Embryonic Origins of Vascular Smooth Muscle Cells and Implications for Disease

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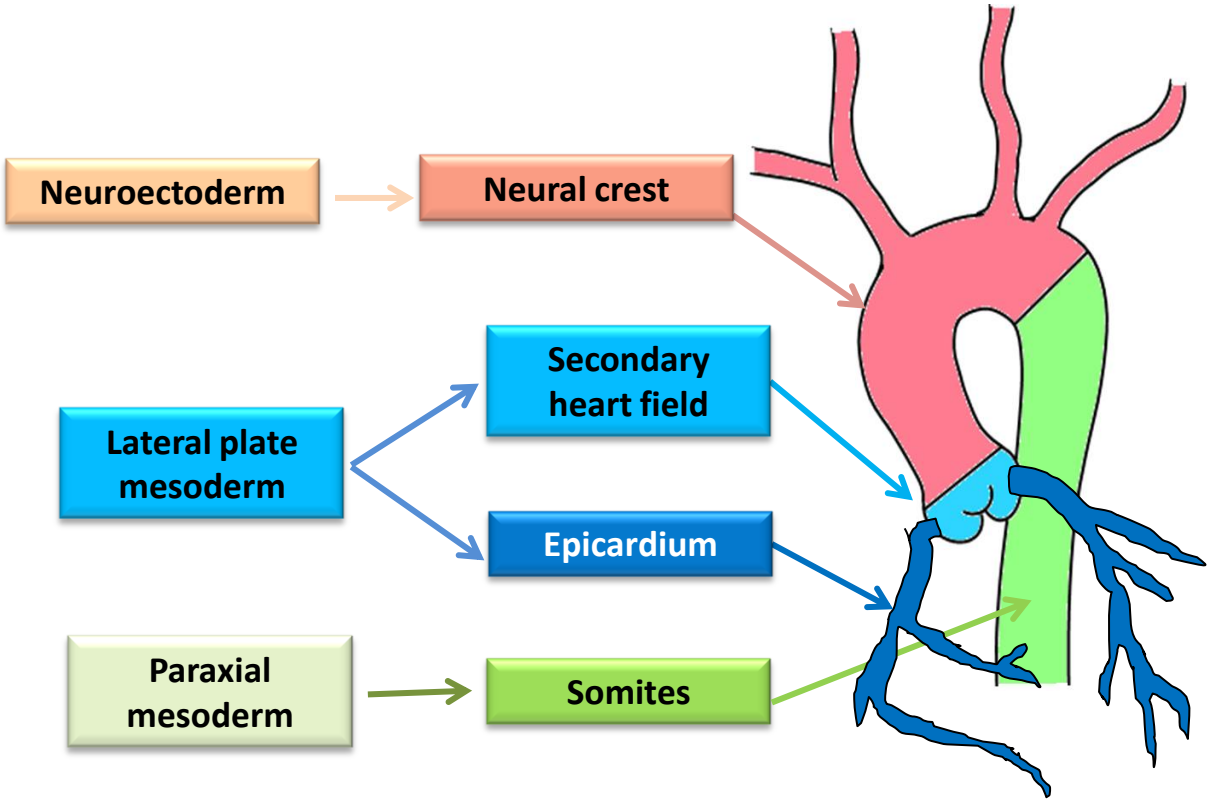
University of Cambridge

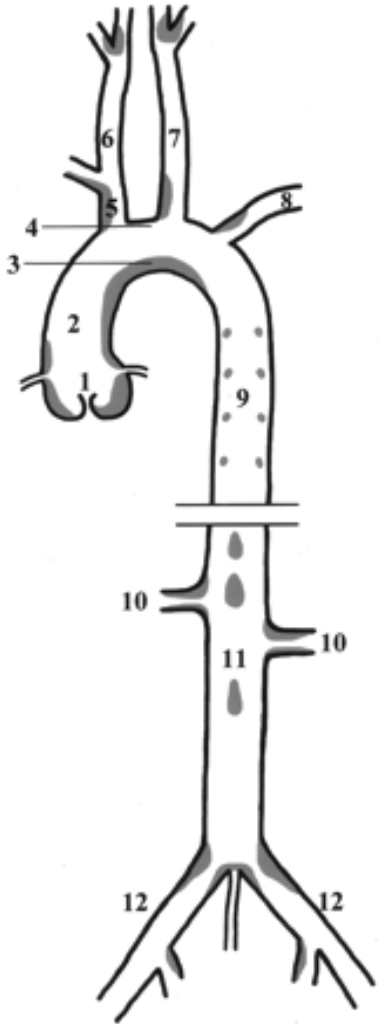
A SMC means a SMC?

