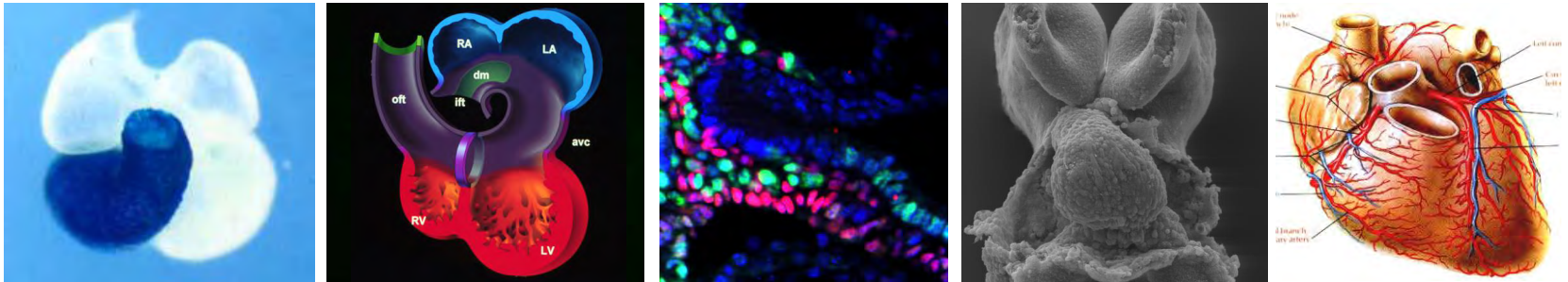


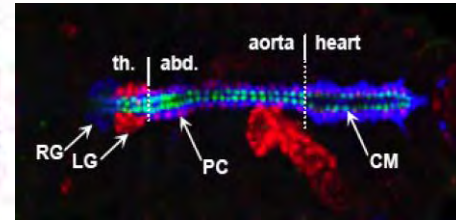
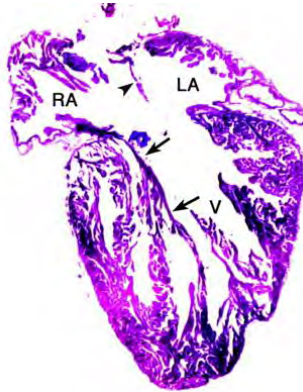
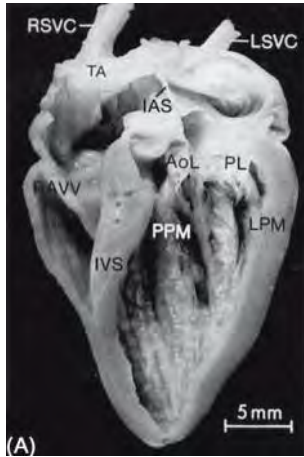
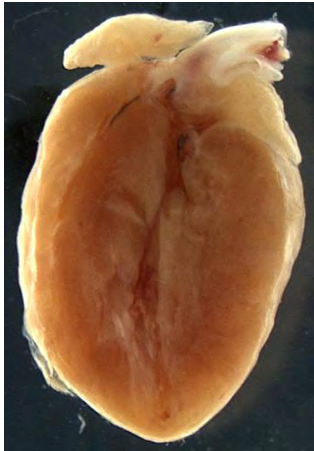
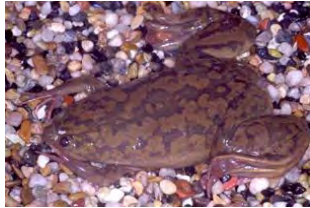
# Heart Development



Robert G. Kelly  
Developmental Biology Institute of Marseilles - Luminy



# Animal models of heart development



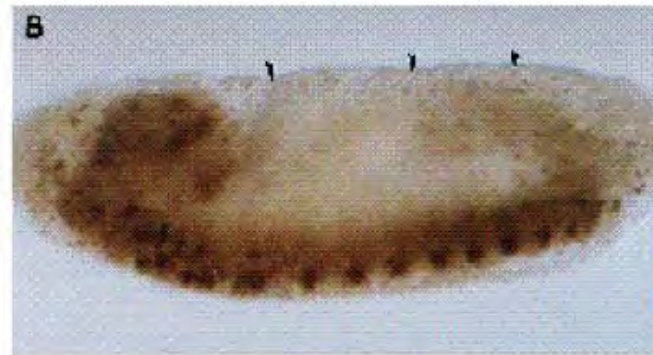
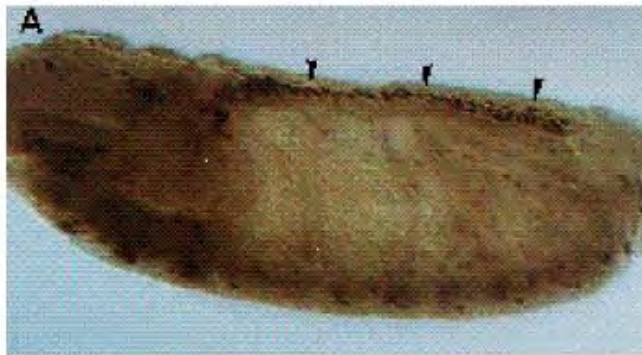


Development 118, 719-729 (1993)

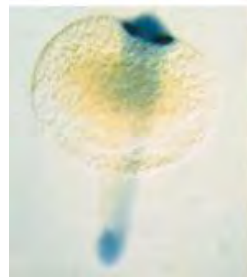
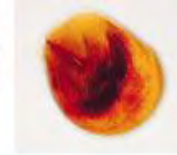
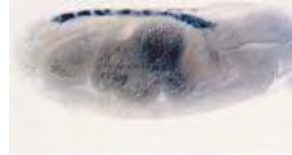
Printed in Great Britain © The Company of Biologists Limited 1993

## 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

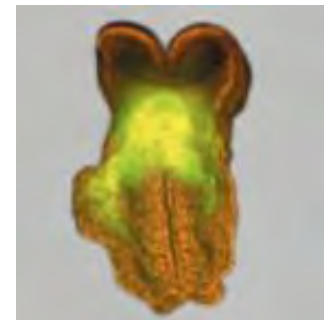
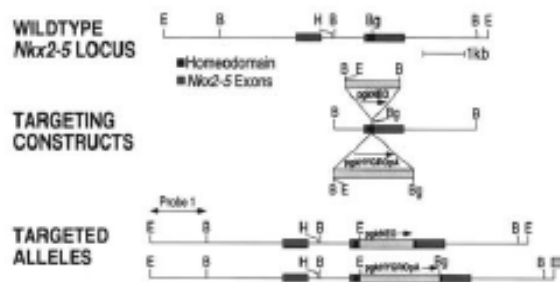
Harvey 1996  
Dev Biol 178:203-16



## 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.

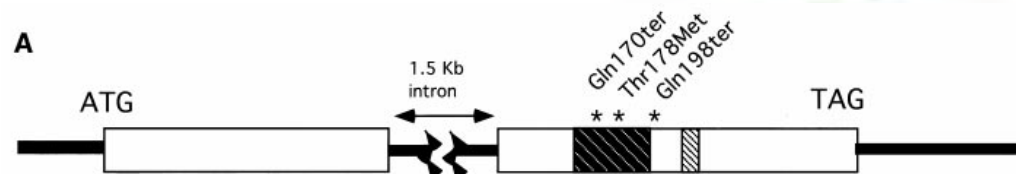
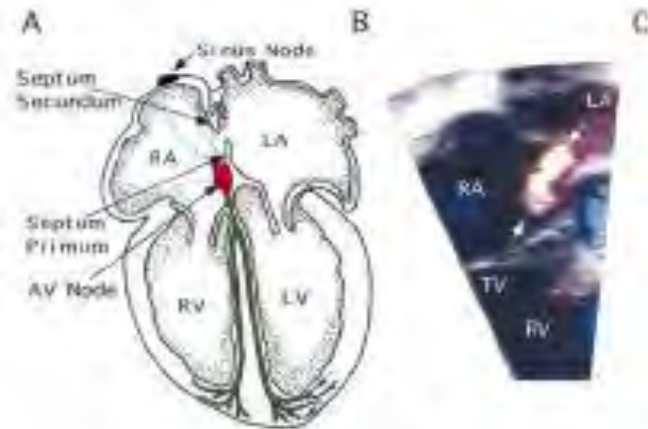
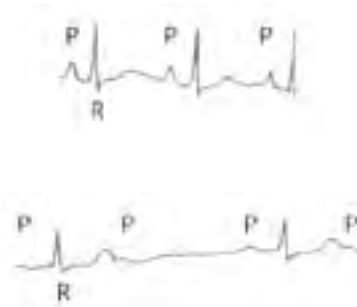
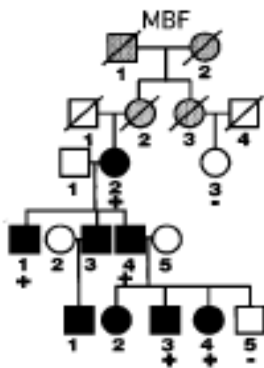
*Genes Dev.* 1995 9: 1654-1666



