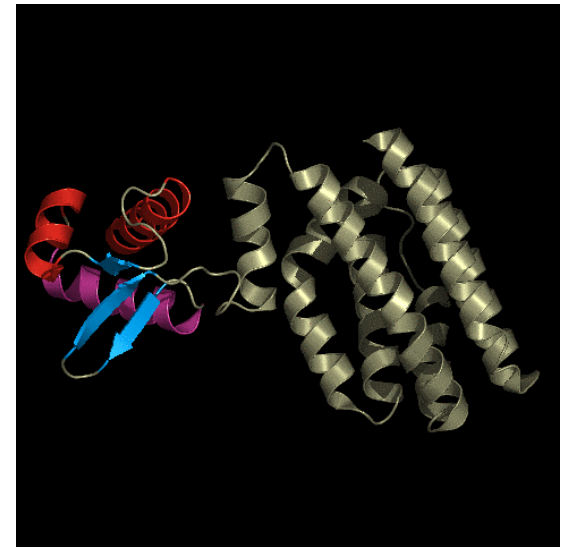


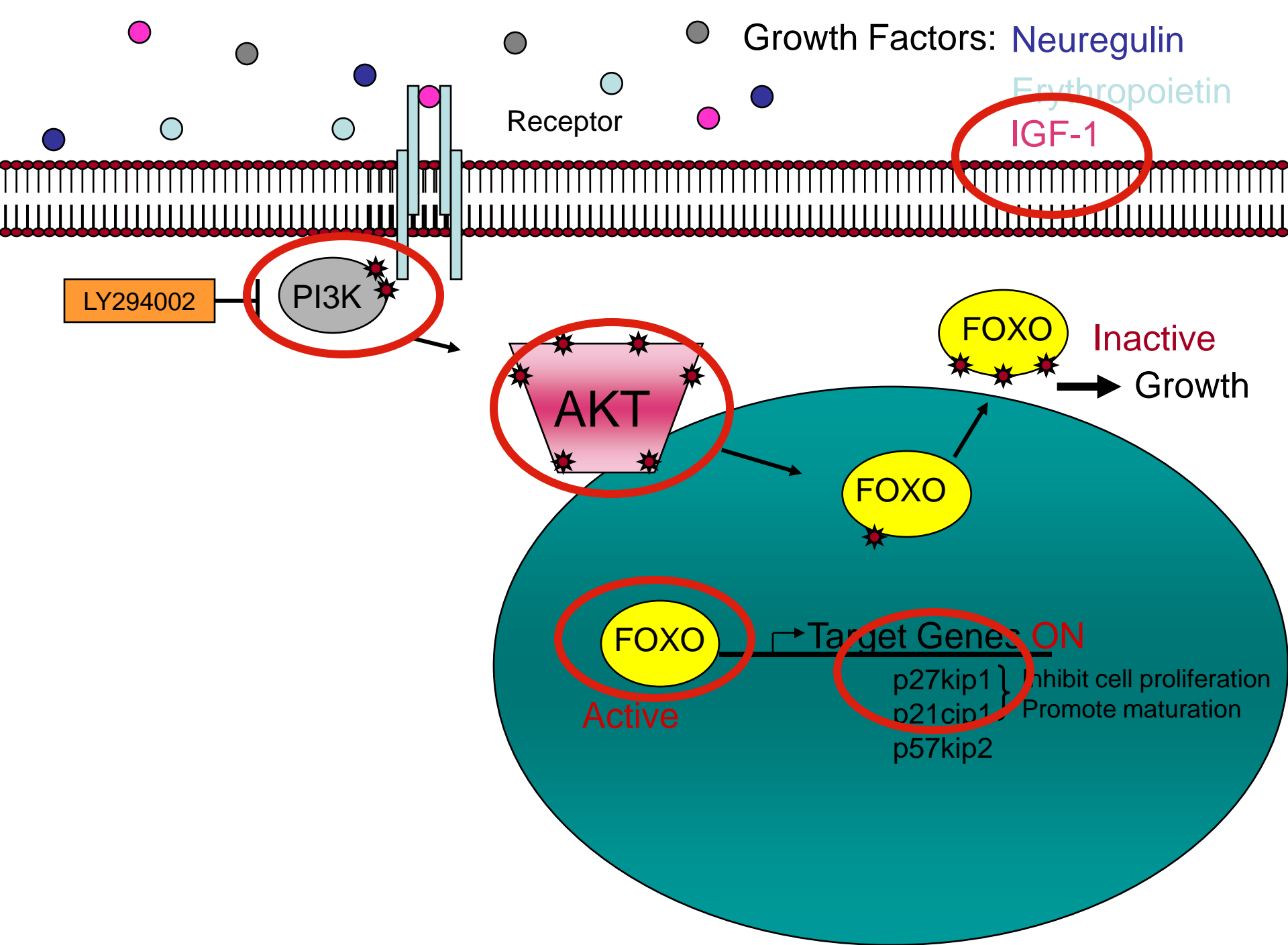
**Loss of FoxO1 in endothelial
cells causes decreased cardiac
myocyte proliferation during
heart development**