Vascular Smooth Muscle Cells Originate from Multiple Embryonic Lineages

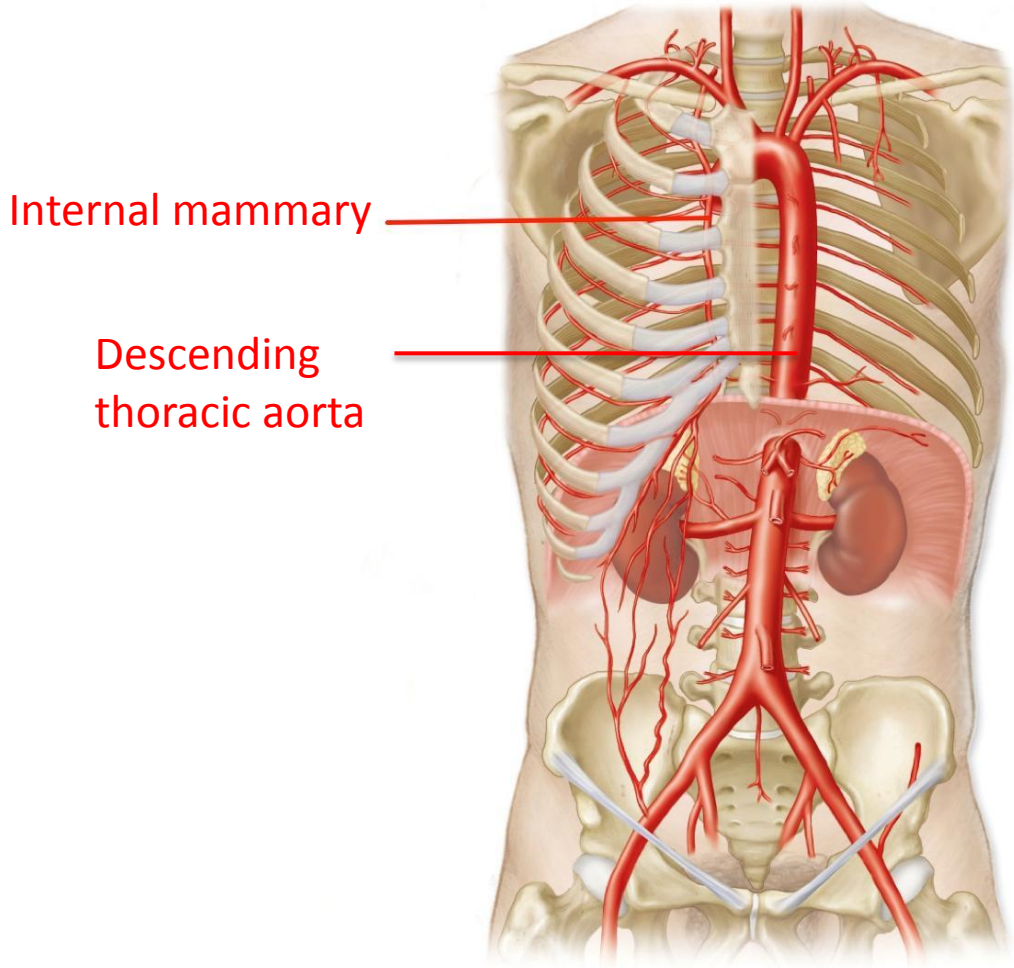


1. Development informs disease
2. Practical examples of using stem cells to model human development and disease

Site-Specific Manifestation of Atherosclerosis



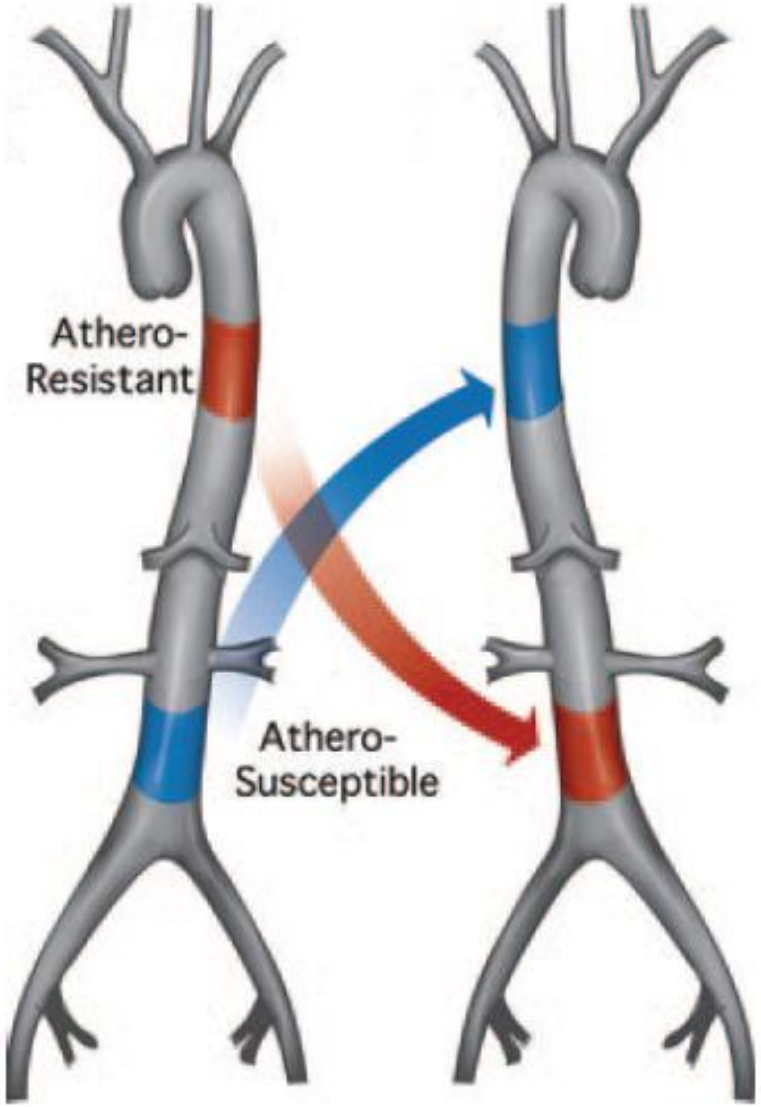
LDLR -/- mouse



Vanderlaan et al. ATVB 2004;24: 12-22

Site-specific manifestation of vascular diseases

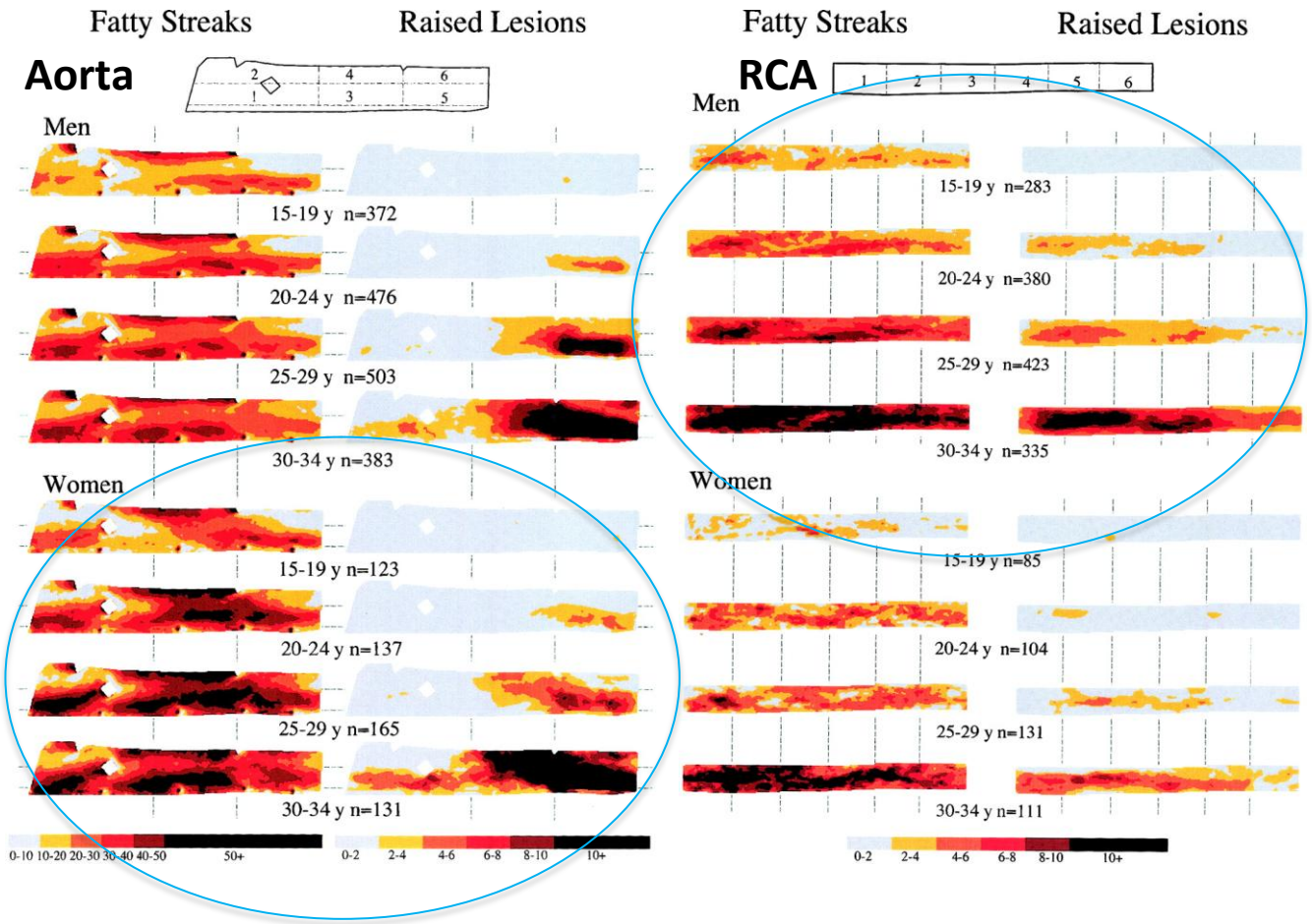
Atherosclerosis



Haimovici & Maier.
Arch Surg 1964
Majesky ATVB 2007

Early Athero: Diverse Regional Responses to Risk factors

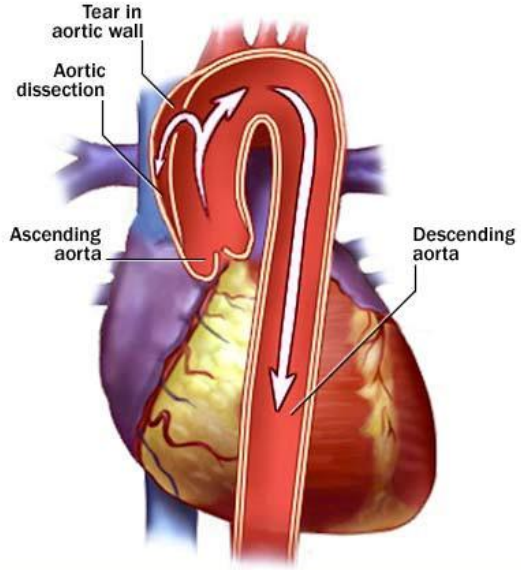
Pathobiological Determinants of Atherosclerosis in Youth (PDAY)

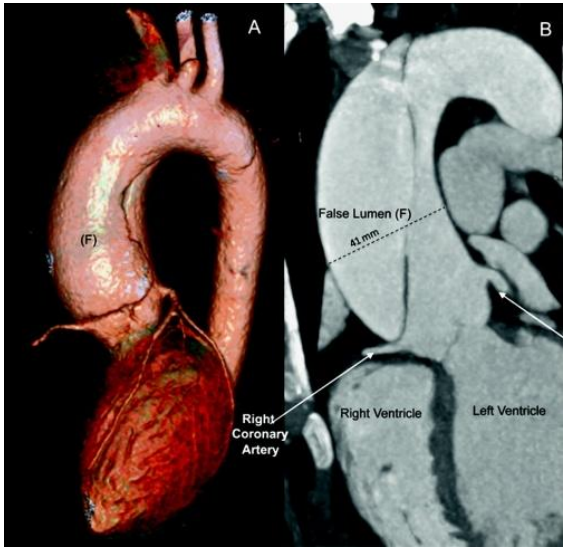


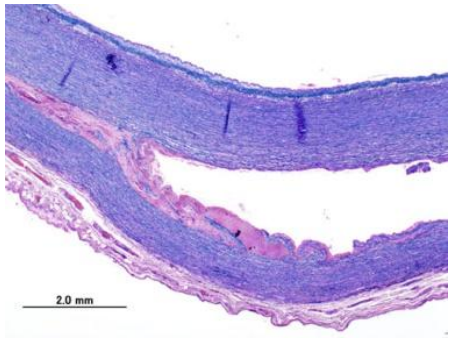
- ♀ → Abdo Aorta
- ♂ → RCA
- Smoking → Abdo Ao
- Gly Hb → RCA

Henry C. McGill, Jr et al. ATVB 2000;20:836-845 & ATVB 2000;20:1998-2004.