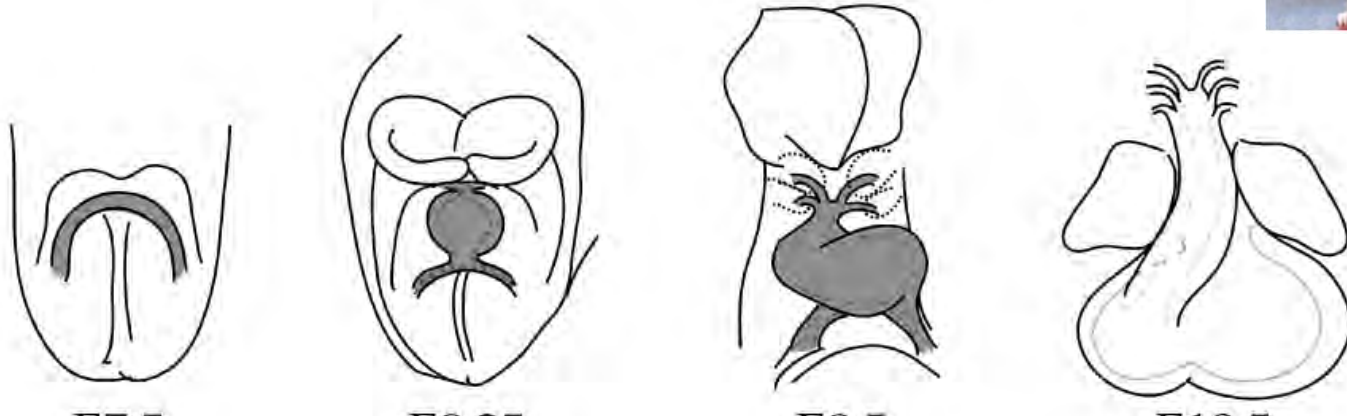


# Congenital Heart Disease Caused by Mutations in the Transcription Factor NKX2-5

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

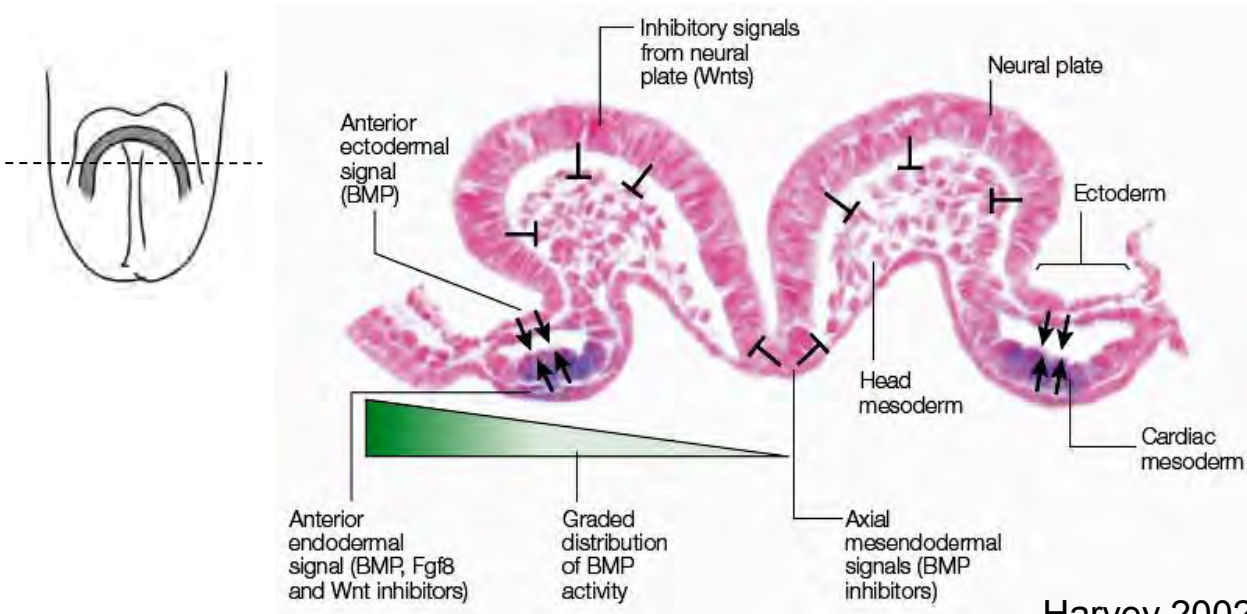


# Heart Development

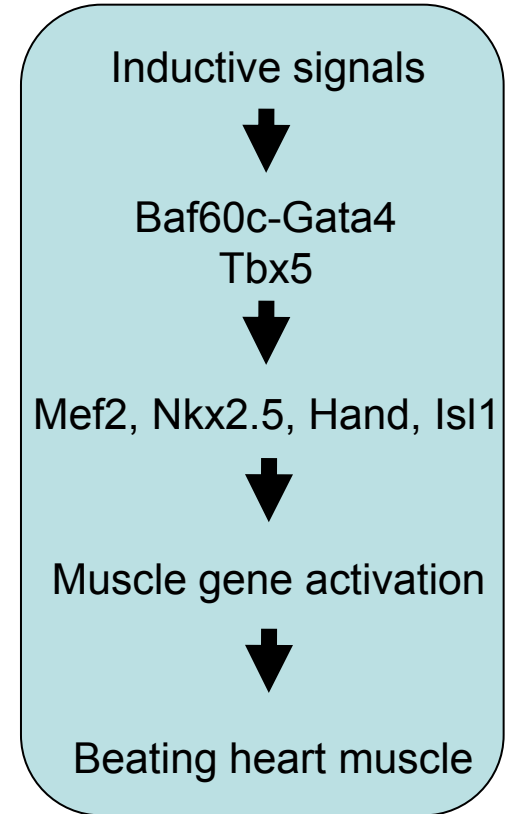


- From the cardiac crescent to the embryonic heart
- Second heart field cardiac progenitor cells
- Cardiac septation and chamber morphogenesis
- Conduction system and epicardial development

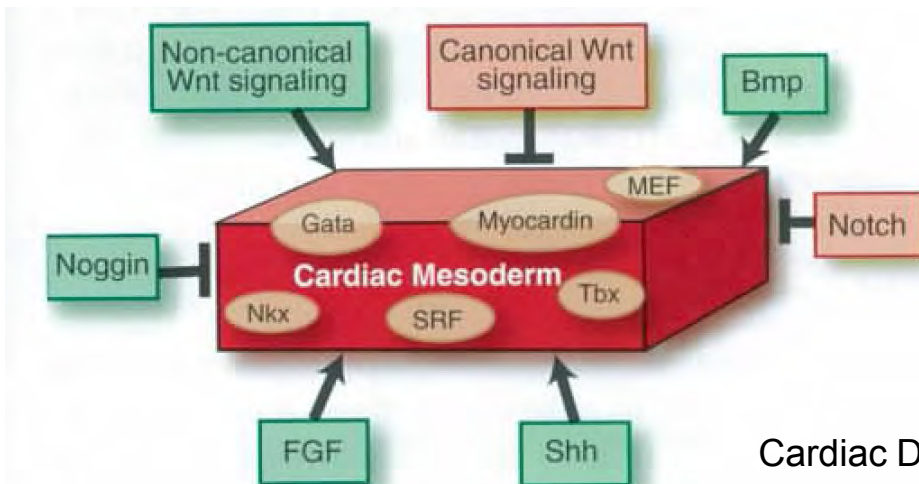
# Specifying cardiac fate in the early embryo



Harvey 2002  
Nat Rev Genet 3:544-56

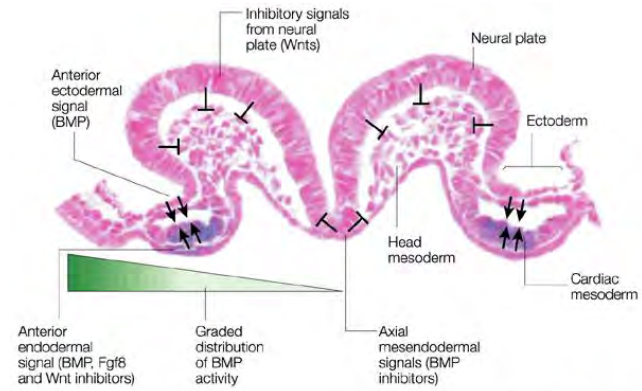
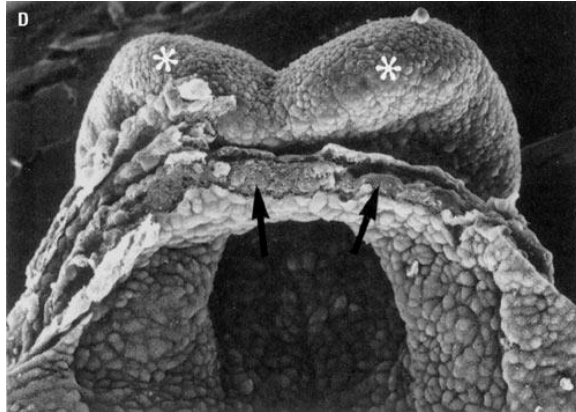


Takeuchi and Bruneau 2009  
Nature 459:708-11

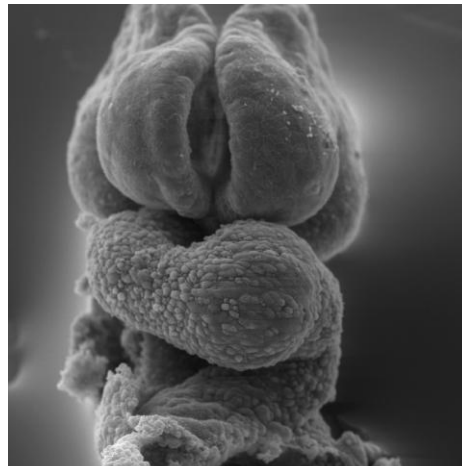
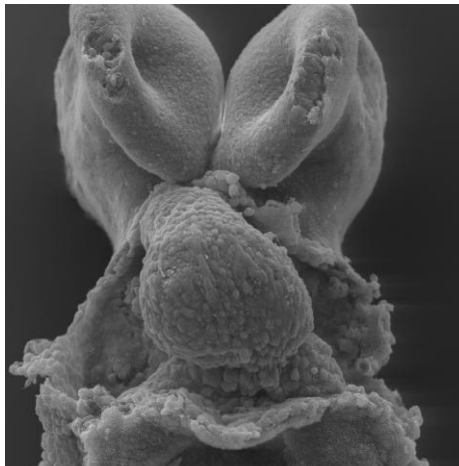


Kirby 2007  
Cardiac Development

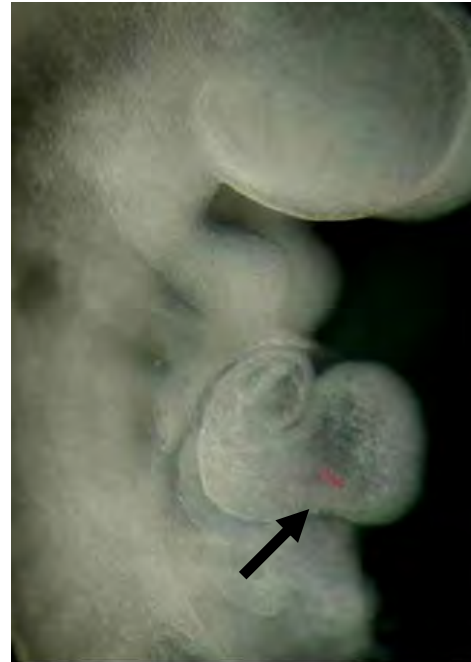
# From the cardiac crescent to the embryonic heart



Nature Reviews | Genetics

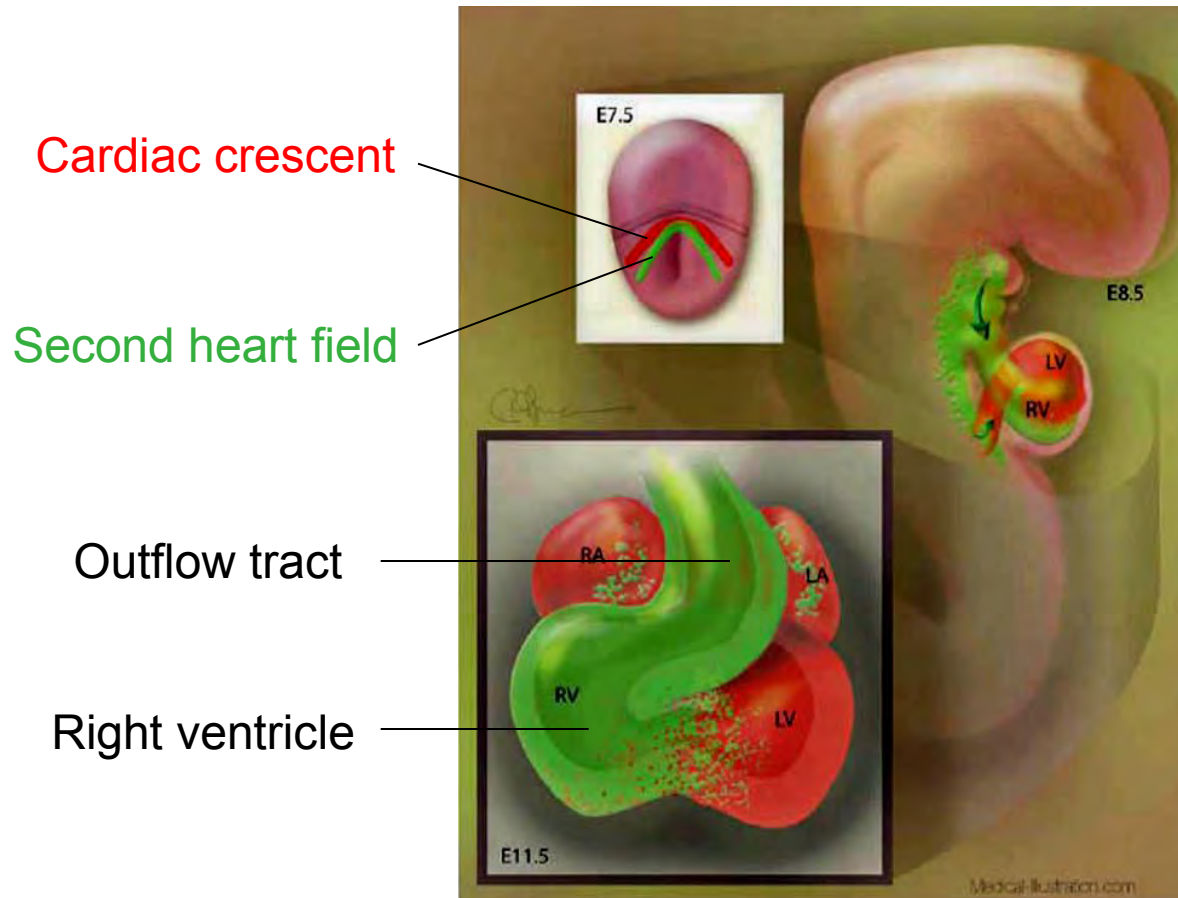


The right ventricle and outflow tract are added progressively to the elongating heart tube