**Heather Evans-Anderson, PhD
Winthrop University**

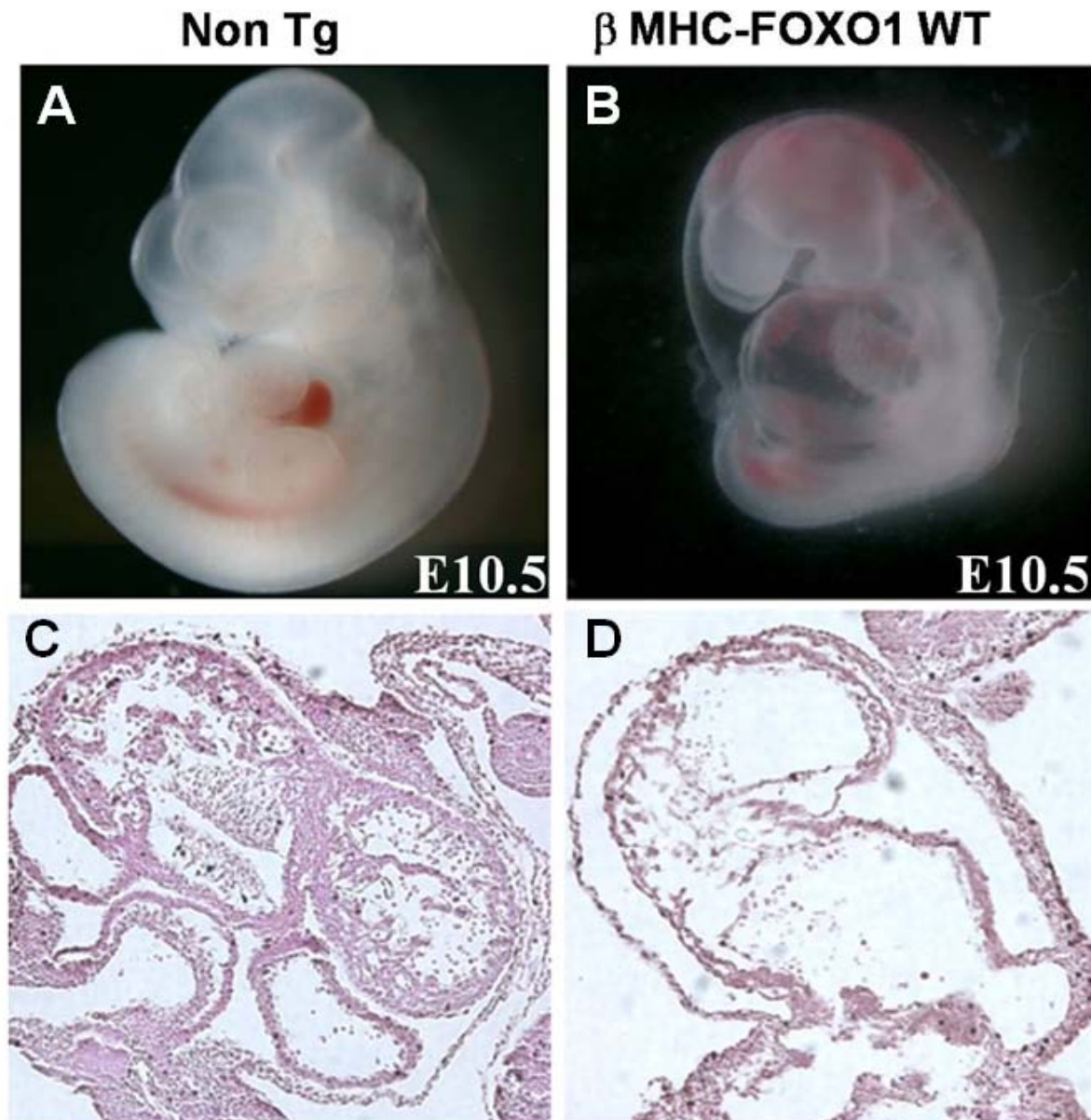
FOX Genes

- Named for Forkhead, winged-heliX DNA-binding domain, 17 subclasses
- FoxO (-1, -3a, and -4) are transcription factors that trigger apoptosis, regulate cell cycle events, and metabolic functions. (consensus DNA binding site = AAACA)
- FoxO's are substrates for AKT. AKT regulates activity by phosphorylation of FoxO's inducing nuclear exclusion.
- Fox01 KO are embryonic lethal at ED10.5 due to defective angiogenesis