Vascular SMC Pathologies: Aortic Aneurysm & Dissection





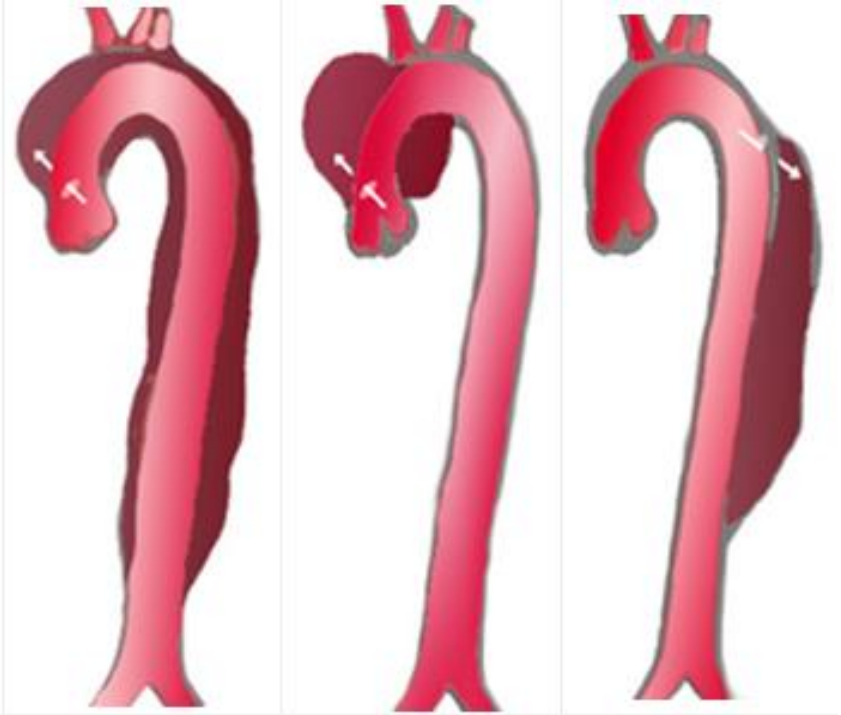


Genetic syndrome – Marfans, Loeys-Dietz
Non-syndromic TAAD

<u>Cystic medial necrosis</u>
SMC death
ECM breakdown

Site-specific manifestation of vascular diseases

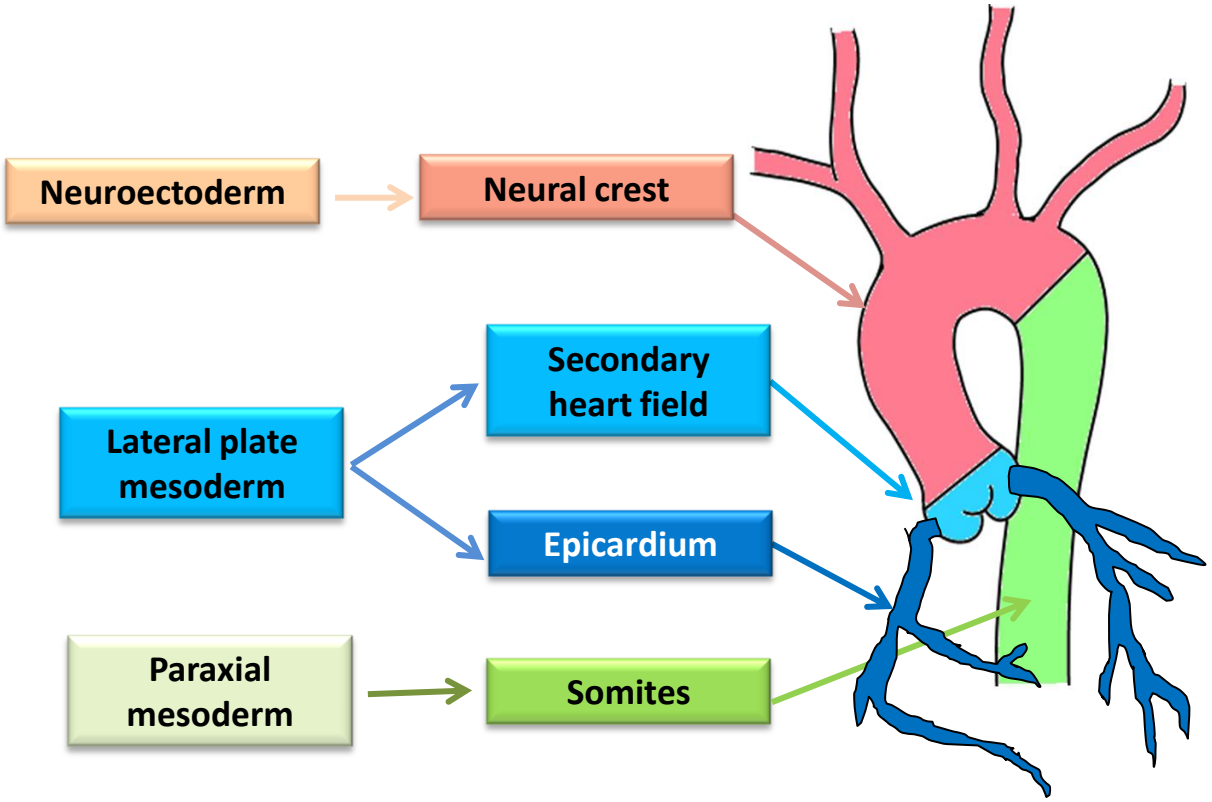
Aortic Aneurysms & Dissections



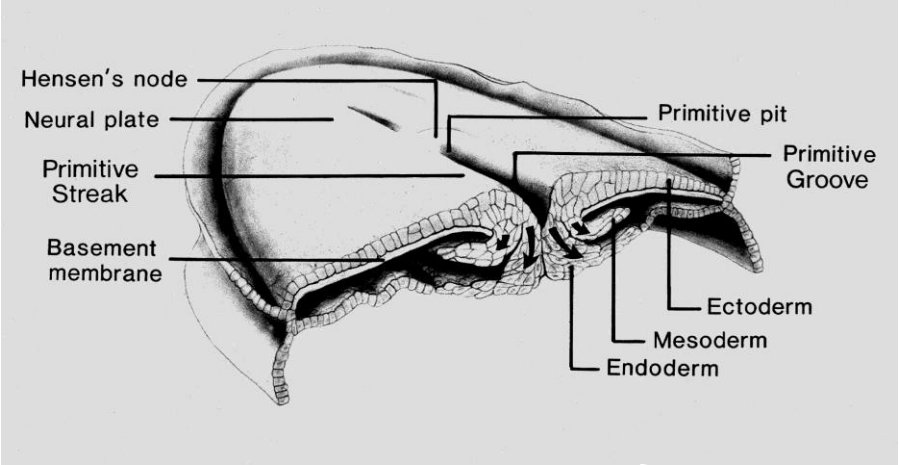
Percentage	60%	10–15%	25–30%
Type	DeBakey I	DeBakey II	DeBakey III
	Stanford A		Stanford B
	Proximal		Distal