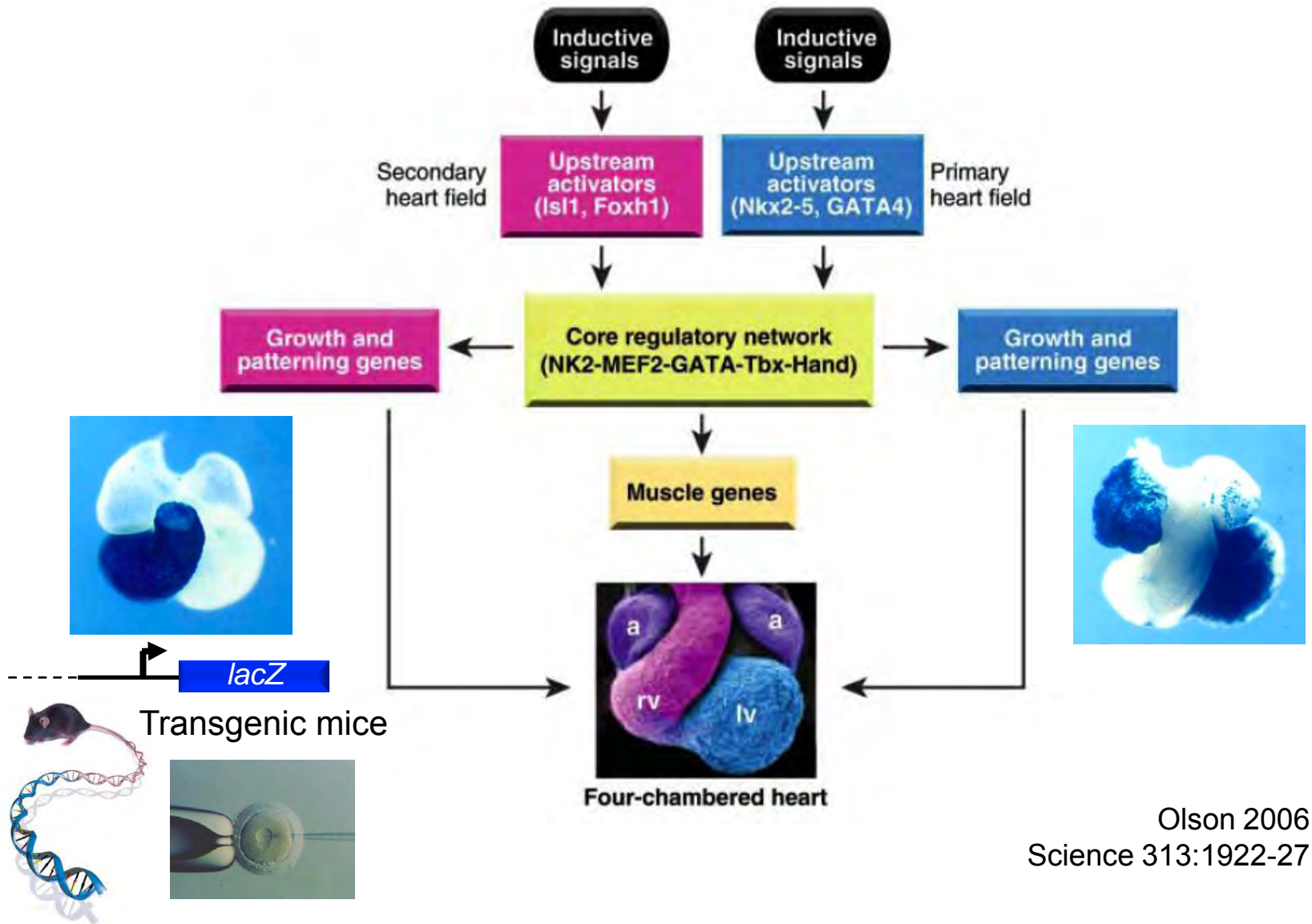
Dil labeling, 24hr embryo culture

# The second heart field



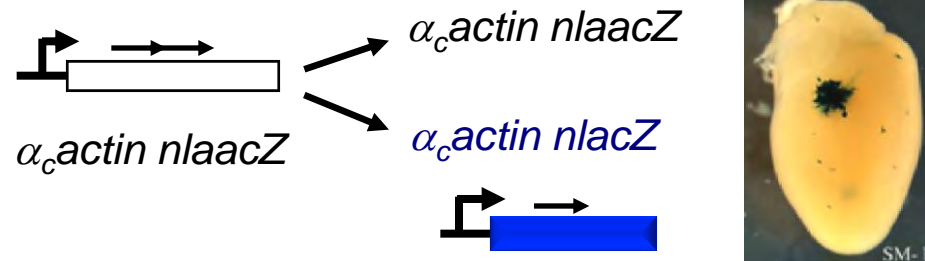
Parmacek and Epstein 2005  
Cell 120:295-298

# Transcriptional programs in the first and second heart field



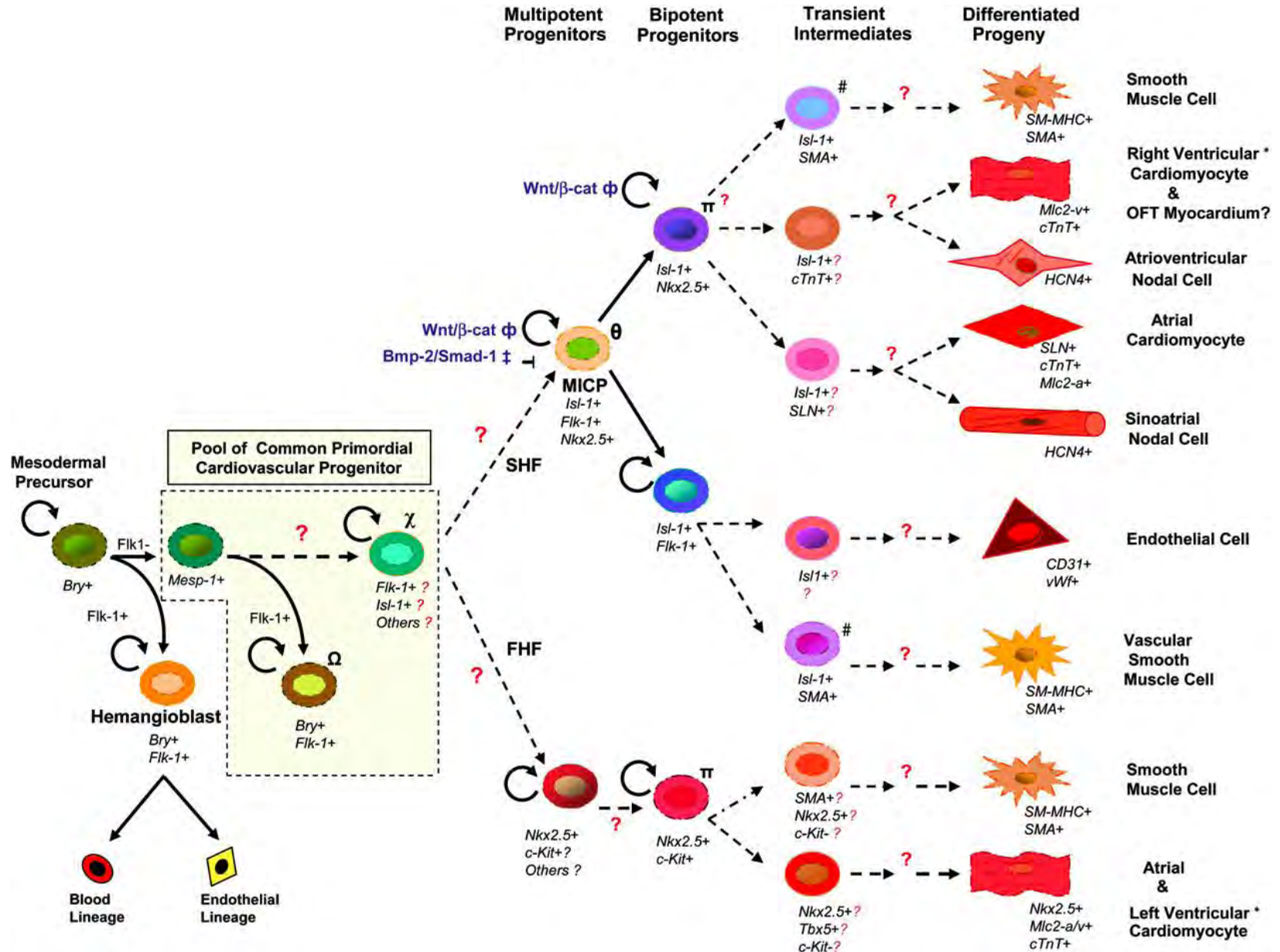
Olson 2006  
Science 313:1922-27

# Clonal analysis in the embryonic heart



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

# Cardiac progenitor cell lineages



# Gene expression in the second heart field

*Fgf10*



E8.5

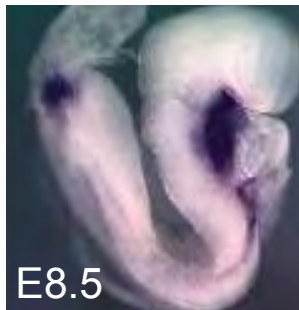


*Fgf10 lacZ*



*Pitx2c*

*Isl1*



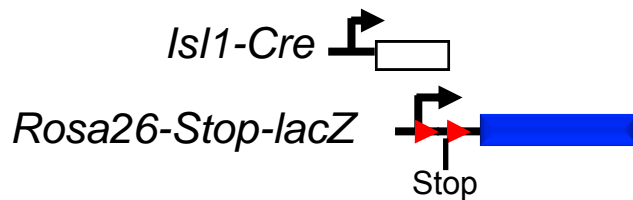
E8.5



Wildtype



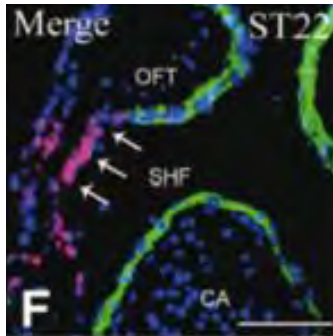
*Isl1*<sup>-/-</sup>



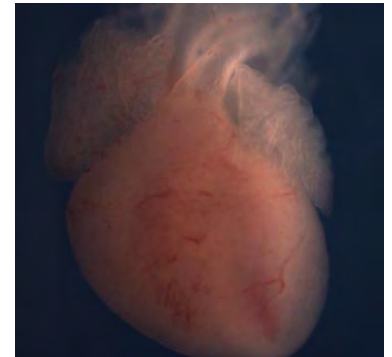
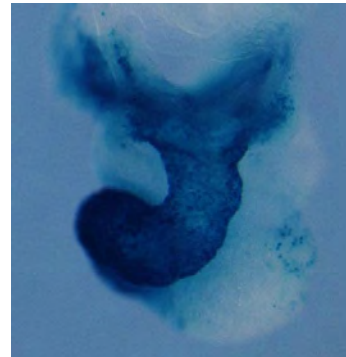
Cai *et al.* 2003  
Dev Cell 5:877-89

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

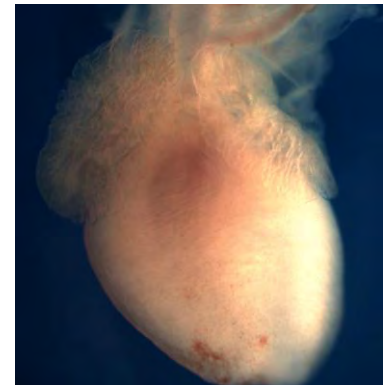
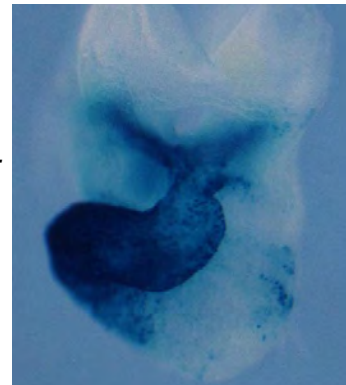
*Tbx1*