Transgenic FOXO1 WT expression in cardiac myocytes causes lethality at E10.5



*Evans Anderson et al,
Circ Res, 2008*

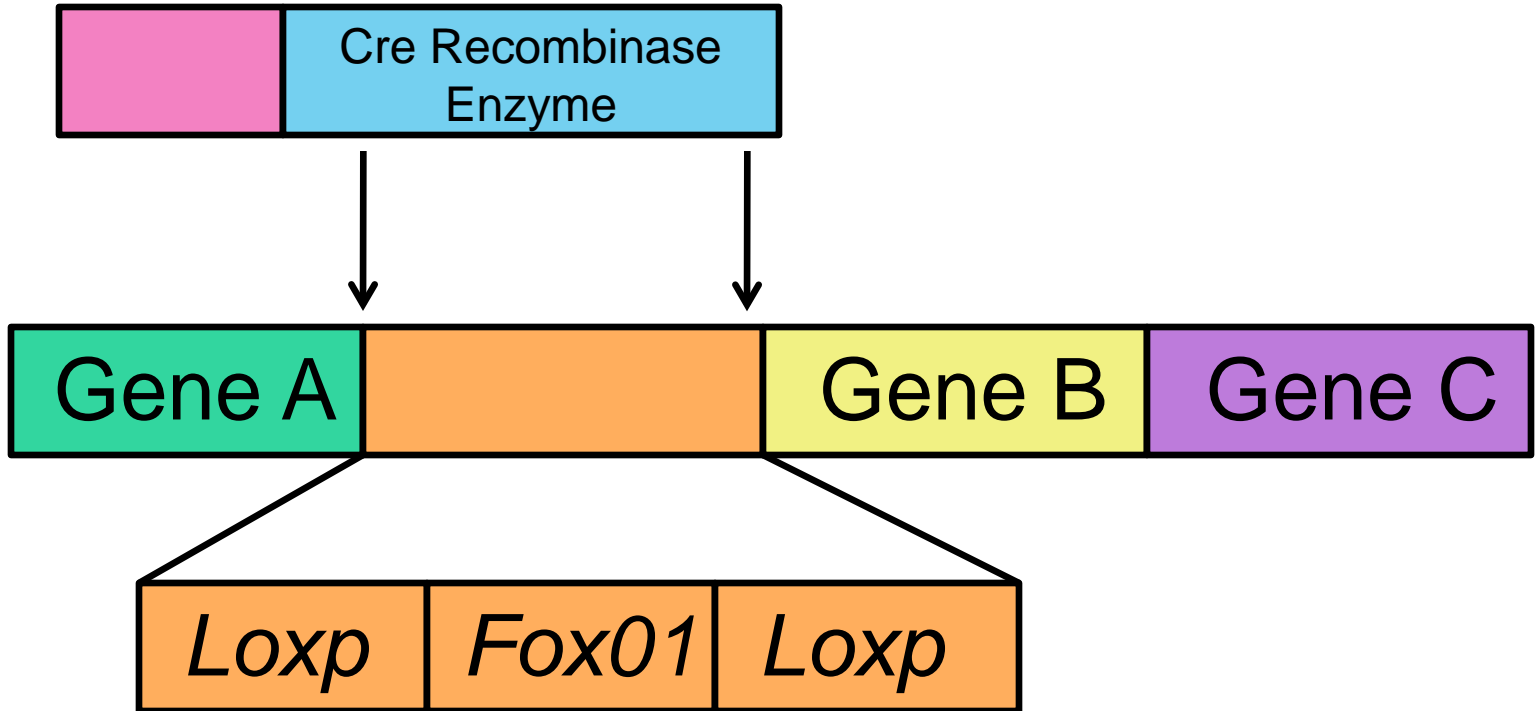
Conditional Knockout Strategy

NKX 2.5

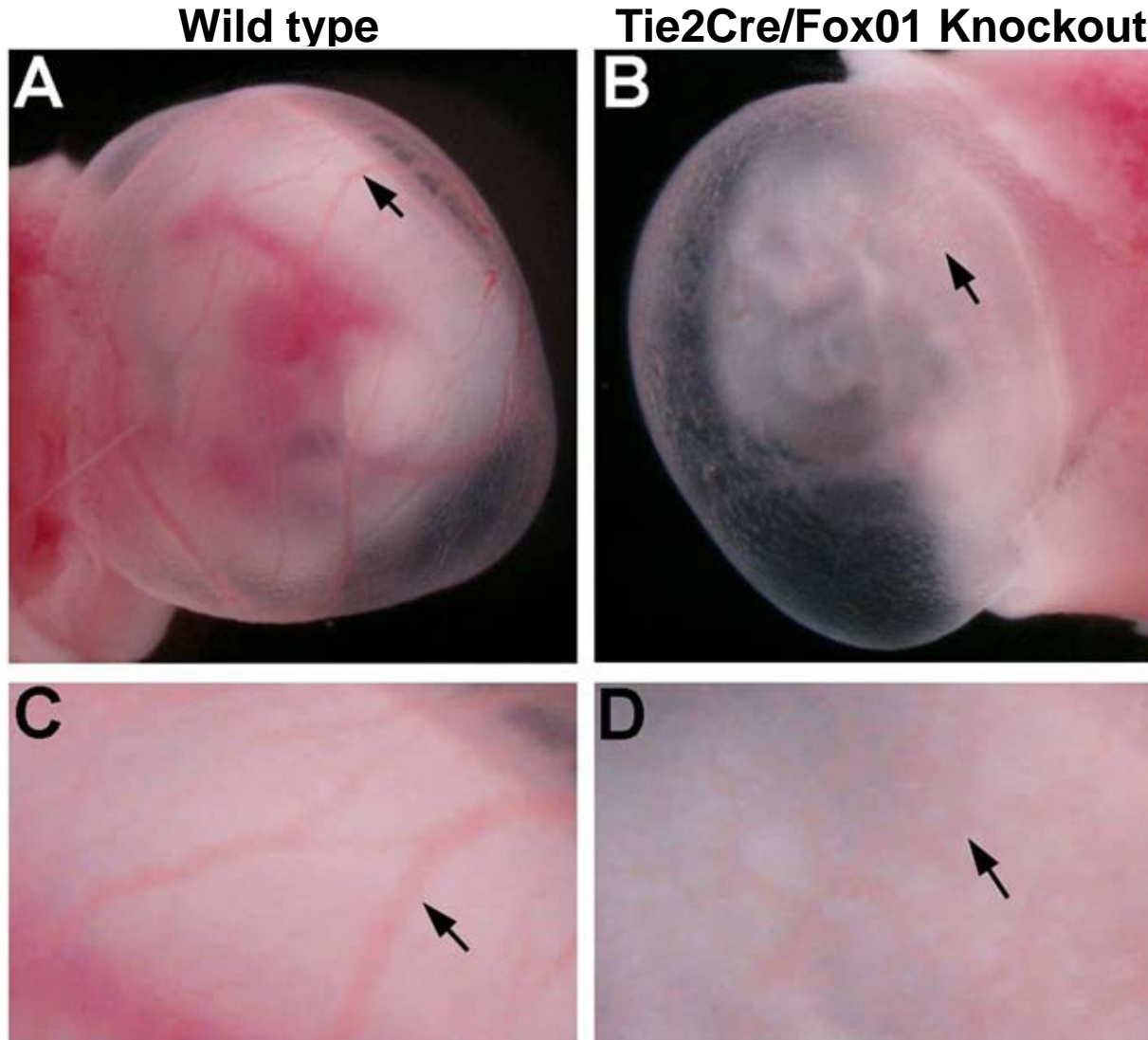
β MHC

α MHC

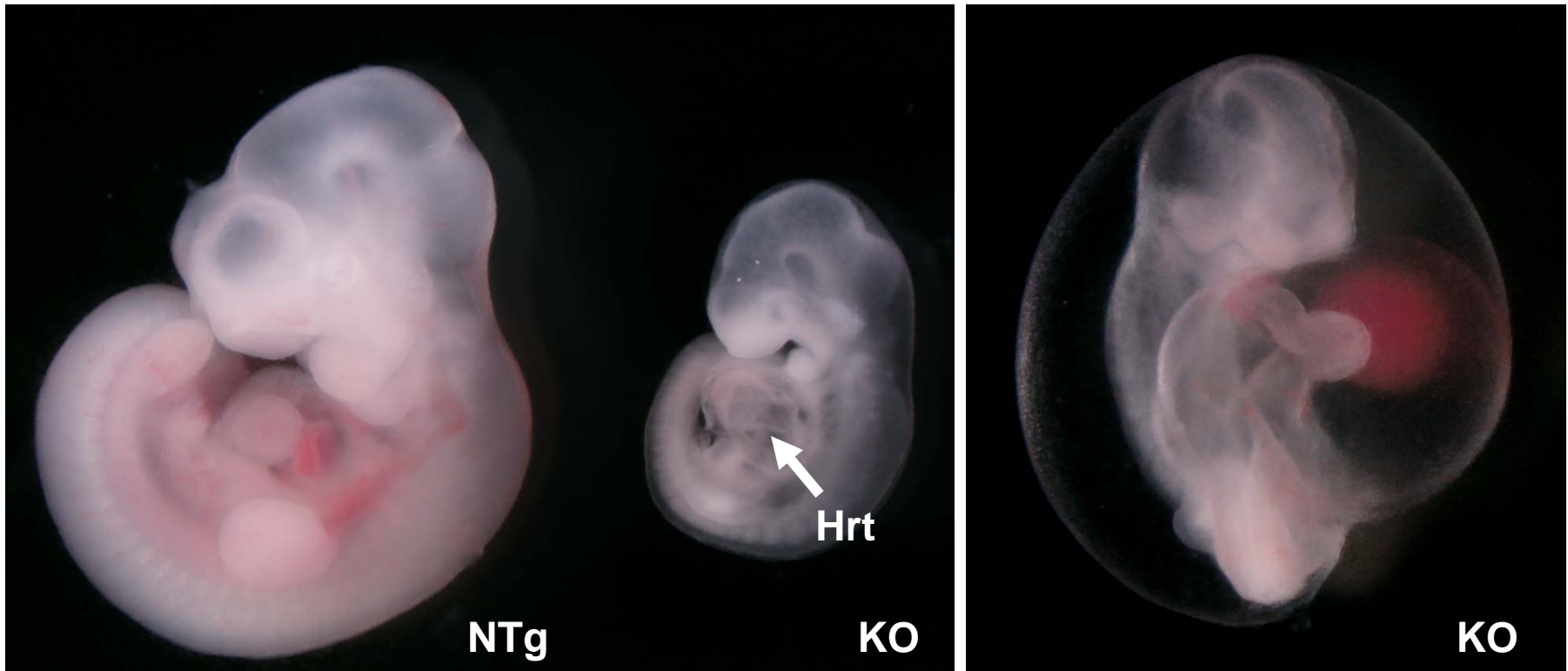
Tie 2 Cre



Tie 2 $Cre^{+/-}/FoxO1^{f/f}$ embryos exhibit yolk sac vascular failure at E10.5