Classification of aortic dissection

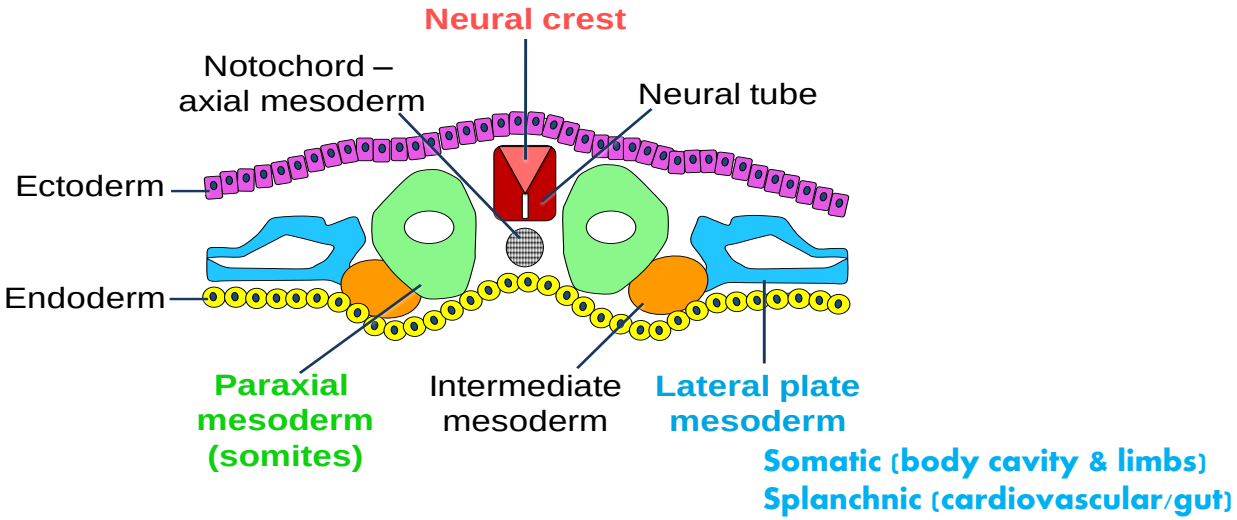
Vascular Smooth Muscle Cells Originate from Multiple Embryonic Lineages



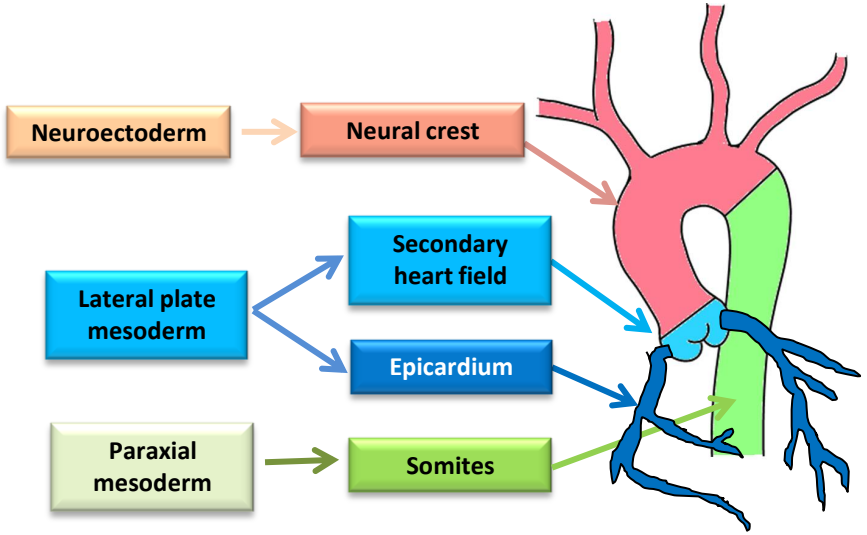
"It is not birth, marriage, or death, but **gastrulation** which is truly the most important time in your life." – Lewis Wolpert (1986)



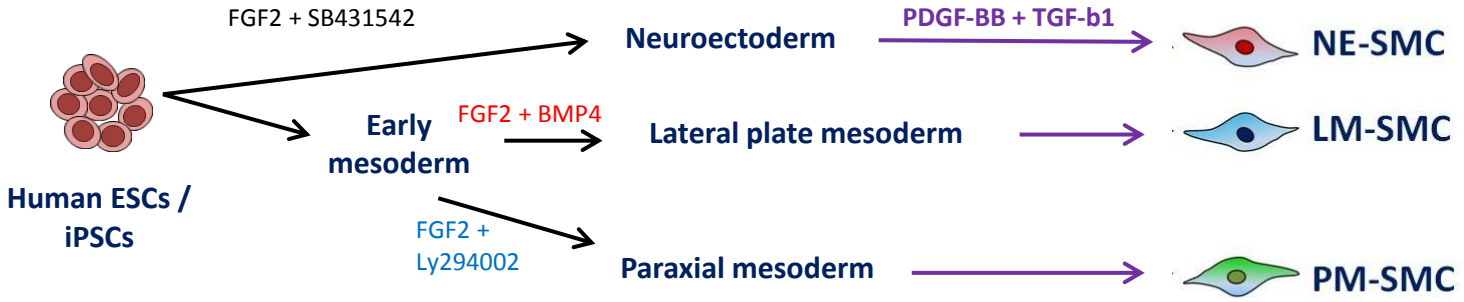
Dias MS, and McLone DG. 2001



Development of Embryonic Lineage-Specific Vascular Smooth Muscle Cells from Human Pluripotent Stem Cells

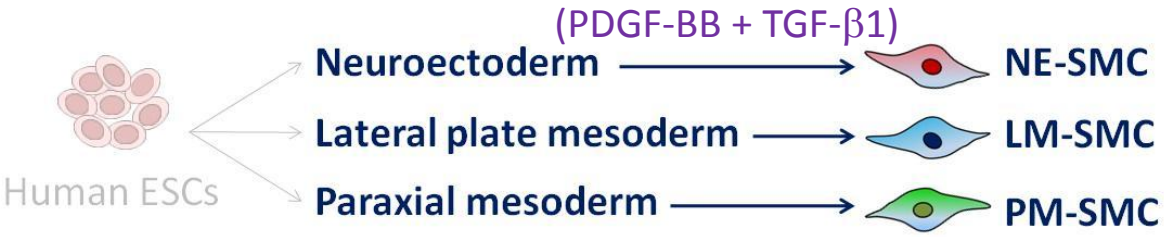


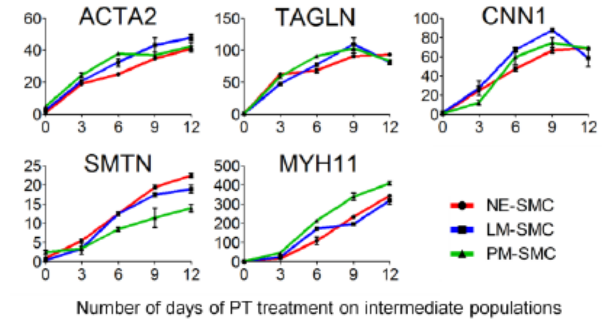
Christine Cheung

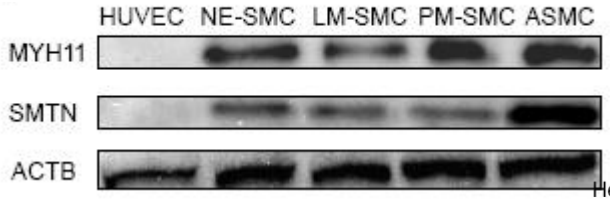


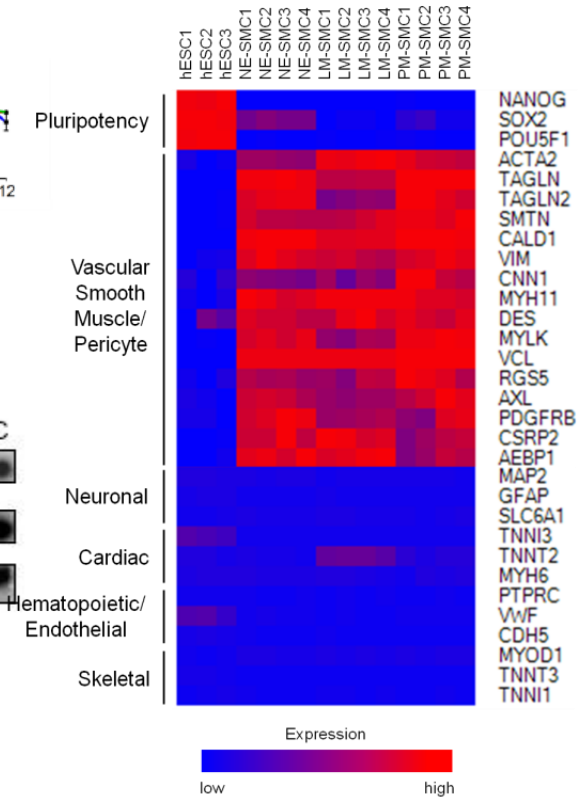
Cheung et al. Nature Biotech 2012;30:165-73
Cheung et al. Nature Protocols 2014;9:929-38