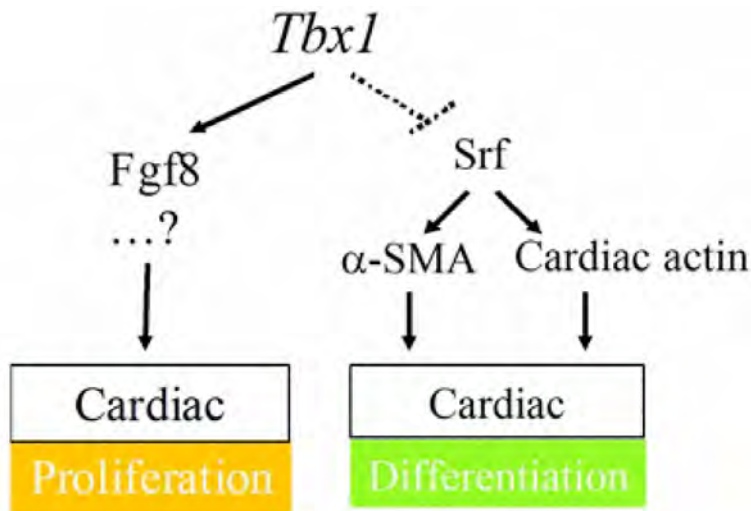
*Tbx1*<sup>+/-</sup>



*Tbx1*<sup>-/-</sup>

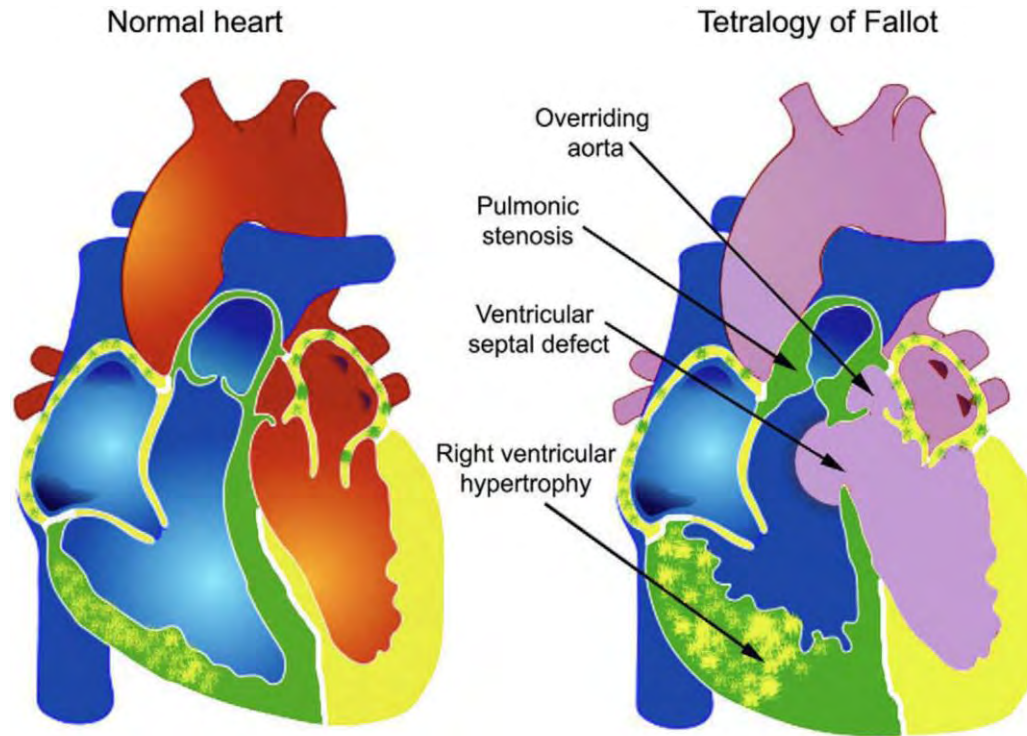


*Fgf10 lacZ*



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

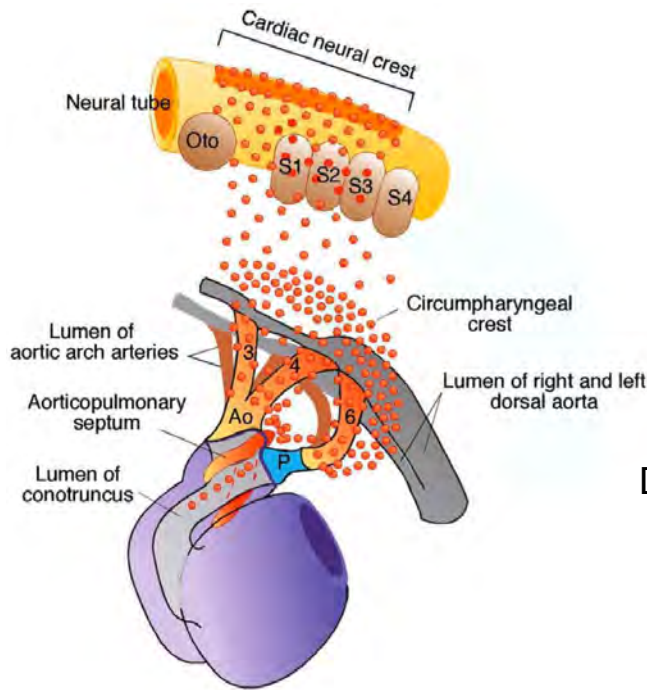
# The second heart field and conotruncal congenital heart defects



Secondary heart field  
Primitive heart tubes

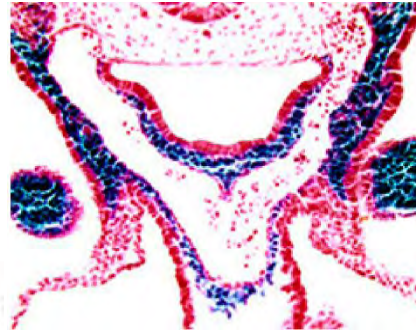
Di Felice and Zummo 2009  
Trends Cardiovasc Med 19:130-5

# The second heart field and cardiac neural crest cells

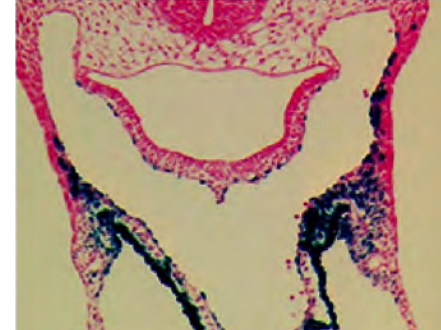


Hutson and Kirby, 2007  
Sem Cell Dev Biol

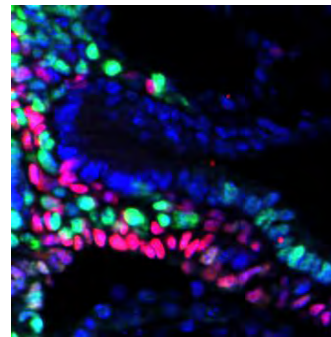
*Wnt1-Cre R26R*



*Fgf10 lacZ*

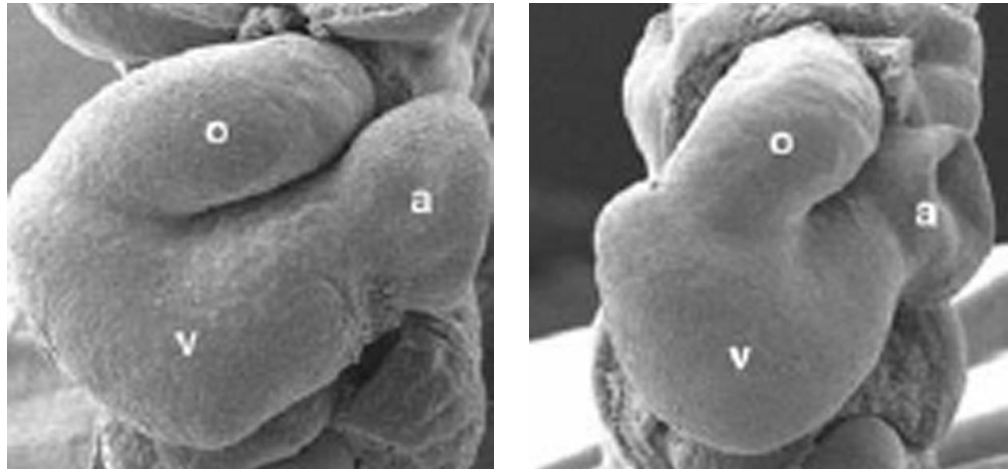


Jiang *et al.* 2000  
Development 127:1607-16

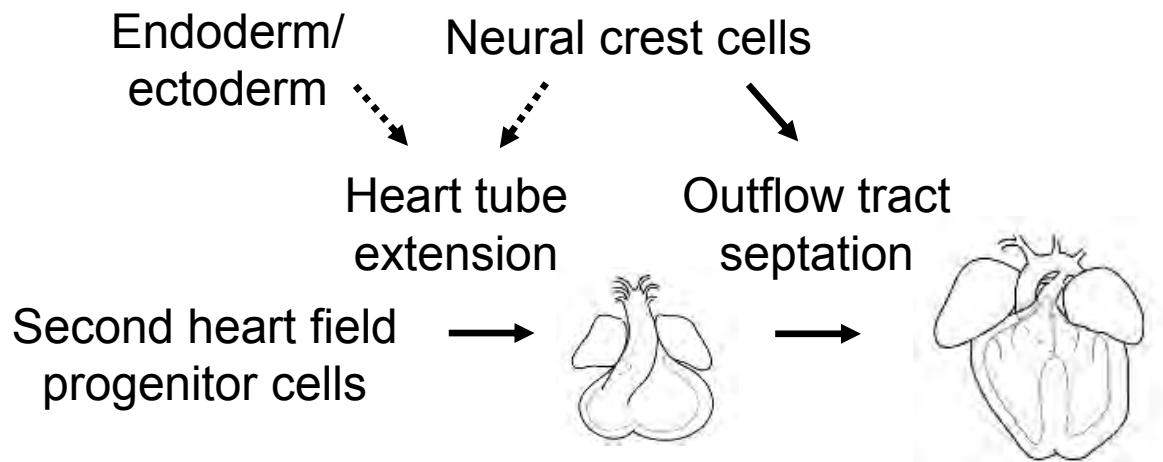


■ Neural crest  
■ Mesoderm

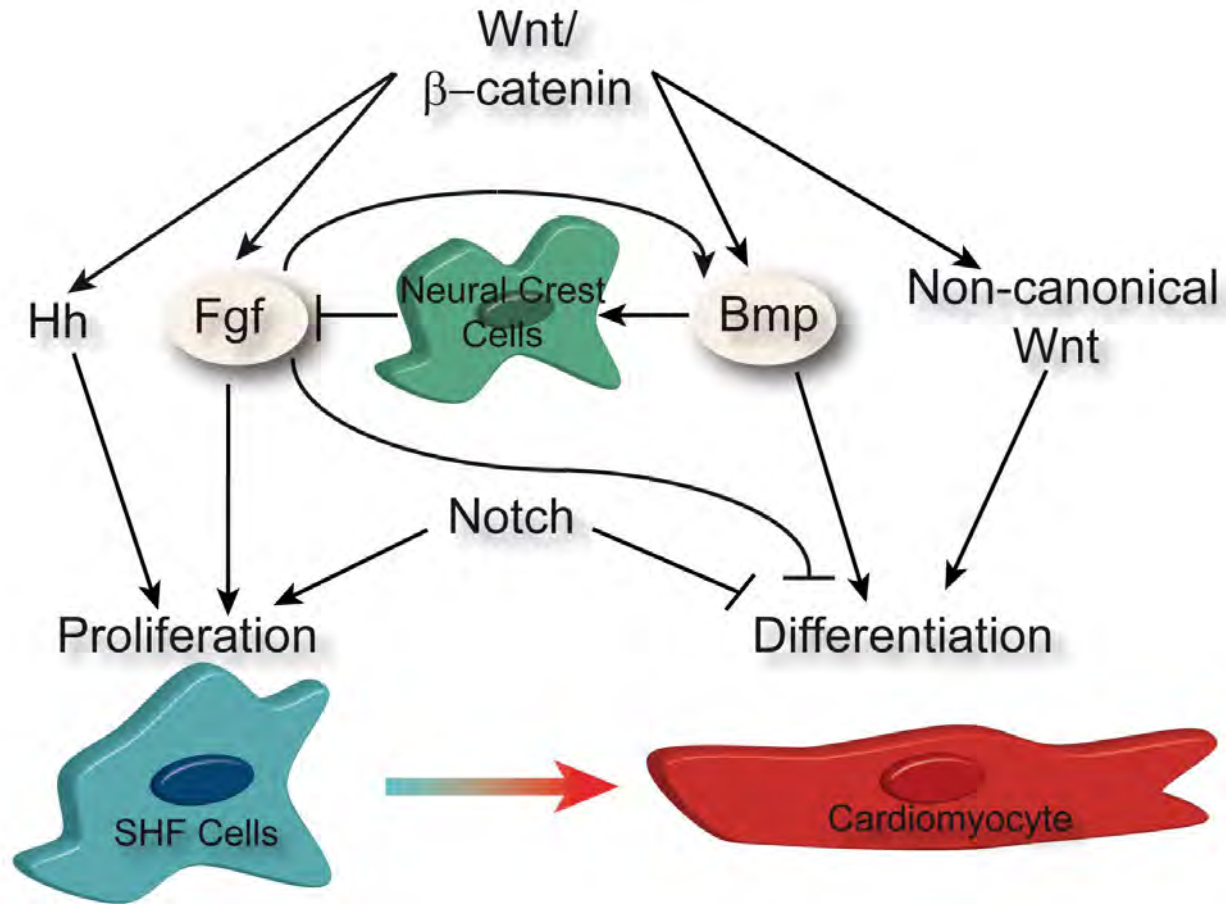
# Ablation of the cardiac neural crest impairs second heart field development



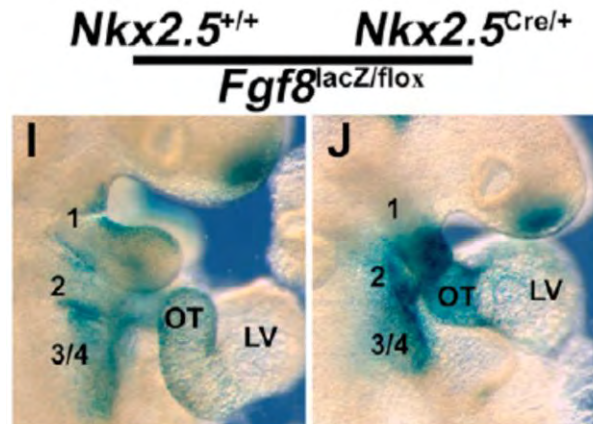
Yelbuz et al, 2002  
Circulation 106:504-10



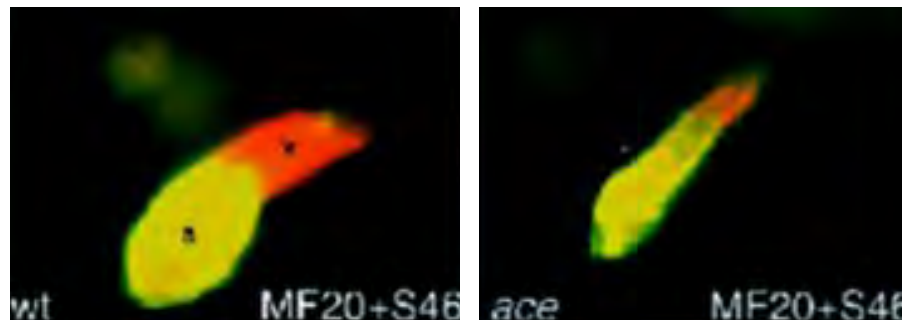
# Signaling pathways controlling second heart field development



# Fgf8 is required for second heart field and outflow tract development

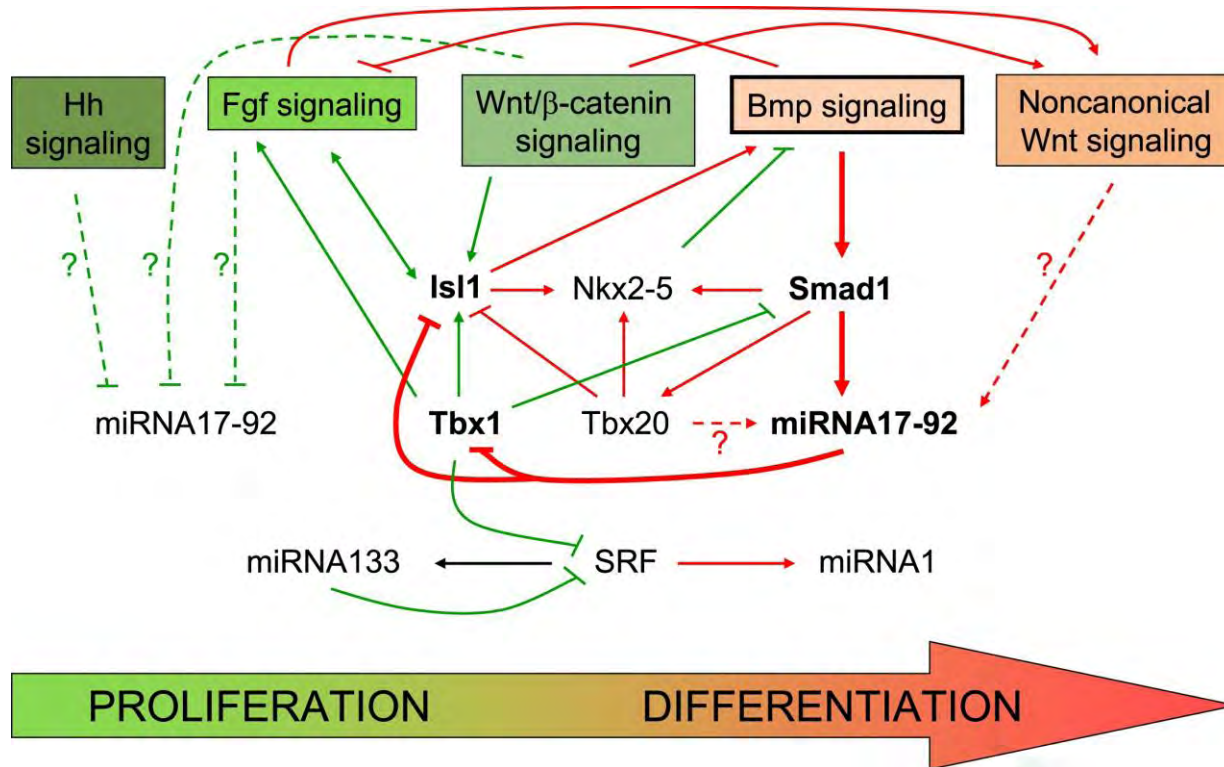


Ilagan *et al.* 2006  
Development 133:2435-45



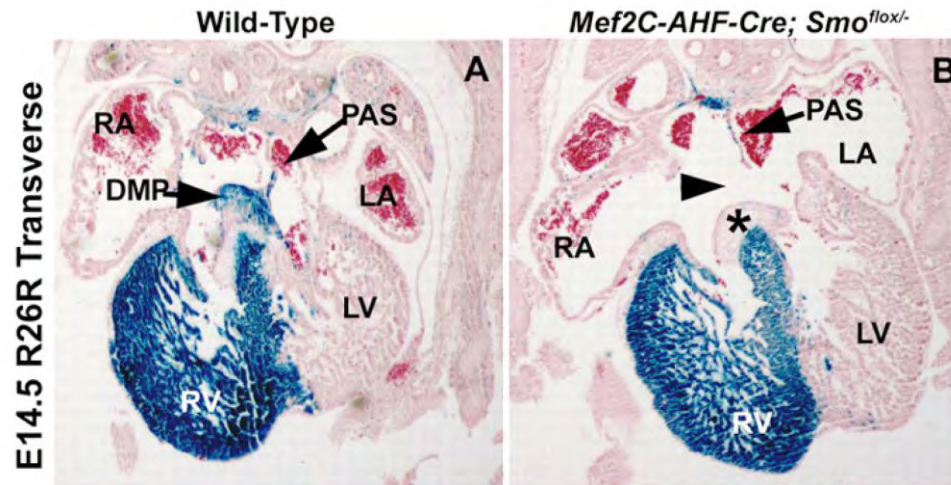
Reifers *et al.* 2001  
Development 126:225-35

# Regulation of second heart field differentiation by microRNAs

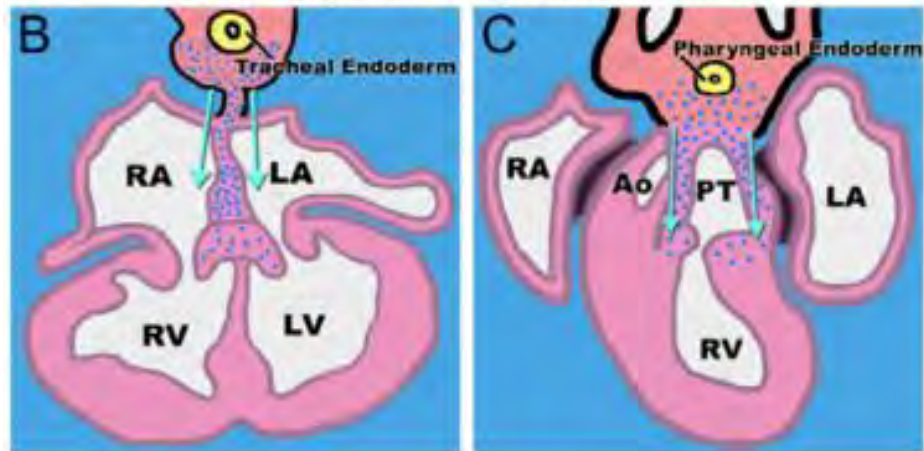


Wang et al 2010  
Dev Cell 19:903-12

# Second heart field contribution to atrial and AV septation

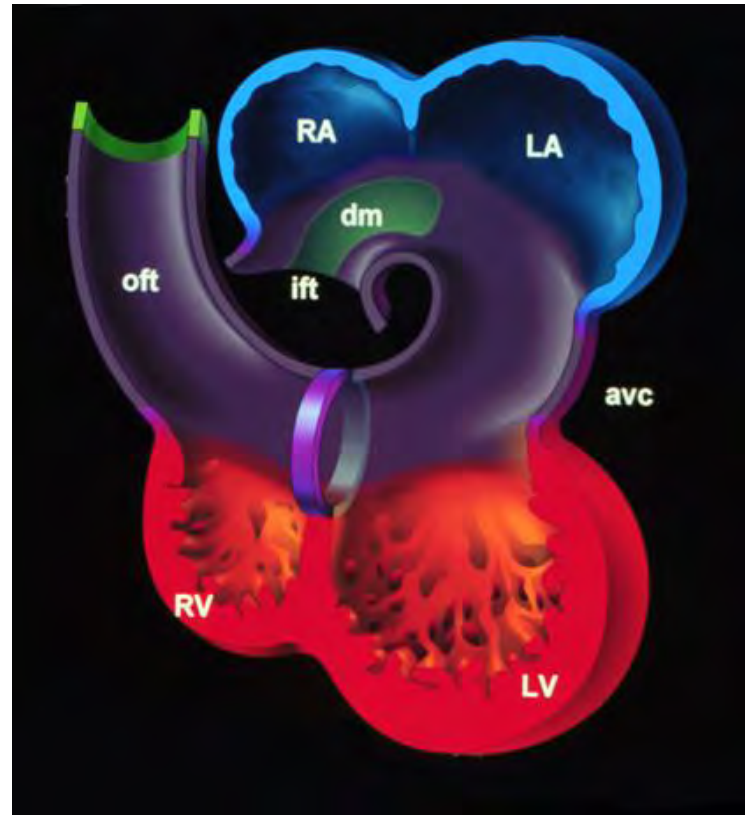


E9-E11 Migration of Hh Responsive cells



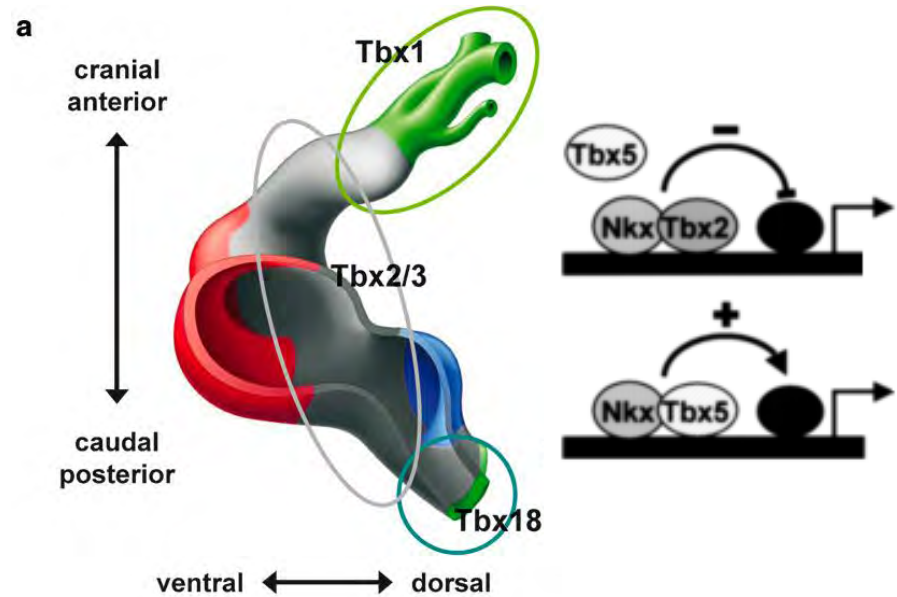
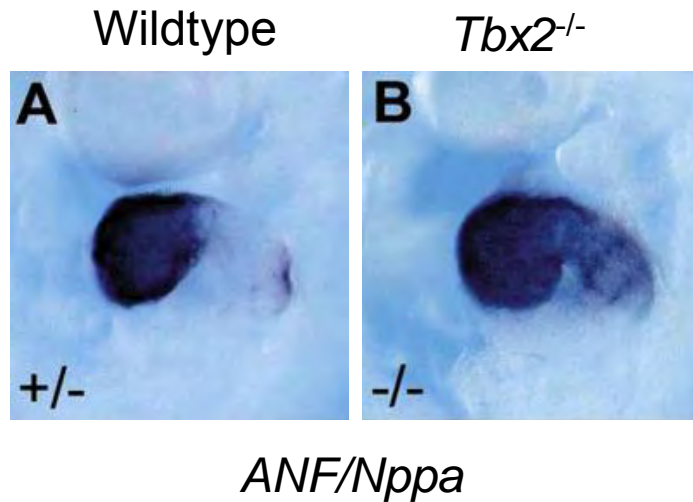
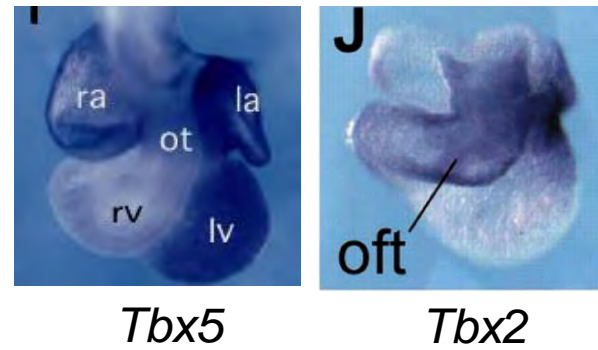
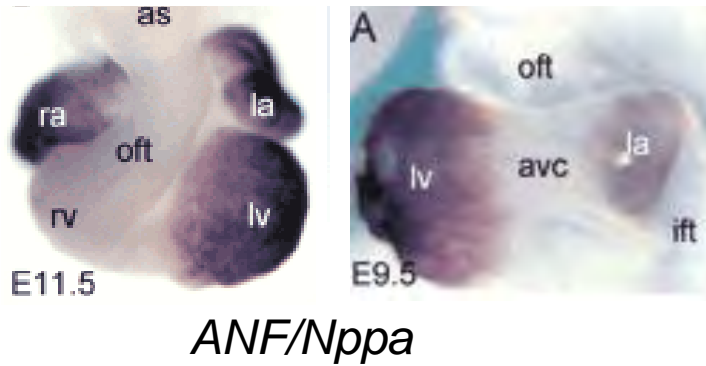
Hoffman et al 2009  
Development 136:1761-70

# Cardiac chamber formation: the ballooning model

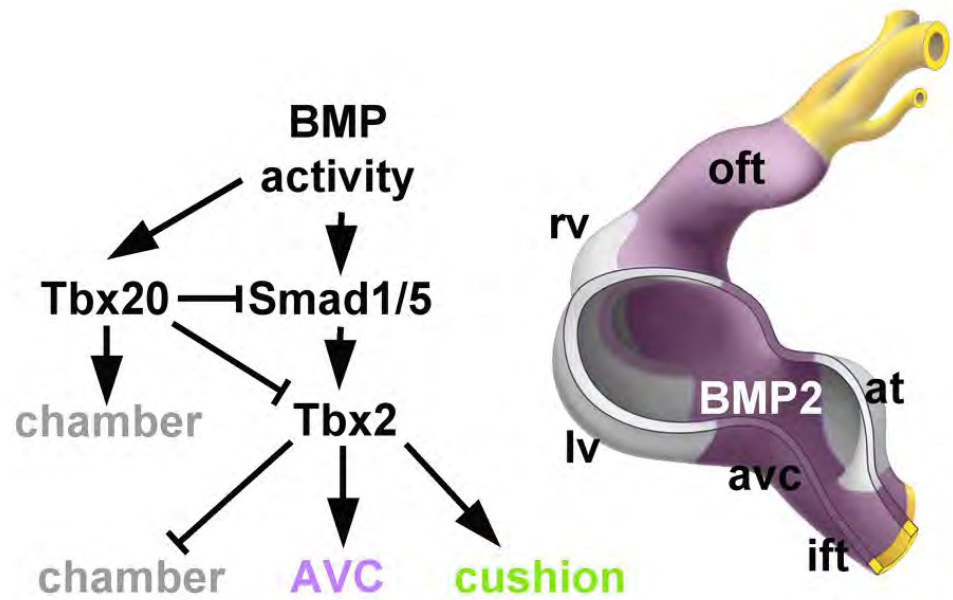
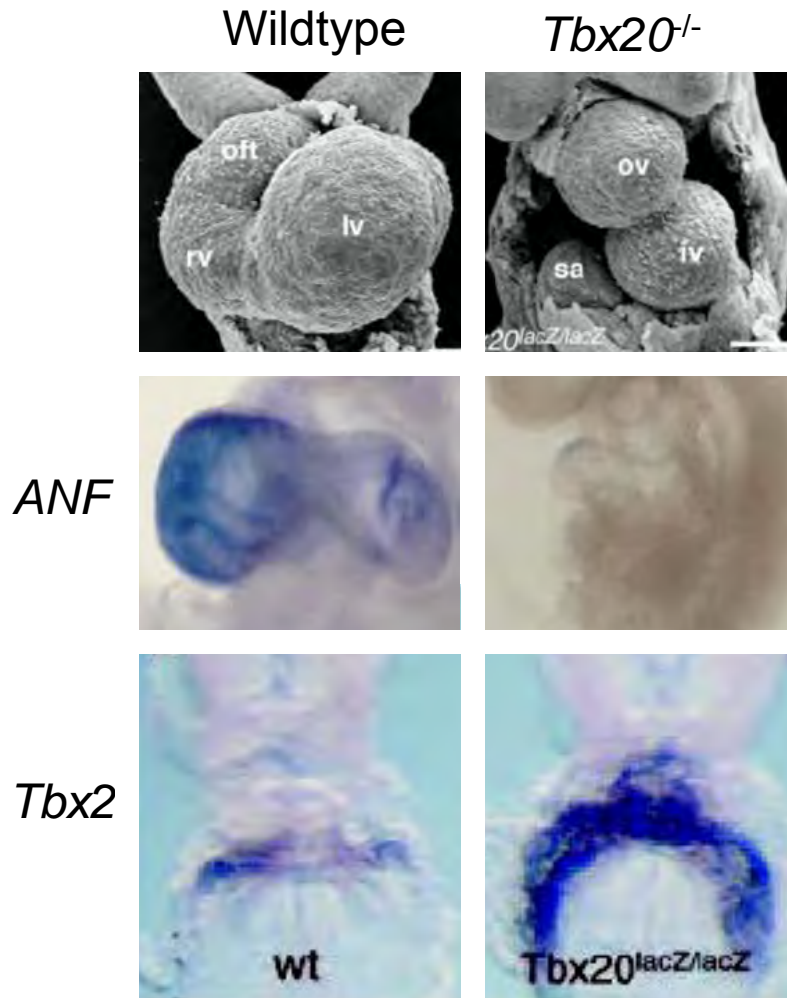


Hoogaars et al. 2007  
Cell Mol Life Sci 64:646-660

# Differential gene expression during chamber formation

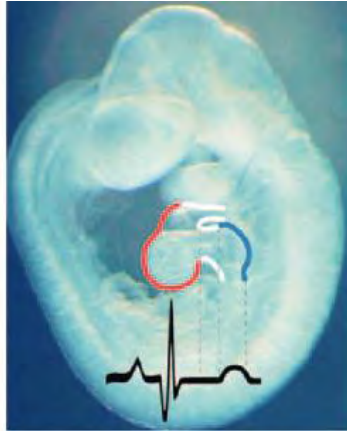


# A T-box gene network regulates chamber formation

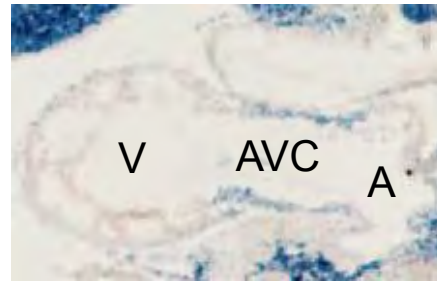


Singh et al. 2009  
Circ Res 105:442-52

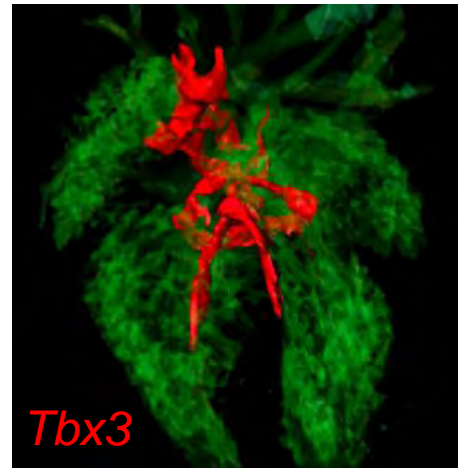
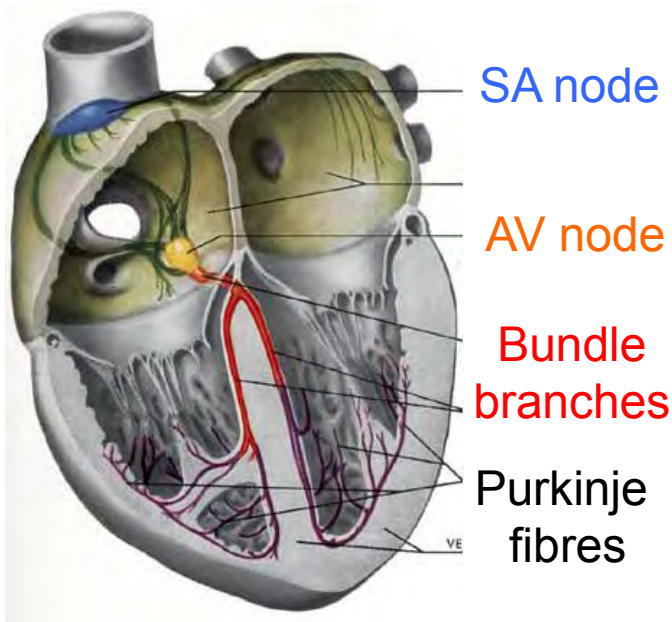
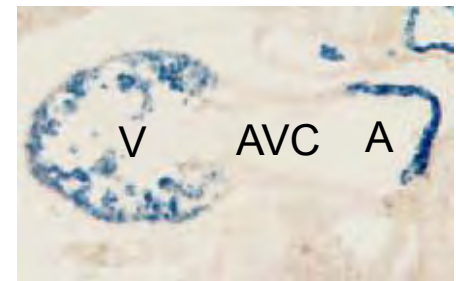
# Conduction system development



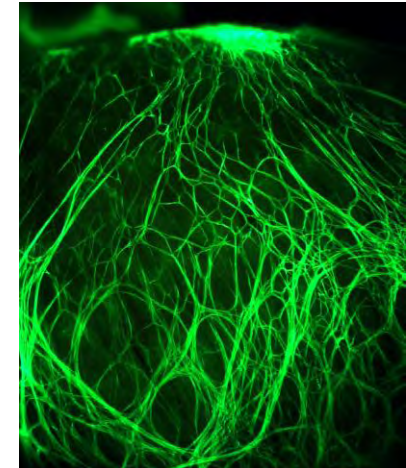
*Tbx3*



*Cx40*



Central conduction system: AV node

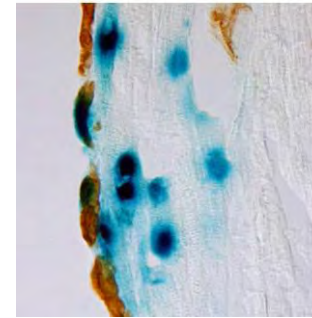
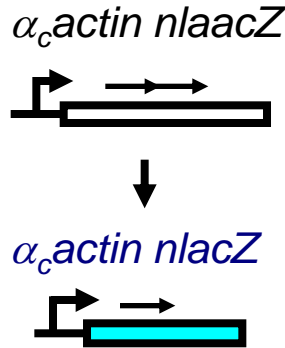
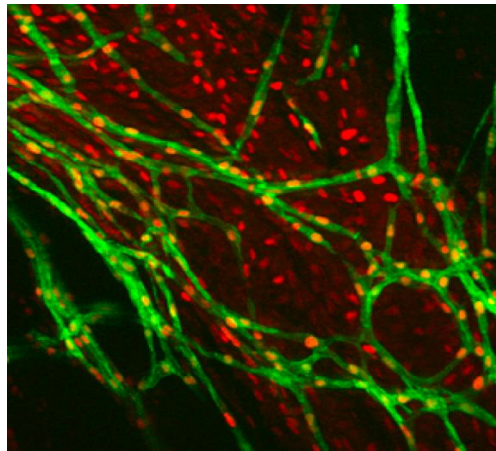


*Cx40 GFP*

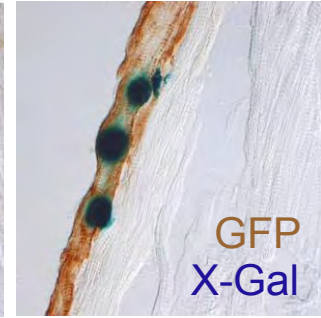


Purkinje fibre network

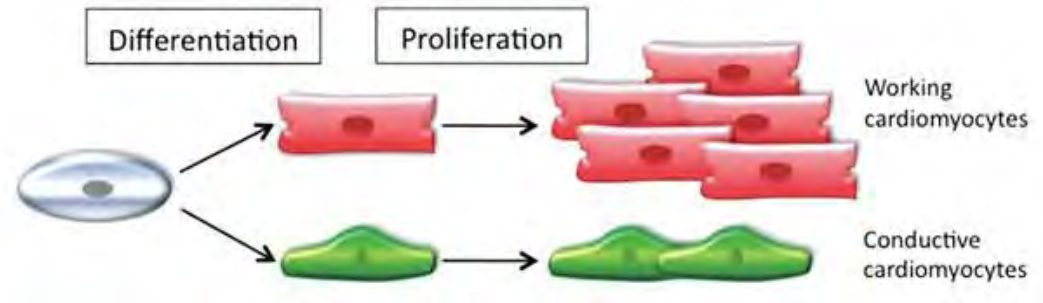
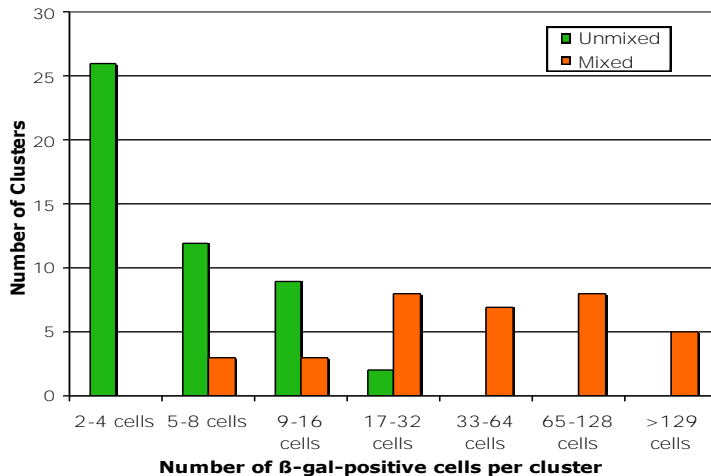
# Clonal analysis of the origin of the ventricular conduction system



Mixed clone

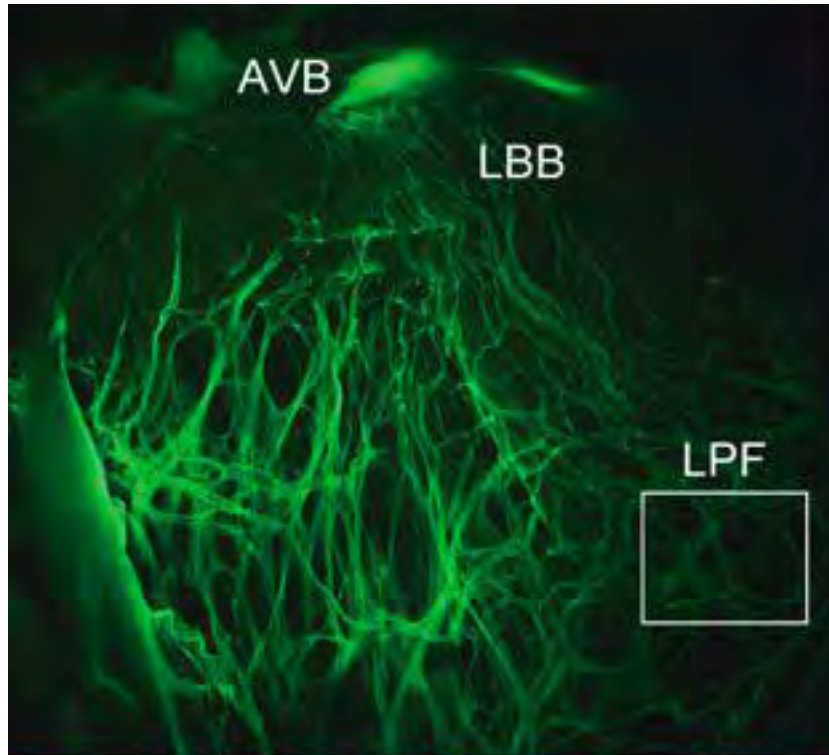


Unmixed clone

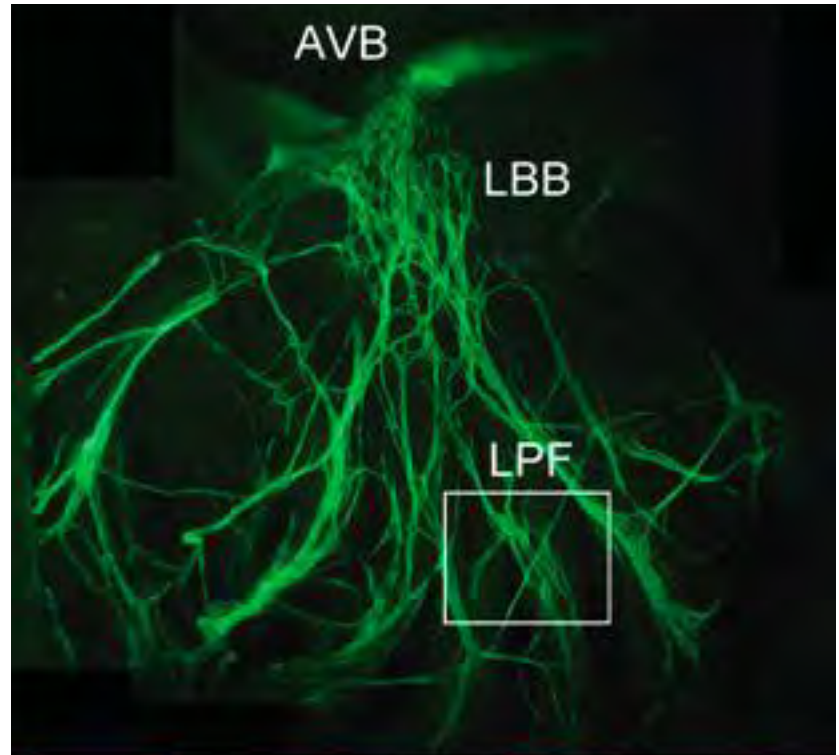


- Biphasic development of the conduction system – specification from a common progenitor followed by outgrowth

# Purkinje fibre hypoplasia in *Nkx2.5* haploinsufficient hearts

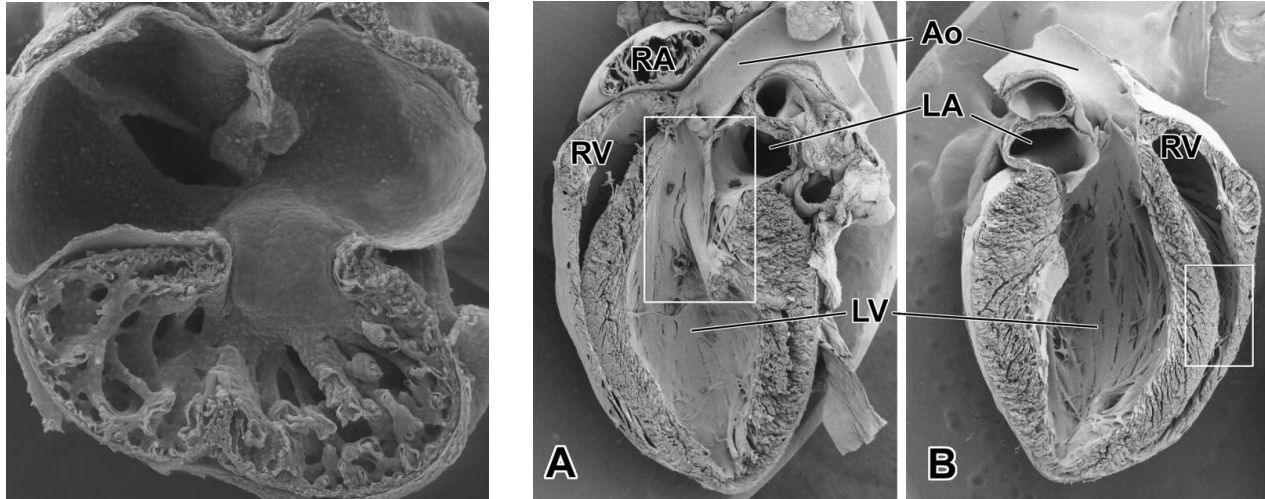


*Cx40<sup>eGFP</sup>*

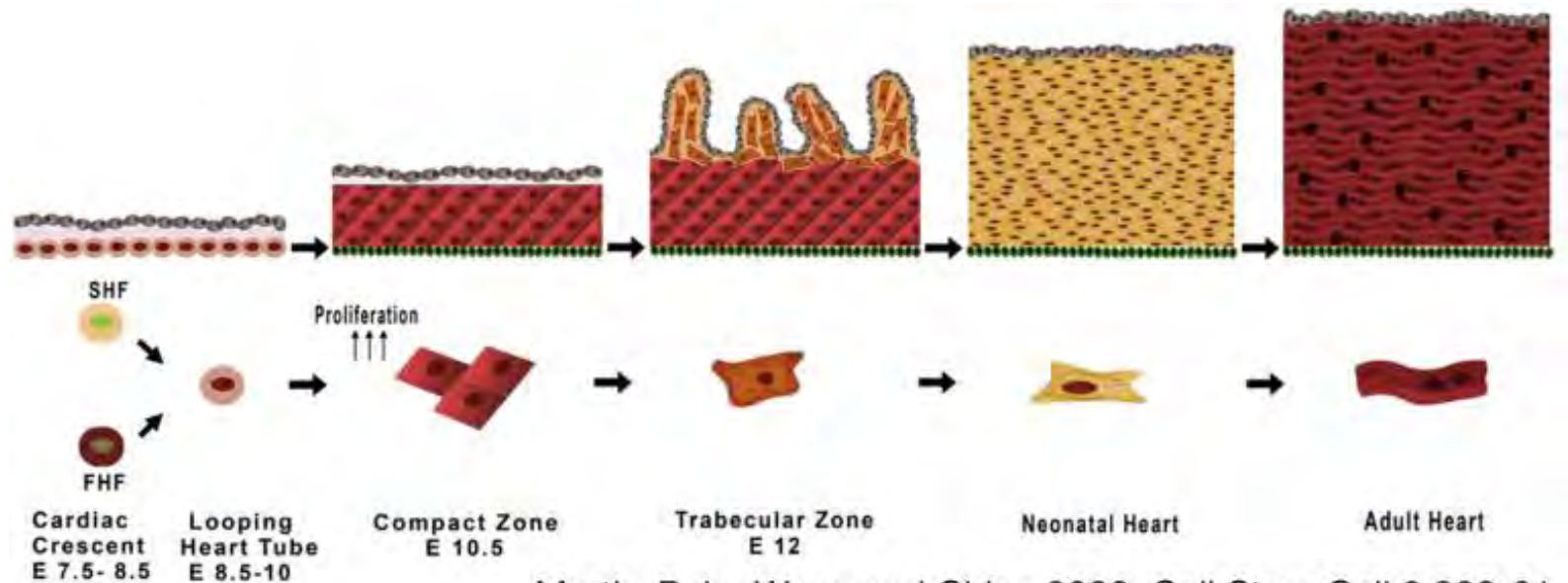


*Cx40<sup>eGFP</sup>;Nkx2.5<sup>+/-</sup>*

# Ventricular growth

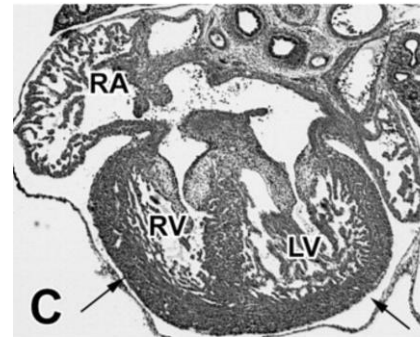
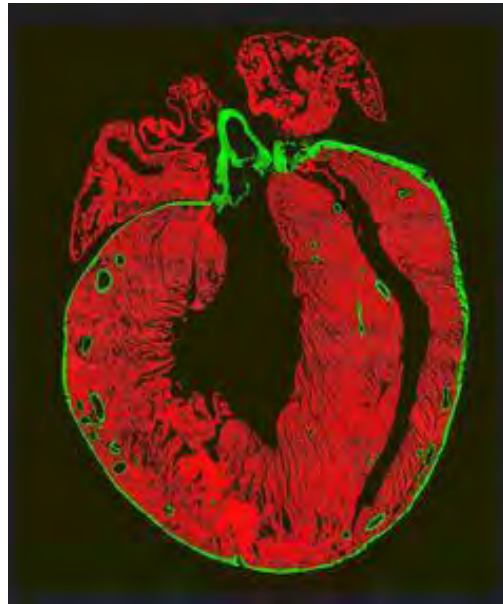


Wessels and Sedmera, 2003  
 Physiol. Genomics 15: 165-176

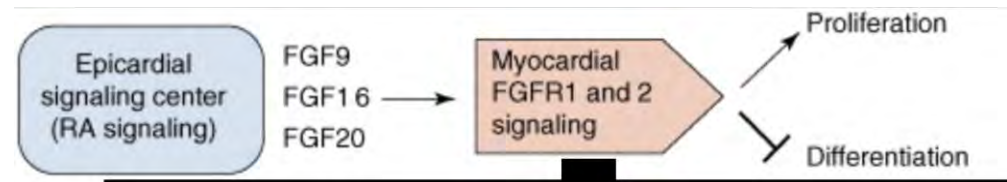
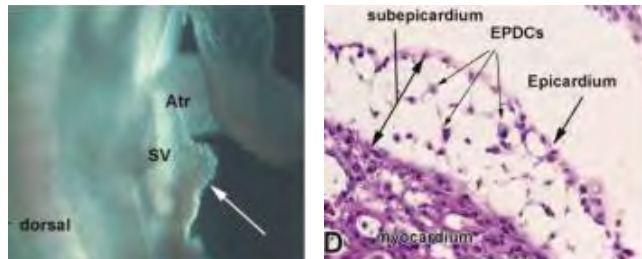
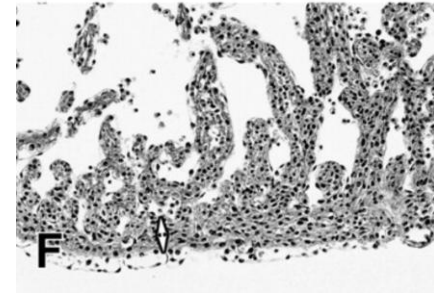
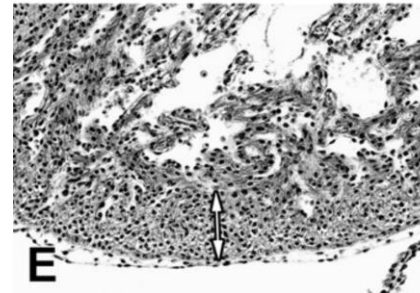
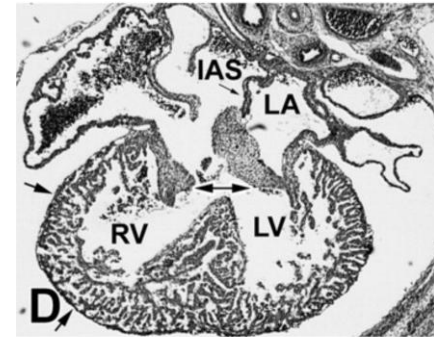


Martin-Puig, Wang and Chien 2008, Cell Stem Cell 2:320-31

# The epicardium regulates ventricular growth

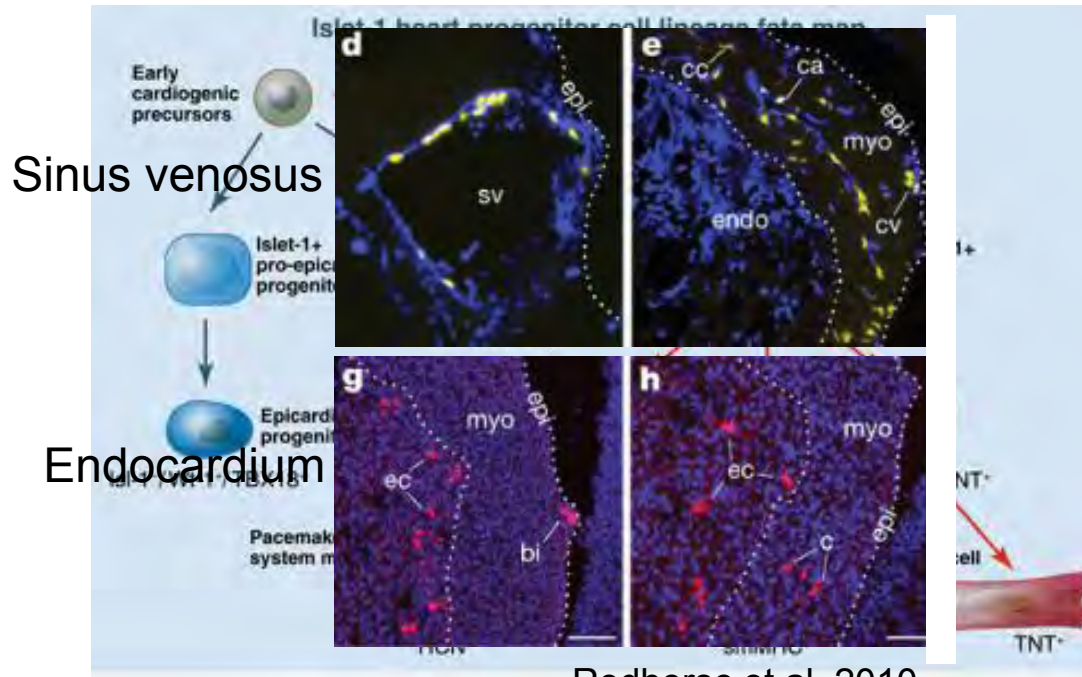


RXR $\alpha$ <sup>-/-</sup>

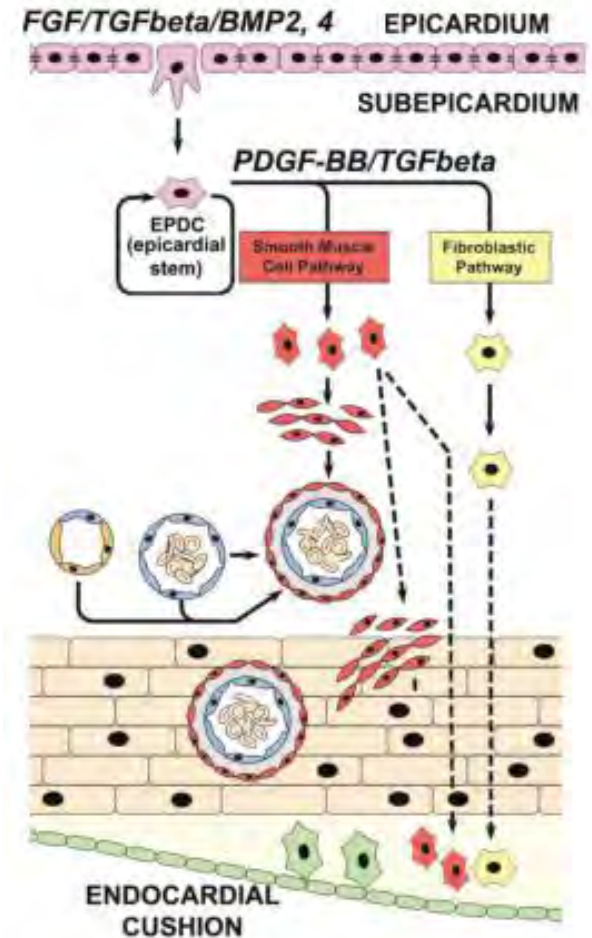


Wessels and Sedmera, 2003  
 Physiol. Genomics 15: 165-176

# Fate of the epicardium and origin of the coronary vasculature



Redhorse et al. 2010  
Chien et al. 2008 Science 322:1494-7



Epicardial-derived cells

Cardiac fibroblasts

Smooth muscle cells

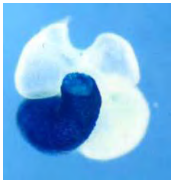
? Myocardium

? Coronary endothelial cells

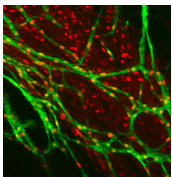
# Heart Development



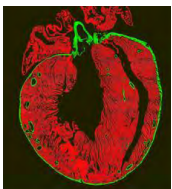
- The second heart field is a population of cardiac progenitor cells in pharyngeal mesoderm



- 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.
- Srivastava D. Making or breaking the heart: from lineage determination to morphogenesis. Cell. 2006 126:1037-48.
- **Cardiovascular Research – Spotlight issue on Cardiac Development, July 2011**

Weinstein Cardiovascular Development Meeting, USA, May

**ESC WG on Developmental Anatomy and Pathology**

**Annual meeting – Liblice, Prague, September 22-25, 2011**



Developmental Biology Institute of Marseilles - Luminy



**Inserm**



EU networks  
Heart Repair  
CardioGeNeT