Tie2Cre/Fox01 knockout mice display gross morphological defects

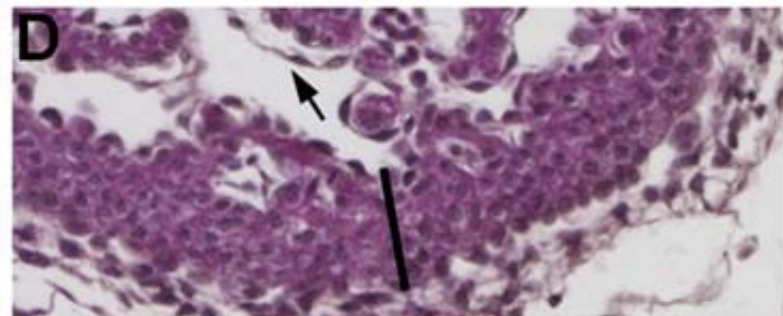
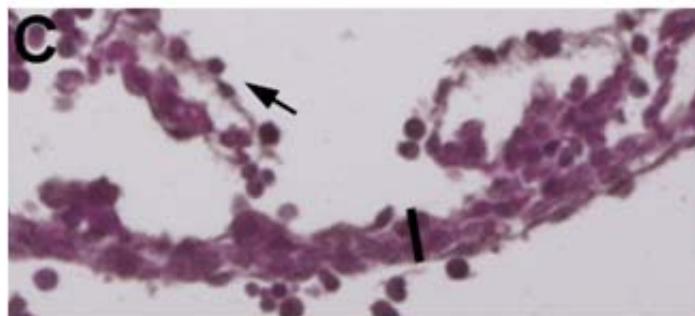
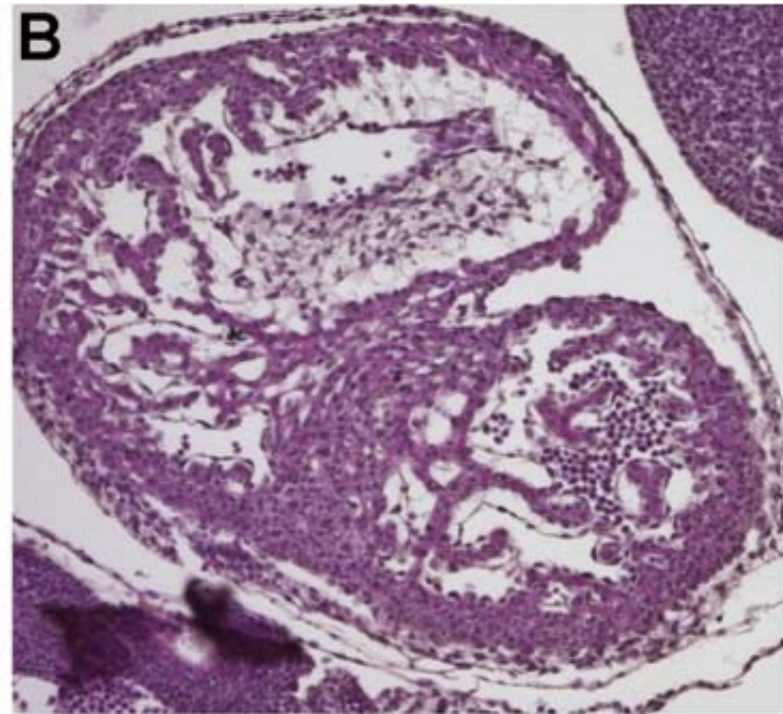
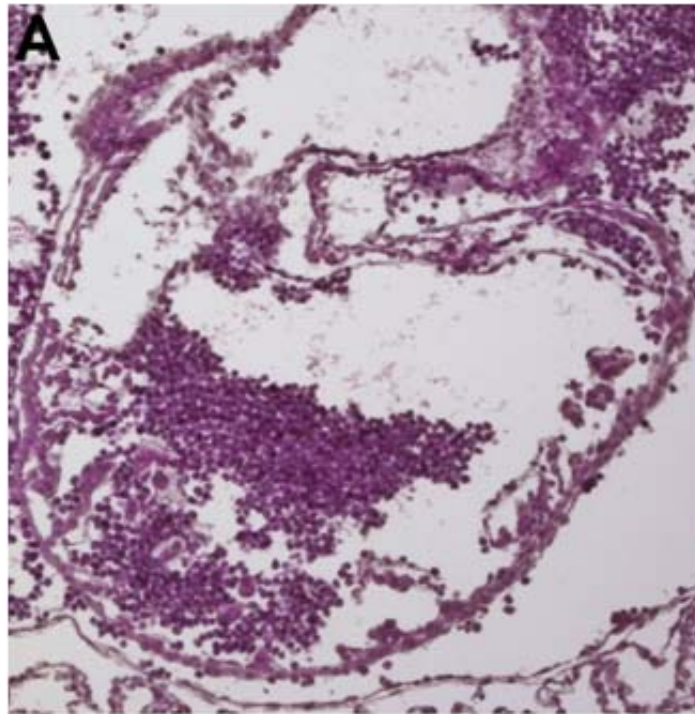


Tie2Cre/Fox01 knockout mice are embryonic lethal at E10.5 due to cardiovascular failure, indicated by pericardial edema

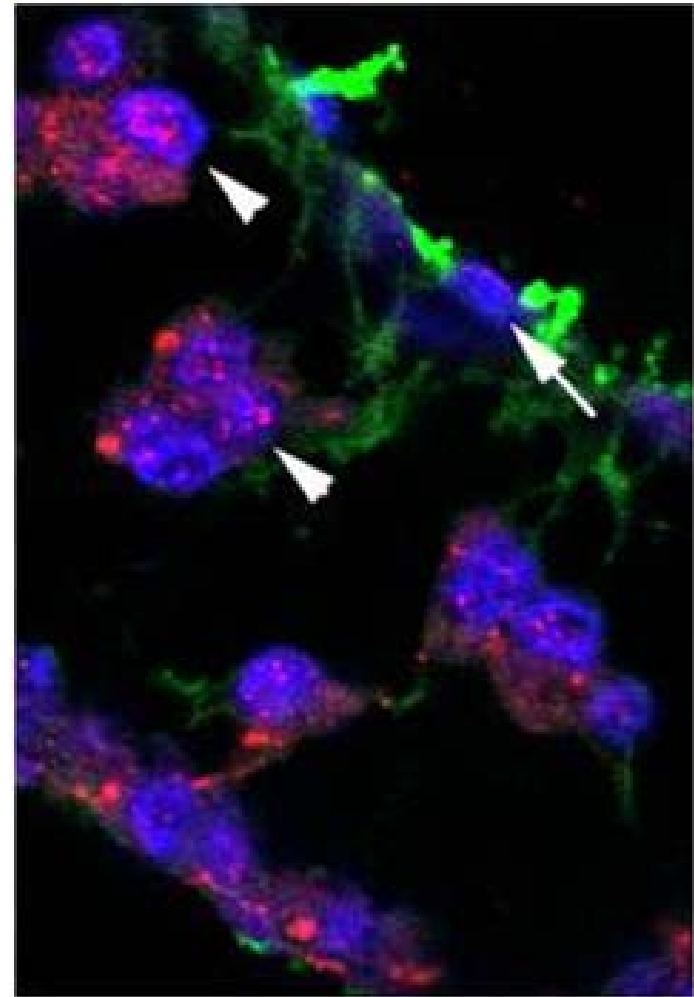
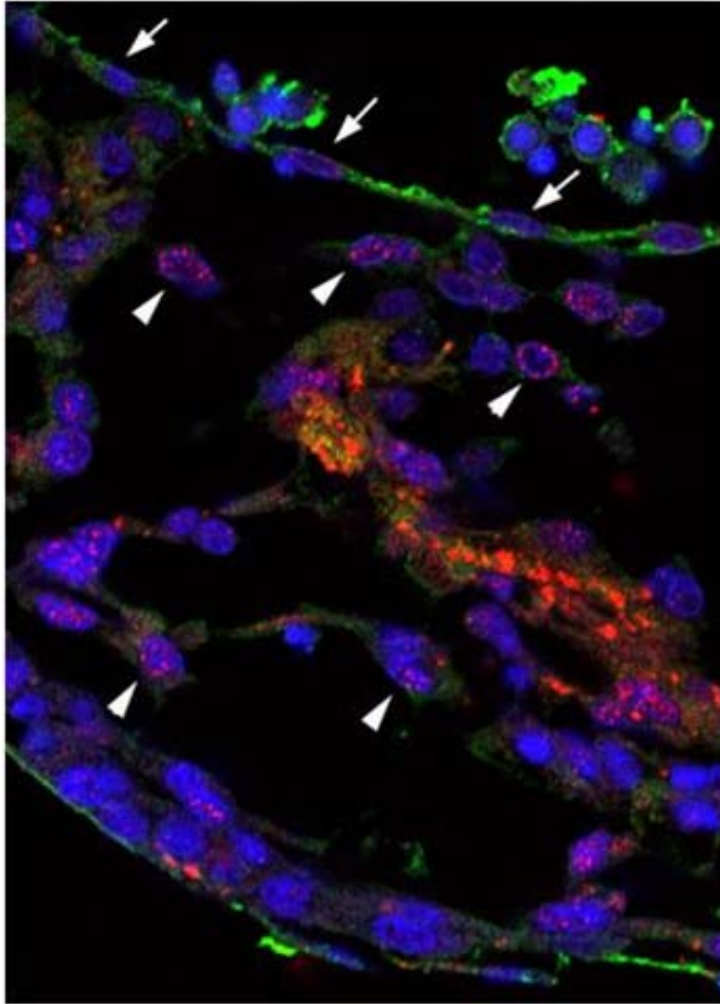
Gross morphological defects in hearts of Tie 2 Cre^{+/-}/FoxO1^{f/f} embryos

Tie2Cre/Fox01 Knockout

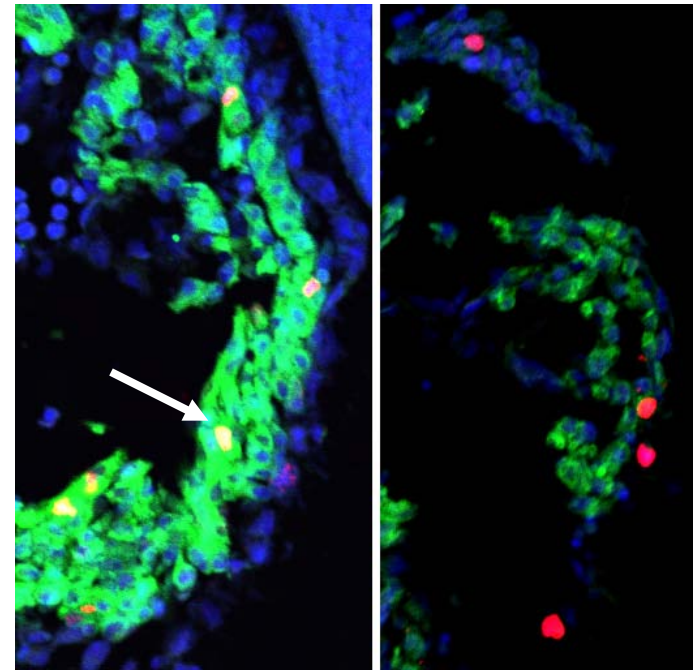
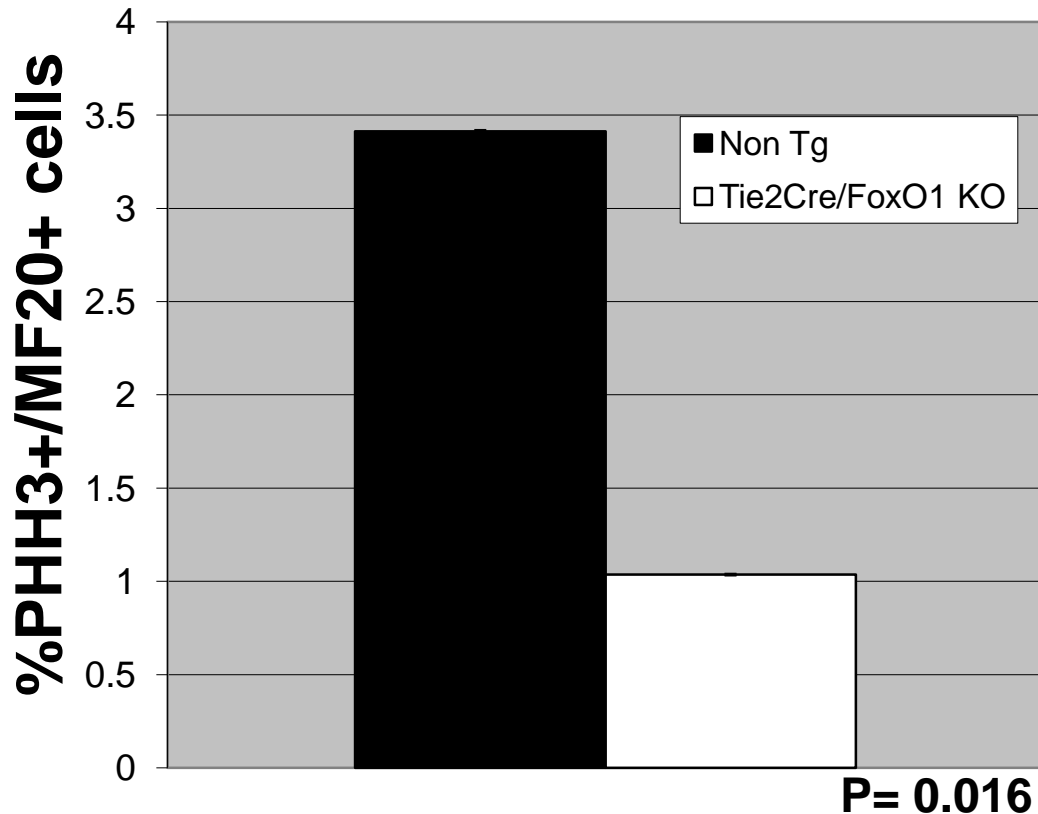
Non-transgenic



FoxO1 is not expressed in endothelial cells of mutant hearts

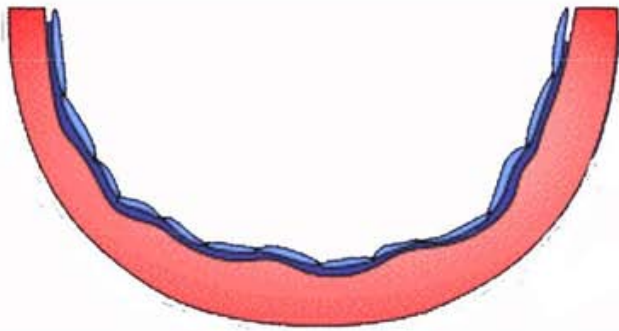


Decreased myocyte proliferation in *Tie2 Cre^{+/-} / FoxO1^{f/f}* compared to wild-type littermates

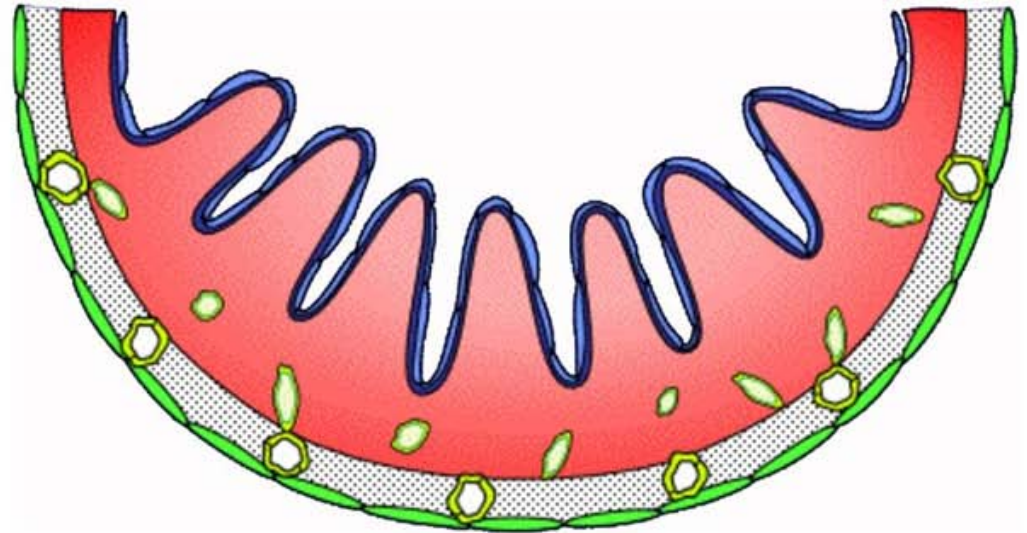
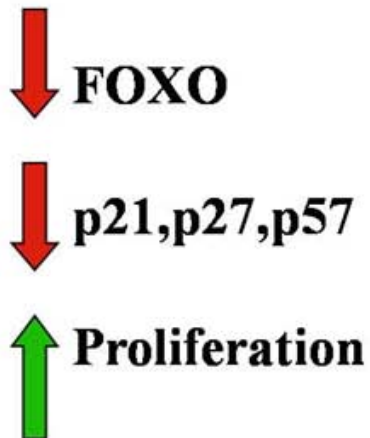


DapiMF20PHH3

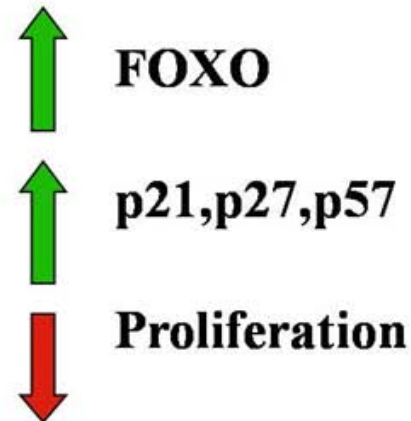
Endothelial regulation of cardiac myocyte proliferation



Primitive Myocardium



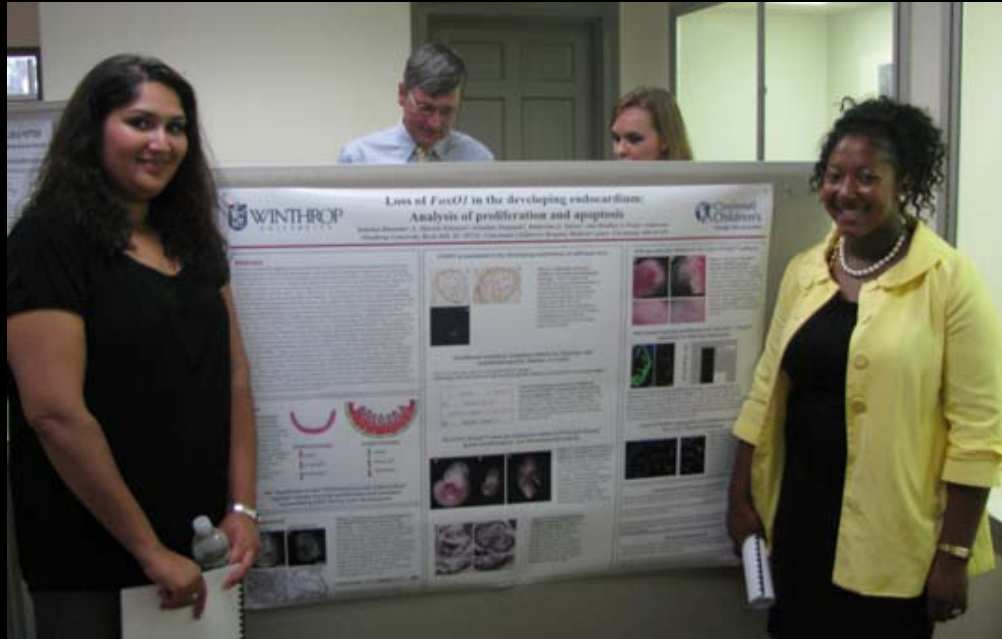
Neonatal Myocardium



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FOXO1 Constructs - D. Accili
(Columbia)
FOXO3 Constructs - K. Walsh
(Boston Univ.)
FOXO1 loxp mouse - R. DePinho
(Harvard)



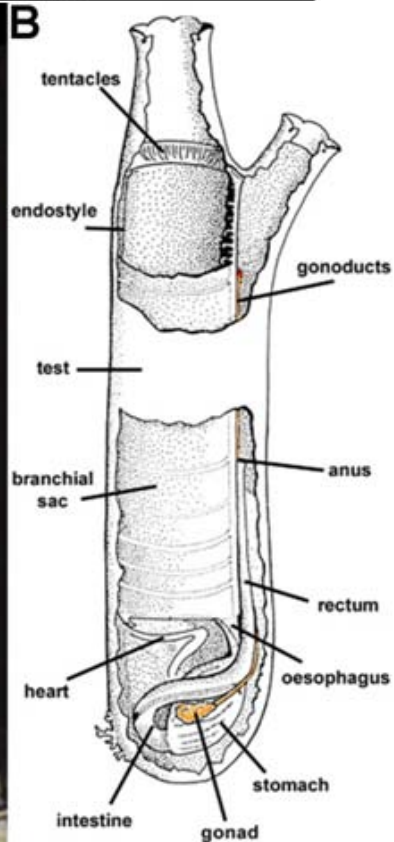
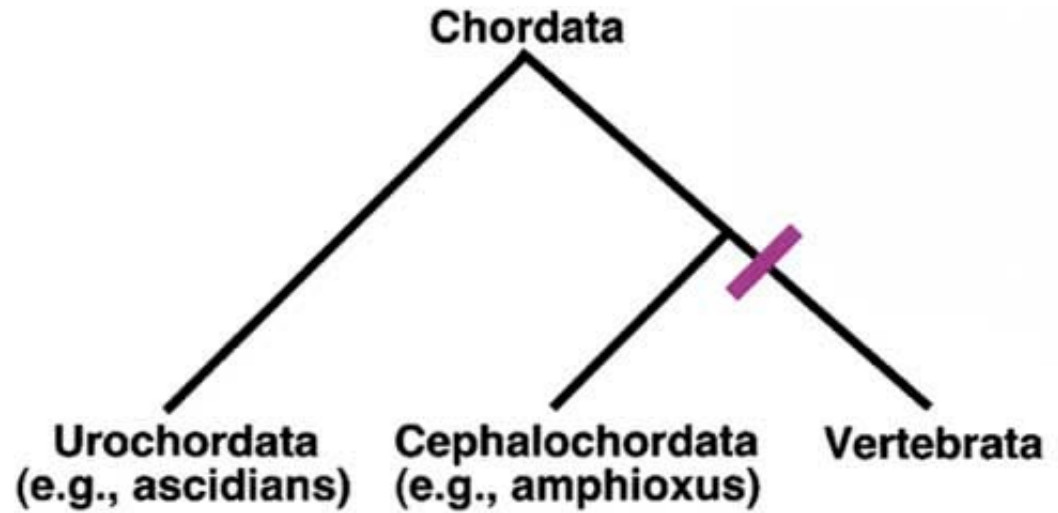
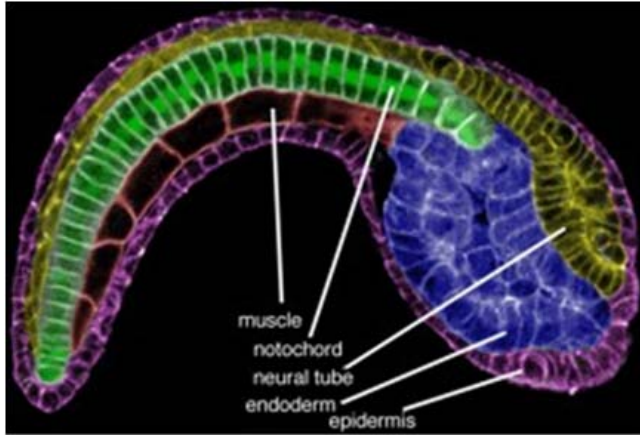
Yutzey Lab

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Santanu Chakraborty

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Transgenic core - Sandy Falcone

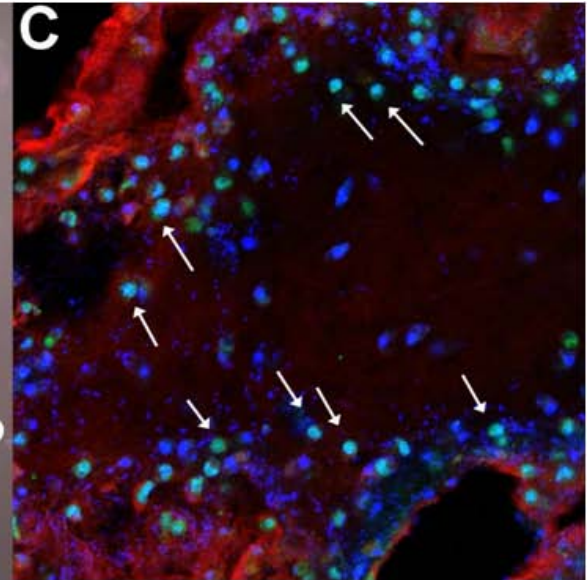
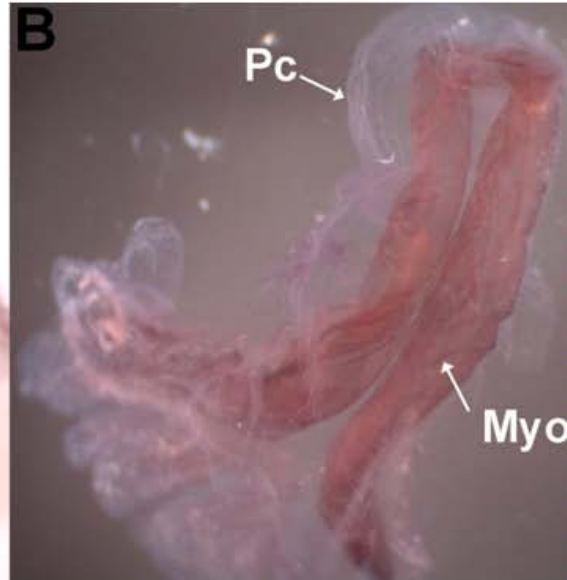
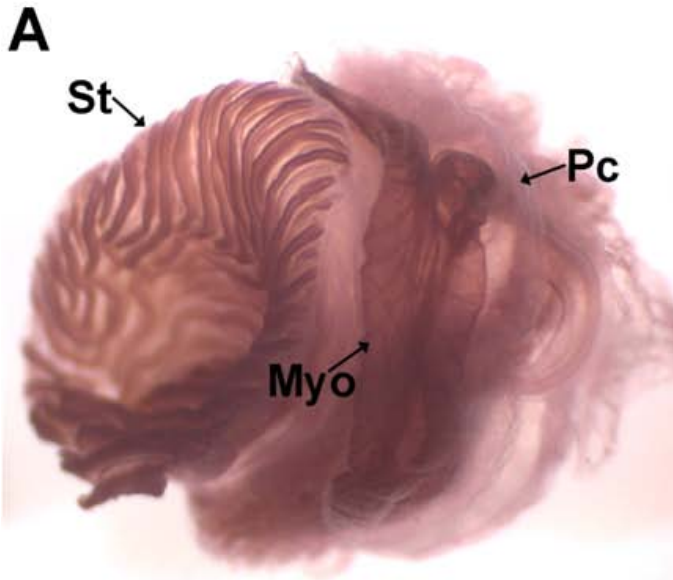
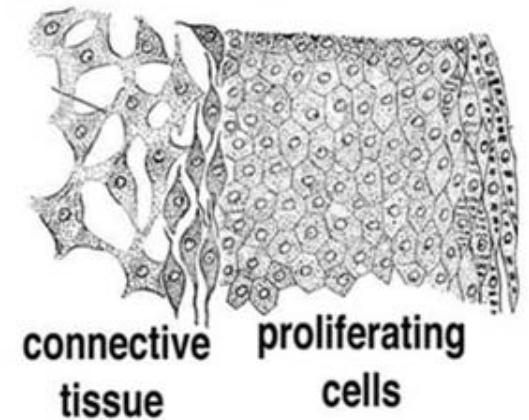
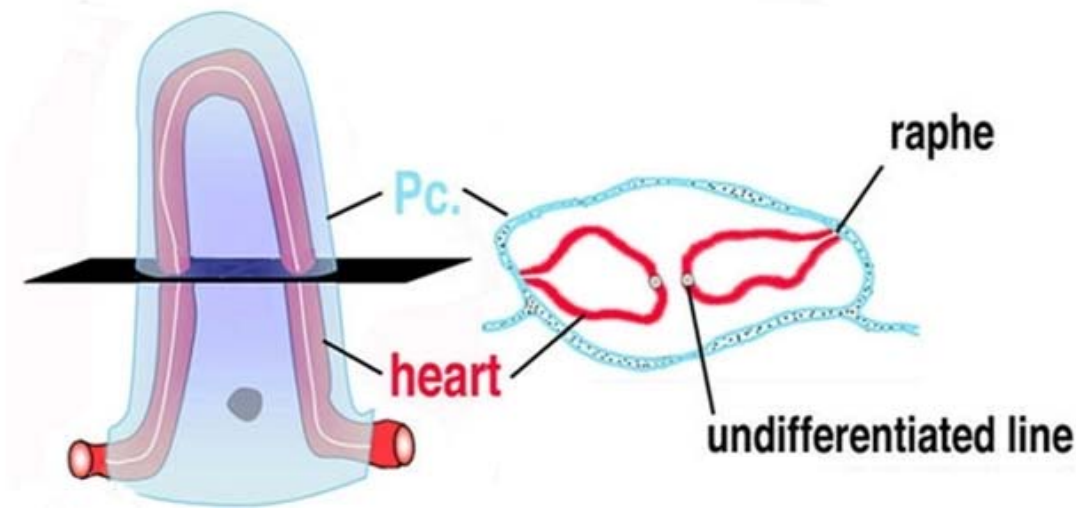


Meet *Ciona intestinalis*

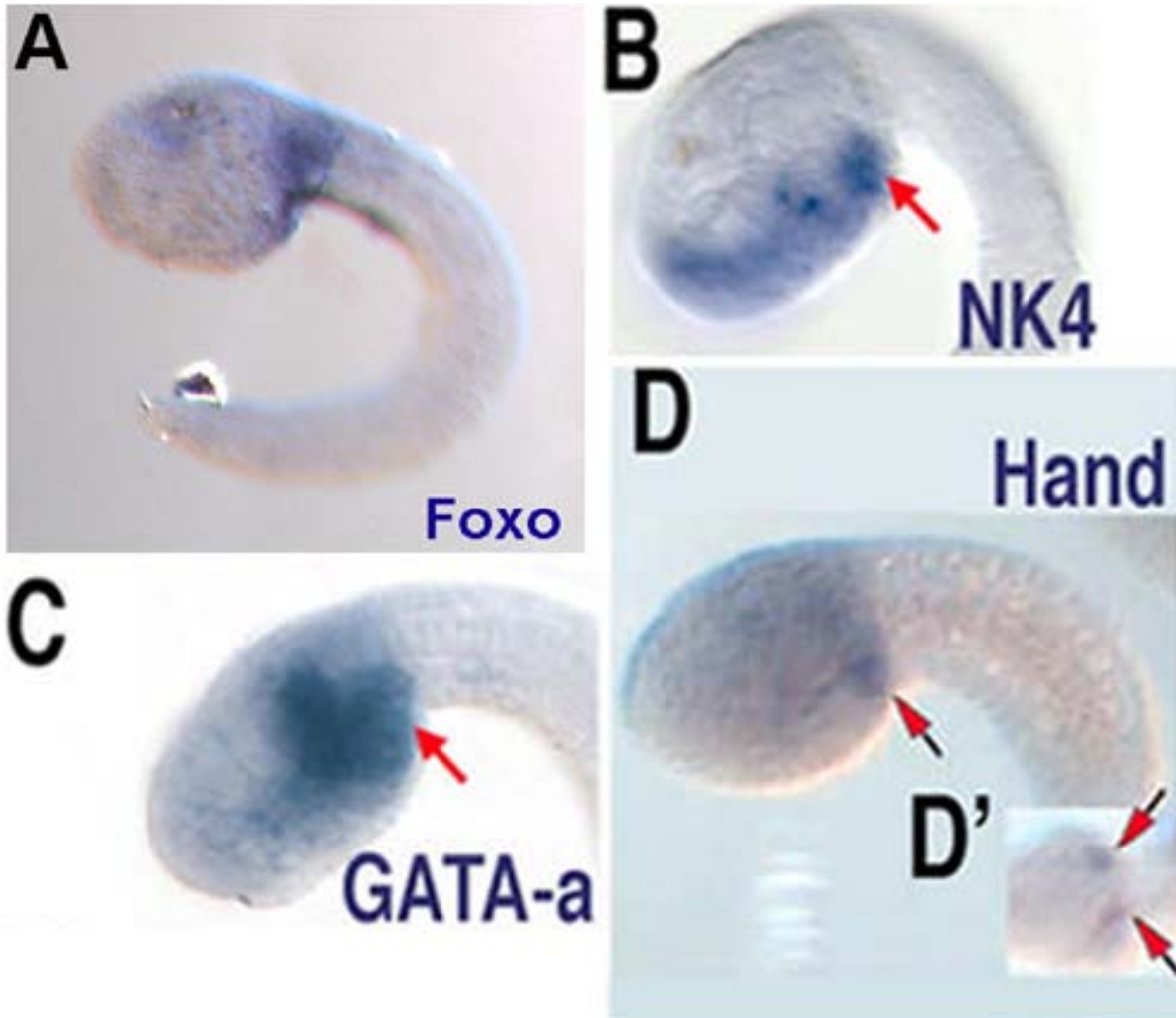


- Benefits of model system:
- Simple genome
 - Easy to study
 - Regenerative capability

Heart development in *Ciona*



Foxo expression in developing Ciona heart



A: Aniseed database; B-D': Davidson 2007