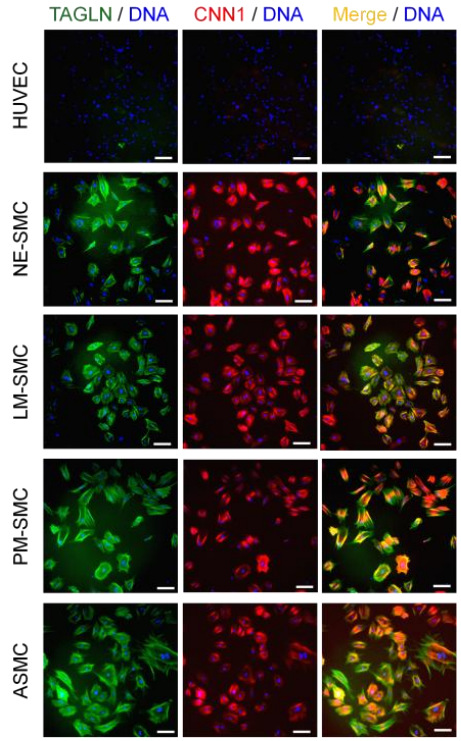
Generation of SMCs from Embryonic Lineages











- ~90% SMCs
- hESCs & iPSCs
- Chemically defined

Lineage-Specific Developmental and Functional Differences Between VSMC

PNAS

Requirement of myocardin-related transcription factor-B for remodeling of branchial arch arteries and smooth muscle differentiation

Jiyeon Oh*, James A. Richardson*†, and Eric N. Olson*‡

Department of *Molecular Biology and †Pathology, University of Texas Southwestern Medical Center, Dallas, TX 75390-9148

Contributed by Eric N. Olson, August 31, 2005

Myocardin and the myocardin-related transcription factors (MRTFs) A and B act as coactivators for serum response factor, defects (18). Mice homozygous for a *lacZ* enhancer trap allele of *MRTF-B* display perinatal lethality (19), which has been attrib-

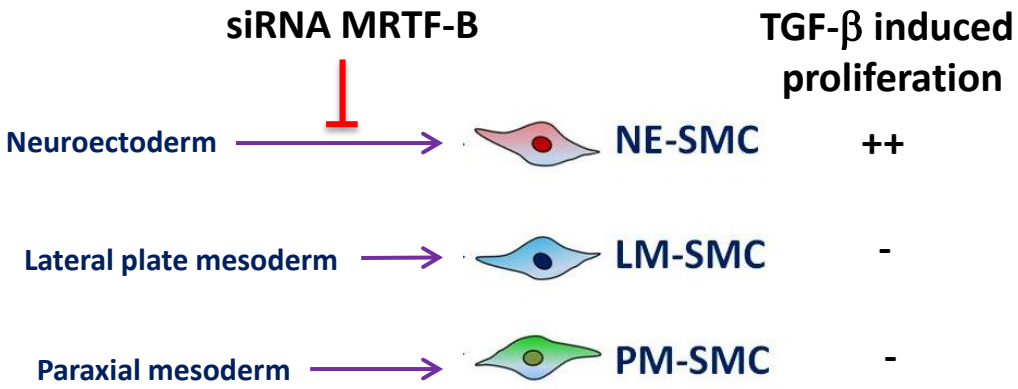
DEVELOPMENTAL BIOLOGY 178, 430–445 (1996)
ARTICLE NO. 0229

Smooth Muscle Lineage Diversity in the Chick Embryo

Two Types of Aortic Smooth Muscle Cell Differ in Growth and Receptor-Mediated Transcriptional Responses to Transforming Growth Factor-β

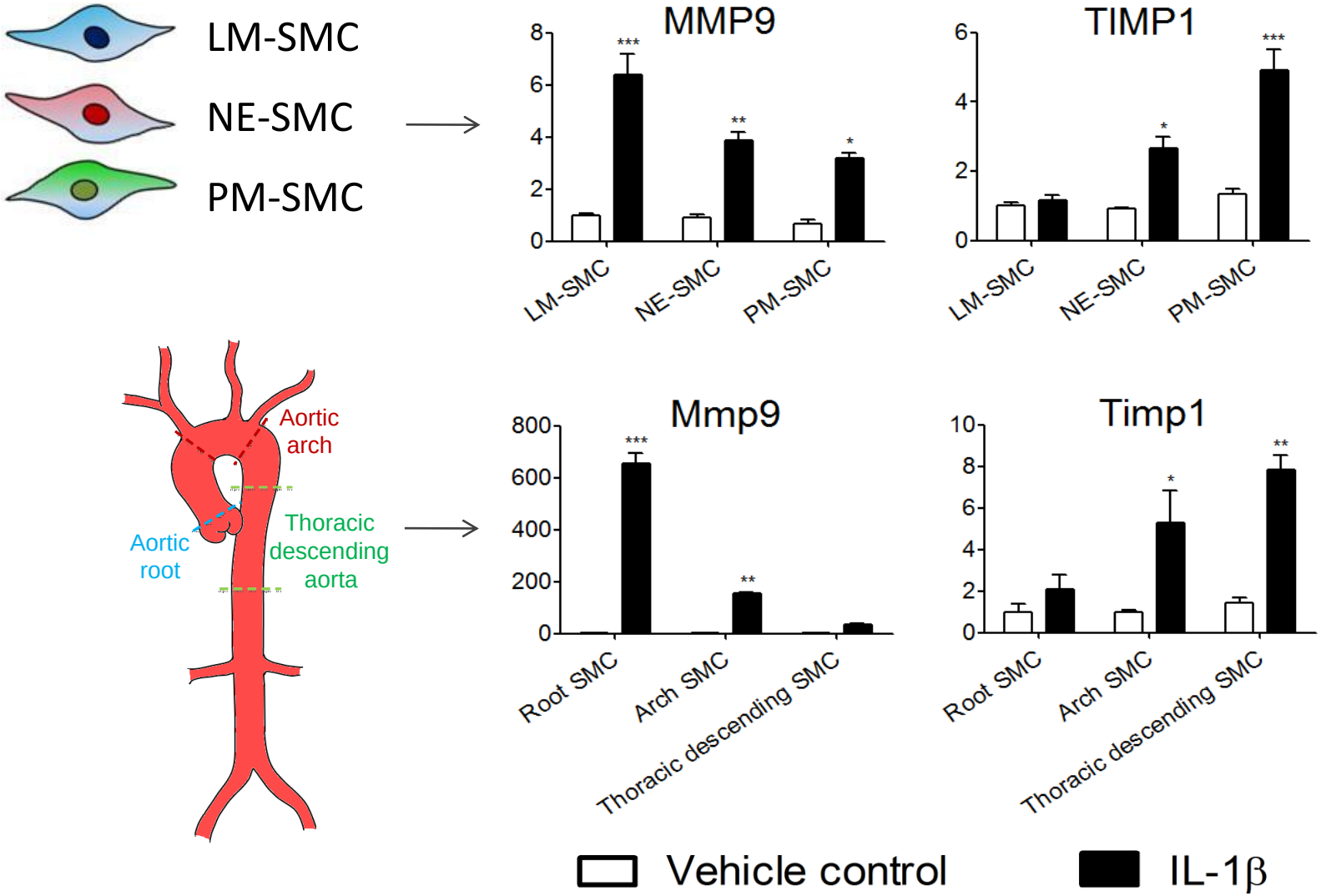
Stavros Topouzis and Mark W. Majesky*,[1]

*Department of Pathology and *Department of Cell Biology, Baylor College of Medicine, One Baylor Plaza, Houston, Texas 77030*

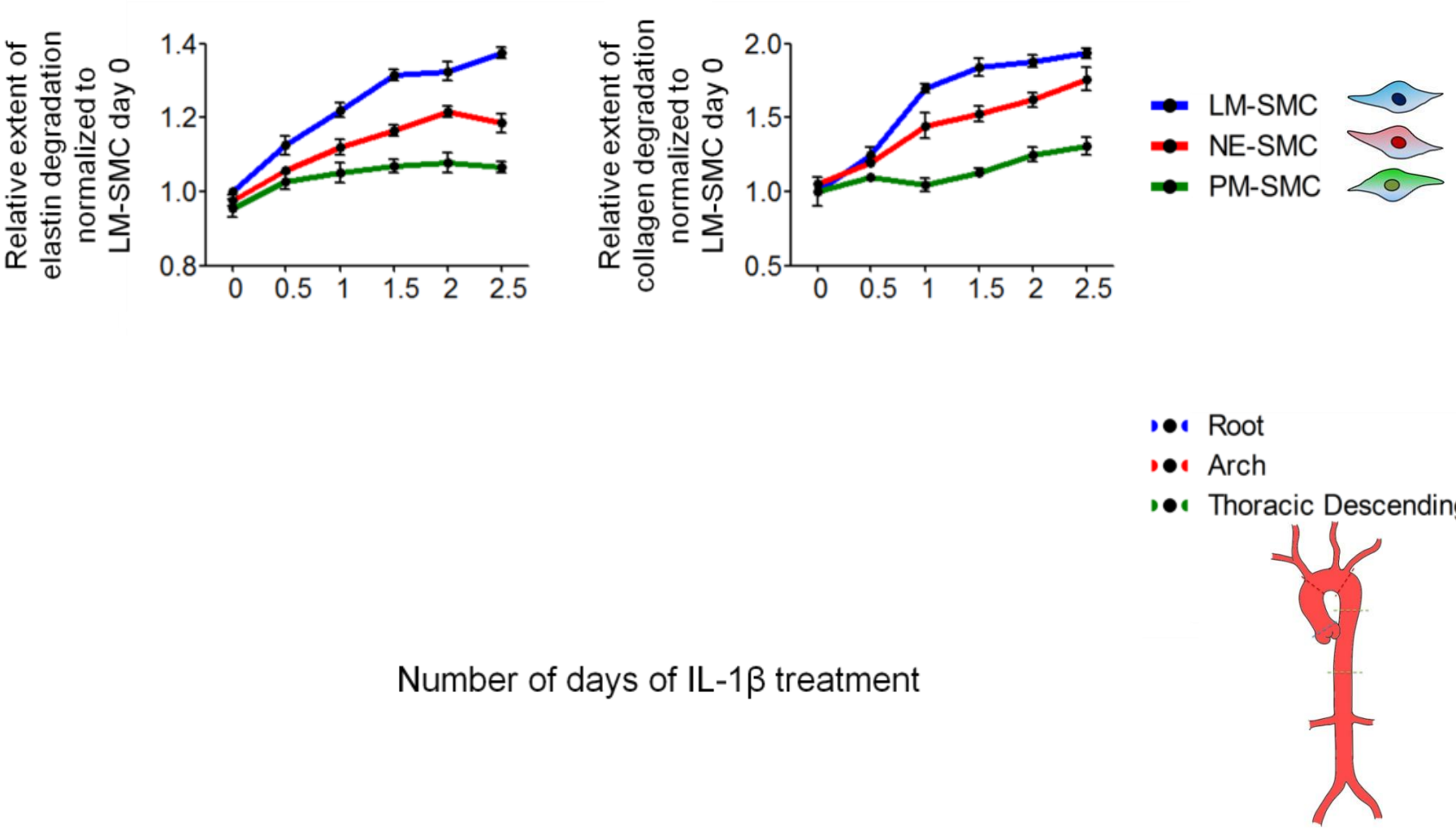


Cheung et al. Nature Biotech 2012;30:165-73

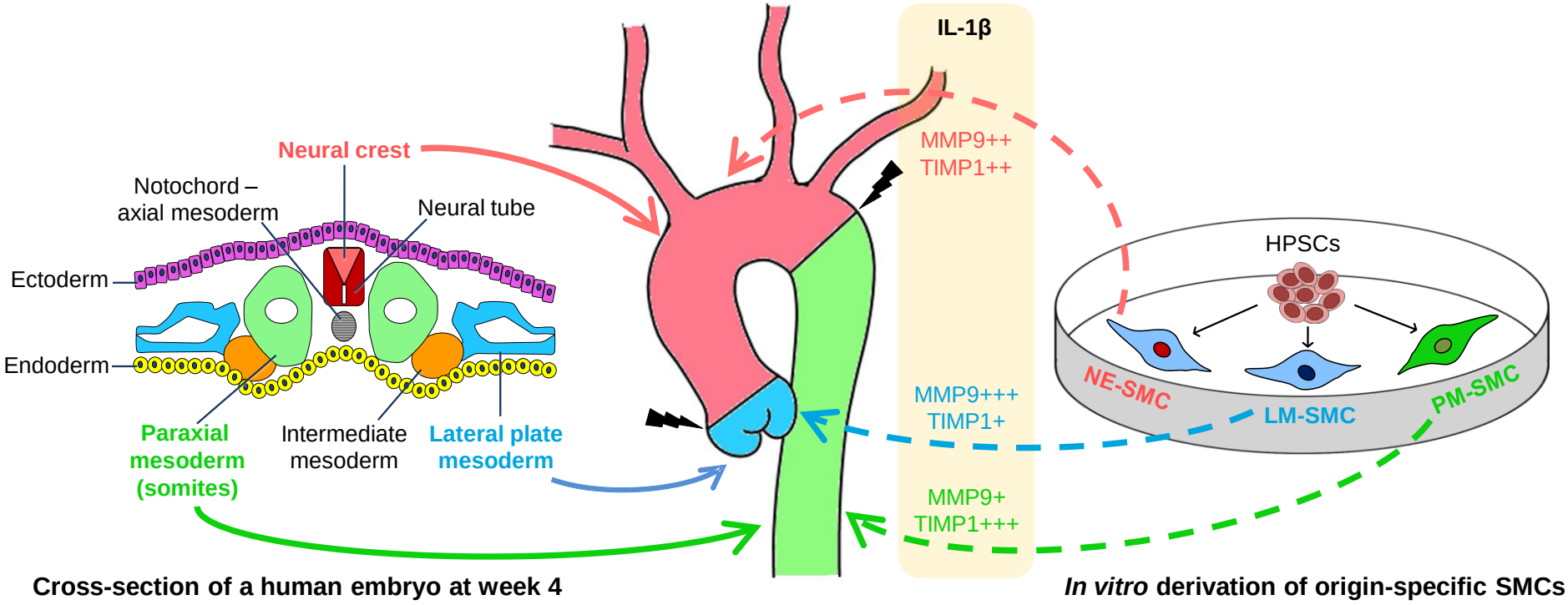
SMC subtypes predict origin-dependent MMP9 and TIMP1 activation



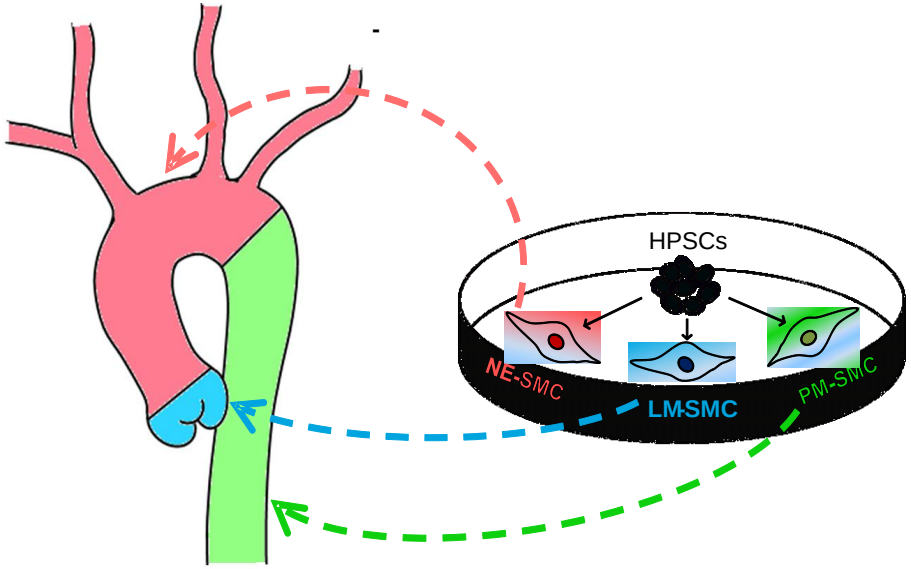
SMC subtypes exhibit differential proteolytic ability



Origin-specific SMCs may contribute to the preferential sites of aortic dissection

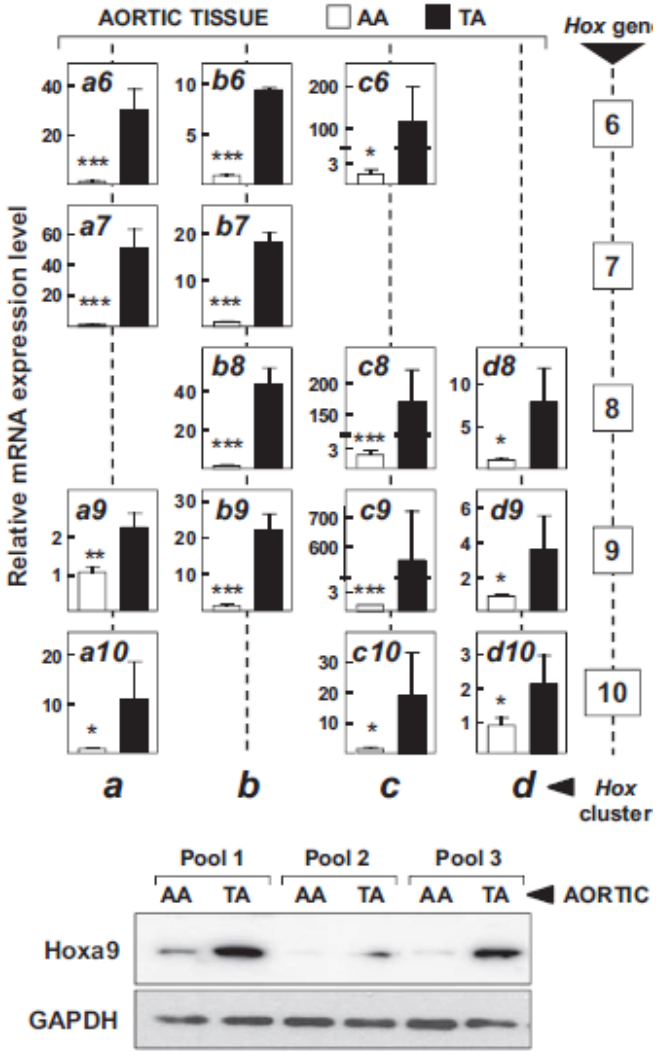


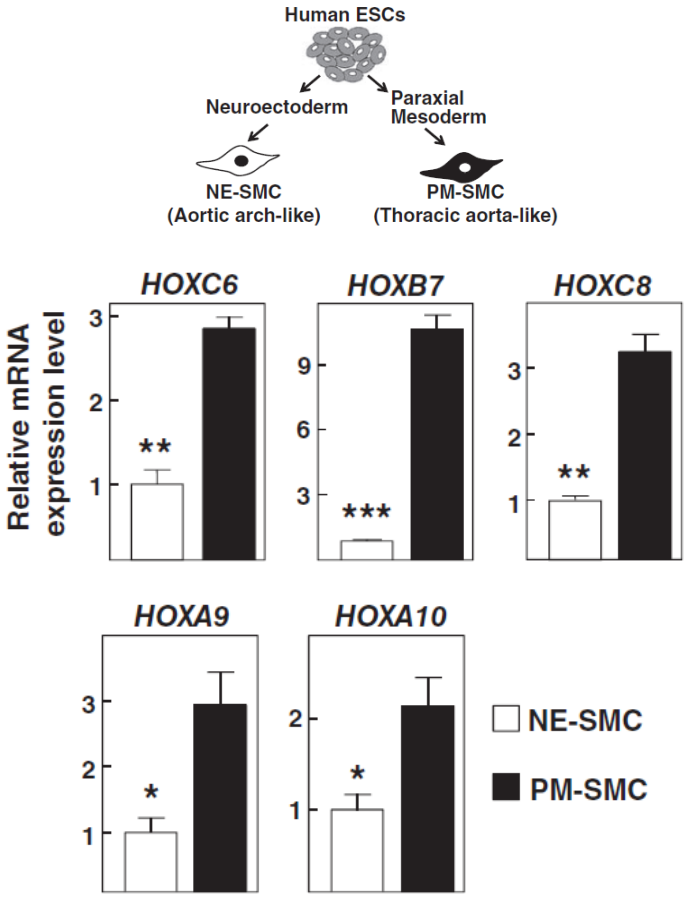
Cheung et al. Nature Biotech 2012;30:165-73
Cheung et al. Nature Protocols 2014;9:929-38



‘Regionality’ and development of VSMC: insights into atherosclerosis?

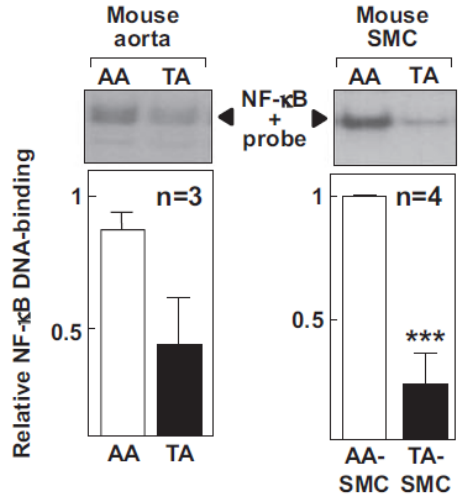
Embryonic origin-dependent differences in Homeobox gene expression

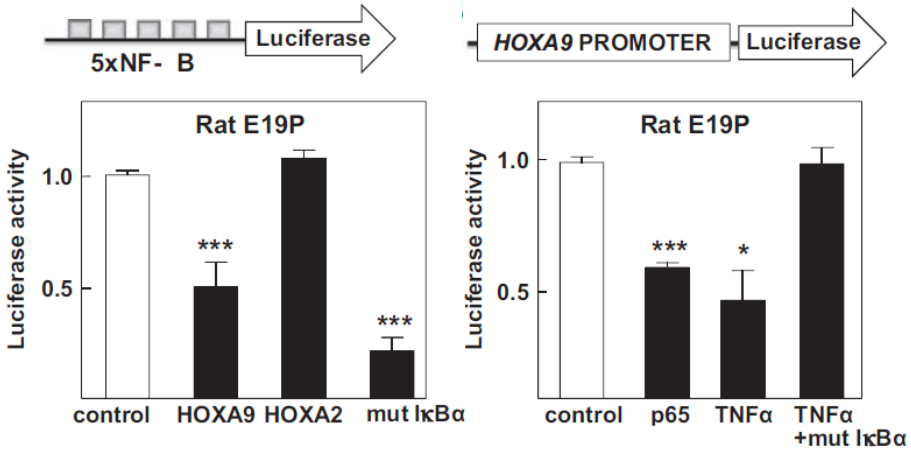


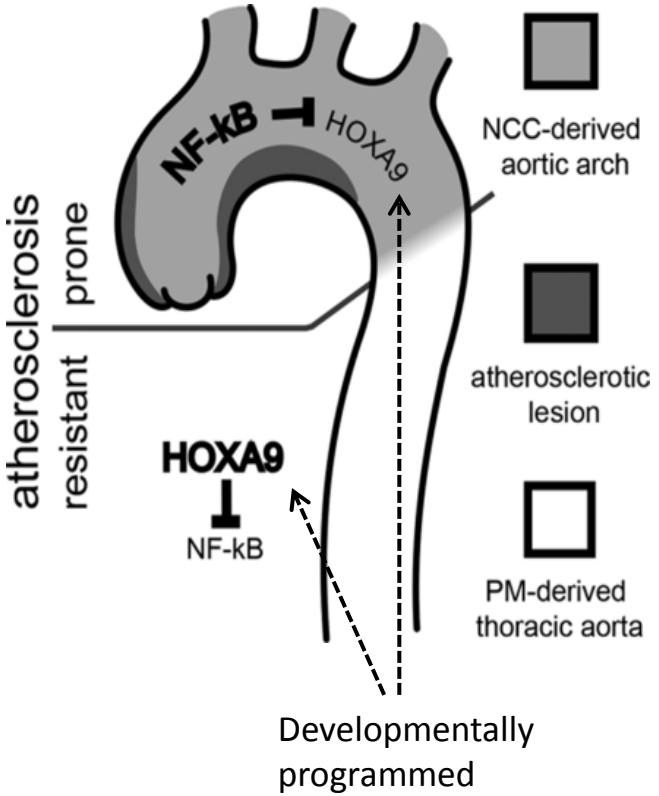


Trigueros-Motos et al. ATVB 2013;33:1248-1256

Reciprocal negative regulation between NF-kB and HoxA9

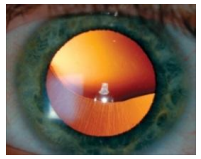


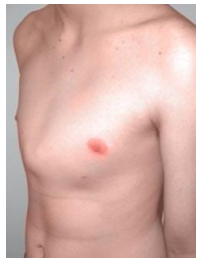


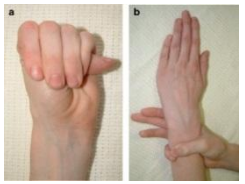


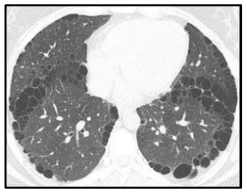
Trigueros-Motos et al. ATVB 2013;33:1248-1256

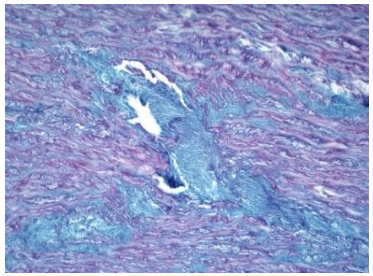
Marfan Syndrome - Clinical Features





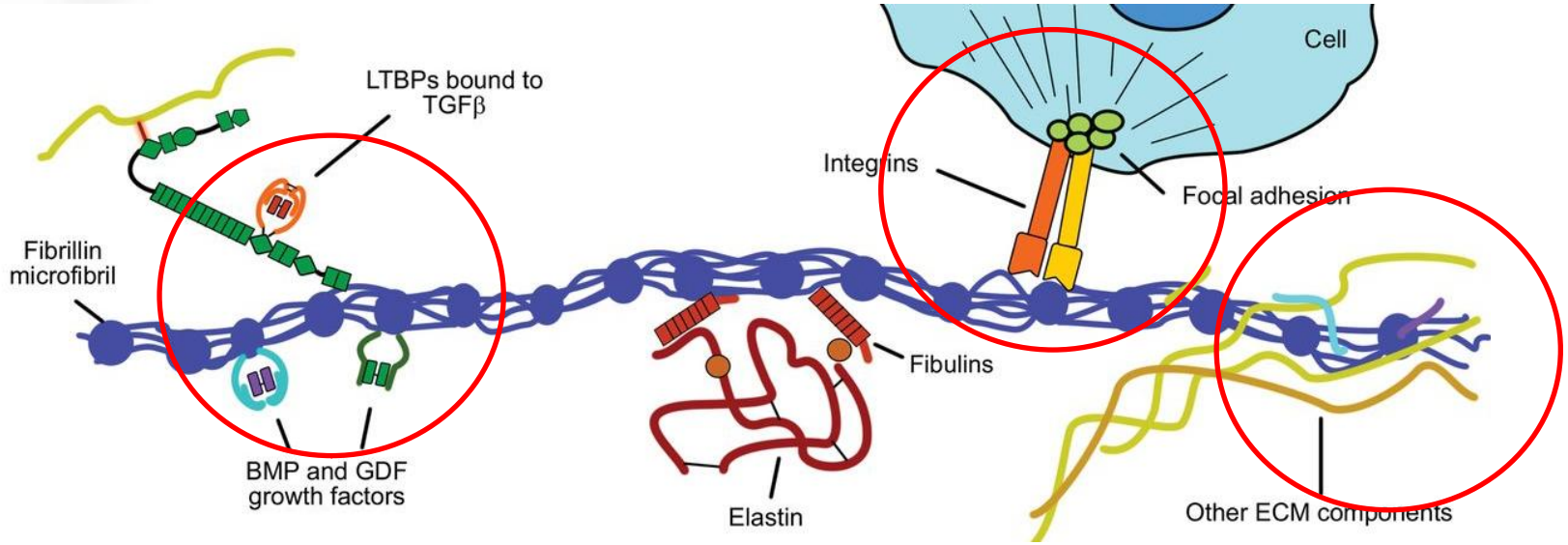






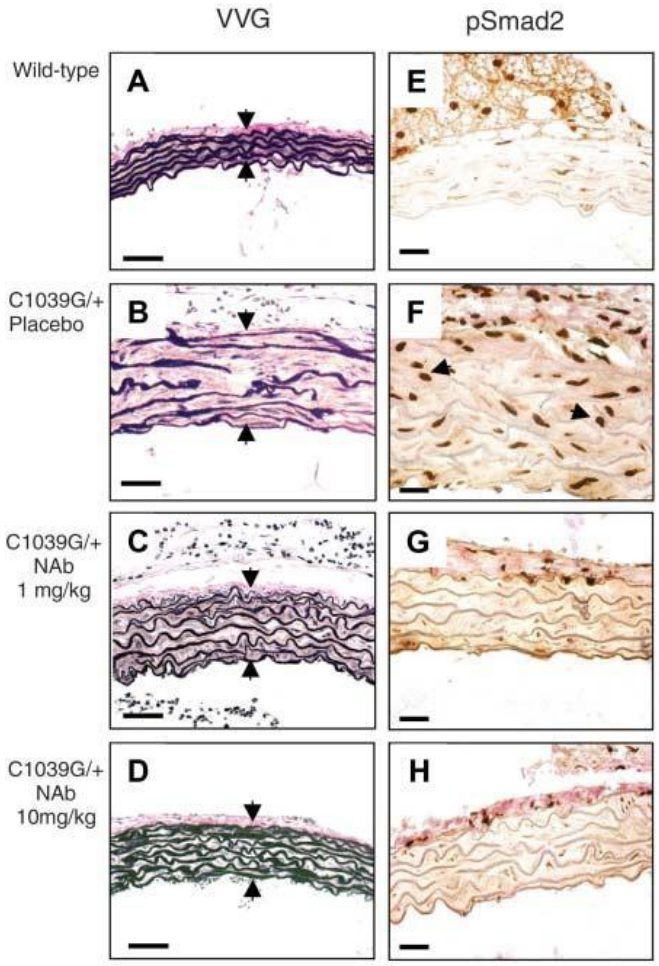
Cystic medial necrosis

Fibrillin-1 mutation

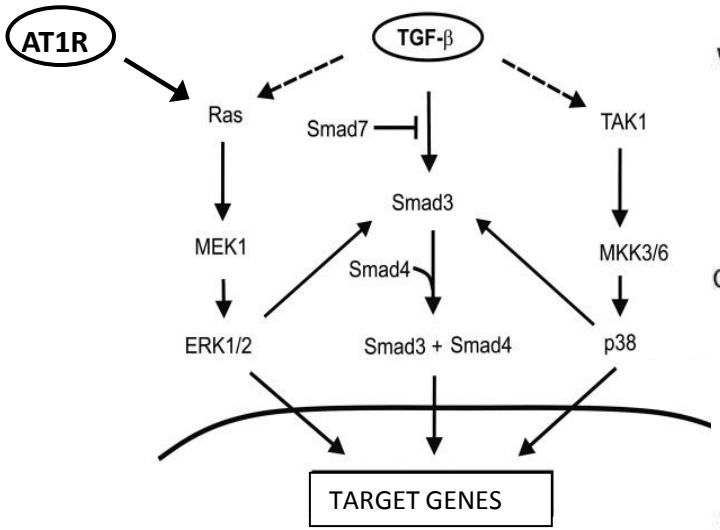


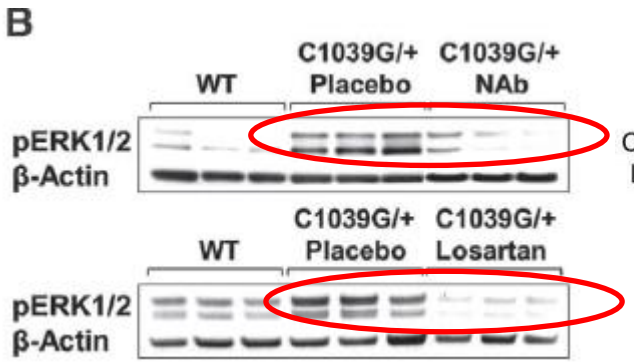
Robertson et al. