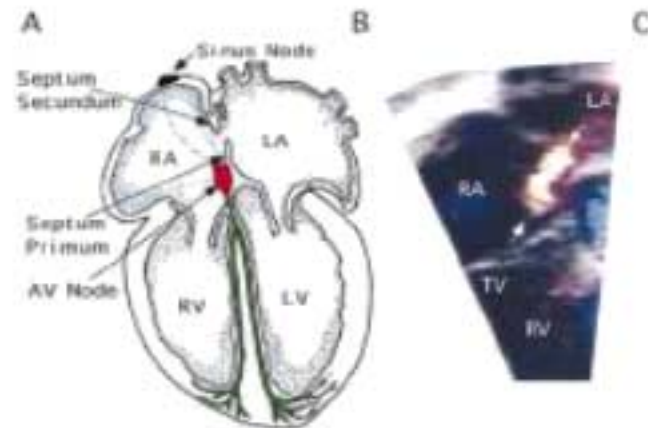
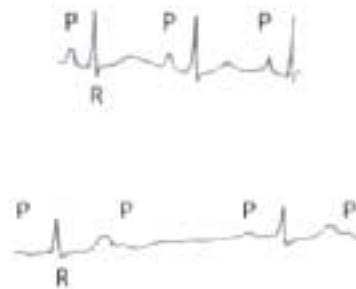
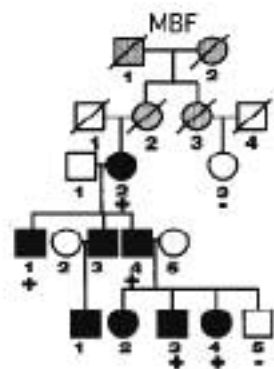


- Biphasic development of the conduction system – specification from a common progenitor followed by outgrowth

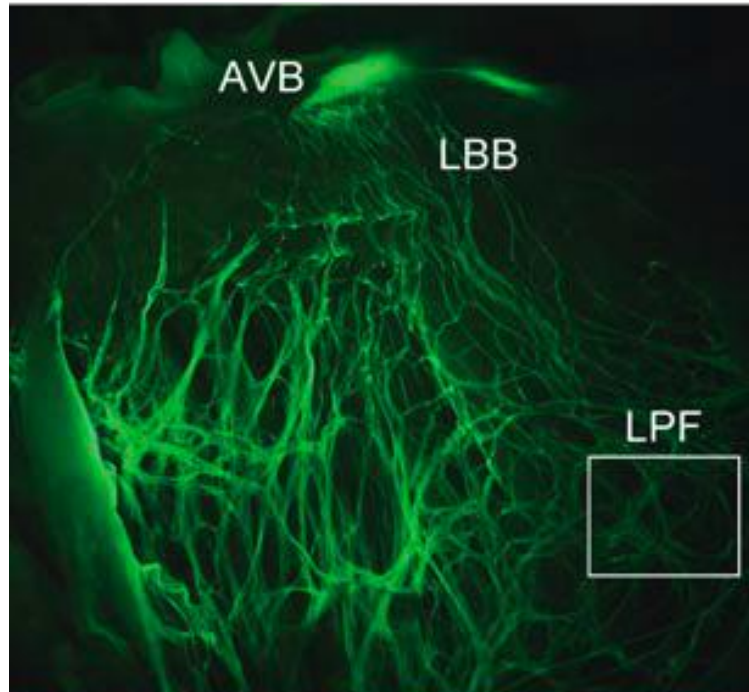


Congenital Heart Disease Caused by Mutations in the Transcription Factor NKX2-5

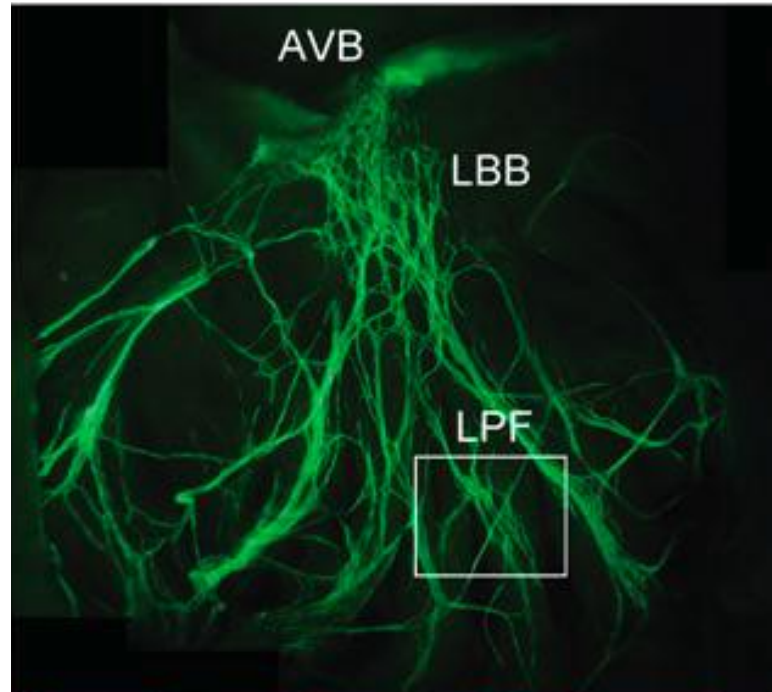
Jean-Jacques Schott, *et al.*
Science **281**, 108 (1998)



Purkinje fibre hypoplasia in *Nkx2.5* haploinsufficient hearts



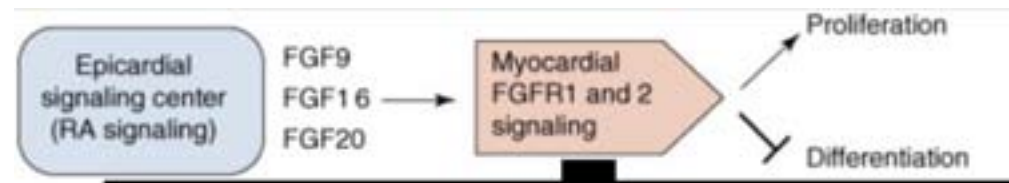
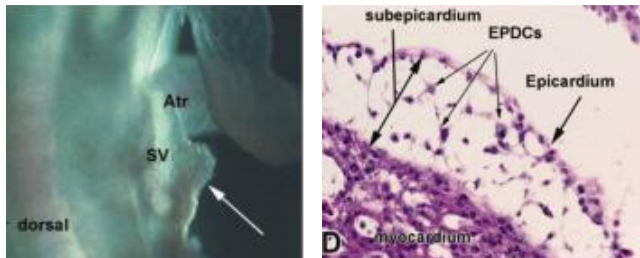
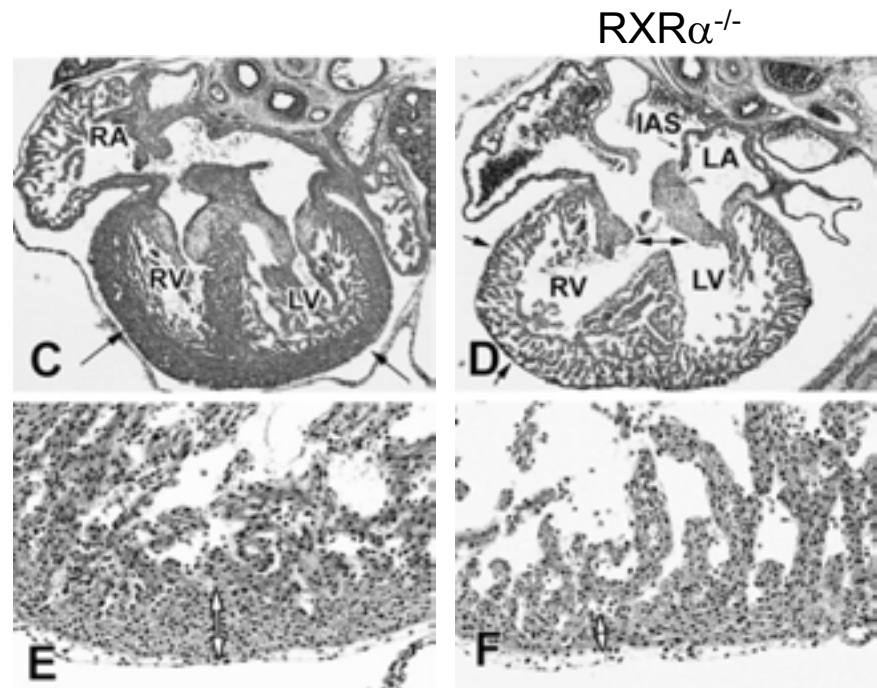
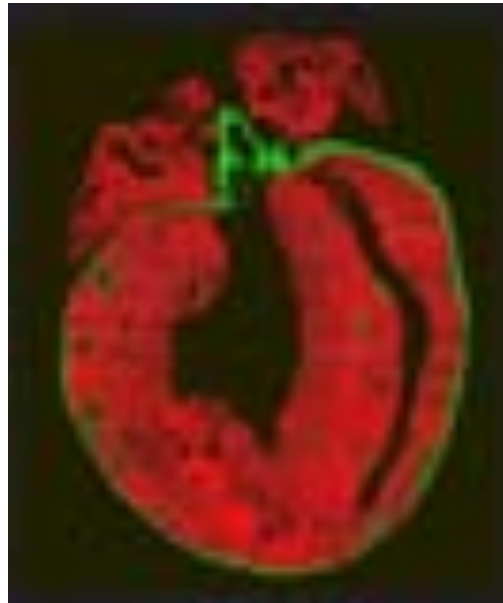
Cx40^{eGFP}



Cx40^{eGFP};Nkx2.5^{+/-}

Meysen et al. 2007
Dev Biol 303:740-51

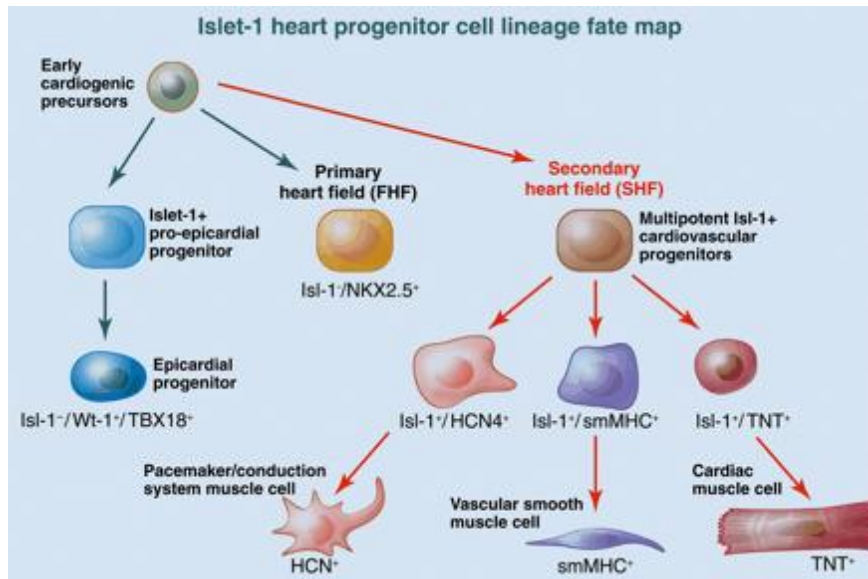
The epicardium regulates ventricular growth



Wessels and Sedmera, 2003
Physiol. Genomics 15: 165-176

Fate of the epicardium and origin of the coronary vasculature

Endocardium is a major source of coronary endothelial cells



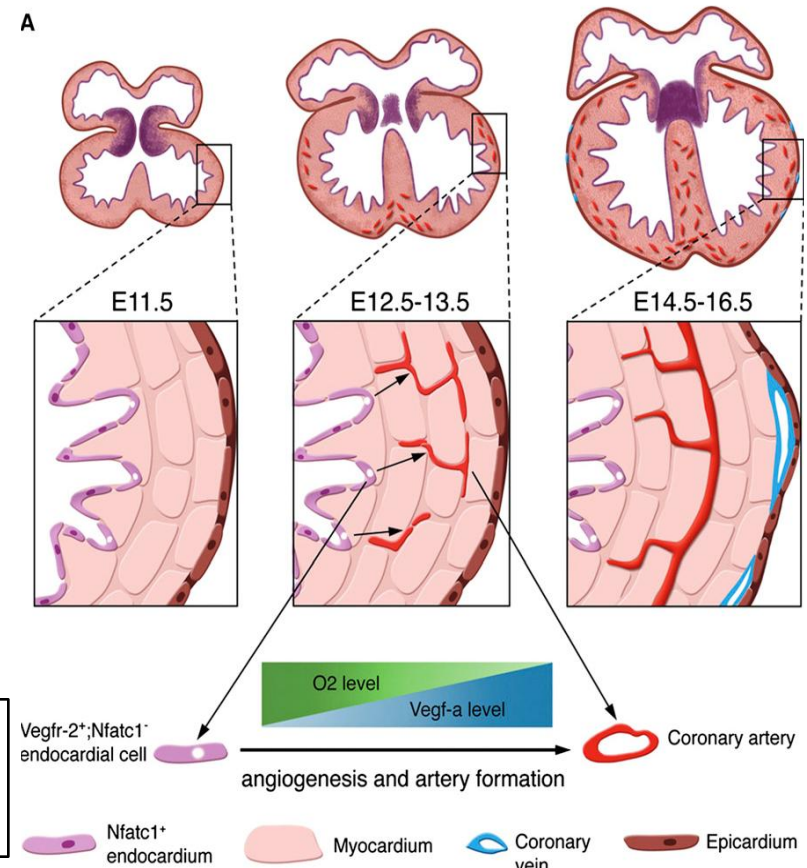
Chien et al. 2008 Science 322:1494-7

Epicardial-derived cells

Cardiac fibroblasts
Smooth muscle cells

? Myocardium

? Coronary endothelial cells



Wu et al. 2012
Cell 151:1083-96

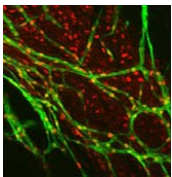
Heart Development



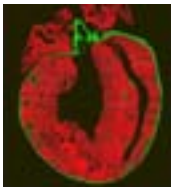
- The second heart field is a population of cardiac progenitor cells in pharyngeal mesoderm



- Perturbation of second heart field development results in congenital heart anomalies



- Chamber formation and conduction system development are regulated by a network of T-box transcription factors



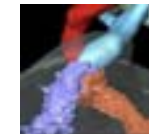
- The epicardium is required for myocardial growth and coronary smooth muscle development

Heart Development – bibliography and meetings

- “Cardiac Development”, 2008, ML Kirby, Oxford
- “Heart Development and Regeneration”, 2009, N Rosenthal and RP Harvey, Academic Press
- Bruneau BG. The developmental genetics of congenital heart disease. Nature. 2008 451:943-8.
- Miquerol L, Kelly RG. Organogenesis of the vertebrate heart. WIREs Dev Biol 2013. 10.1002/wdev.68
- *Cardiovascular Research* – Spotlight issue on Cardiac Development, July 2011

ESC WG on Development, Anatomy and Pathology
Annual meeting – Berlin, 26-29 September 2013

Weinstein Cardiovascular Development Meeting, USA



EU FP7
Cardio
GeNet

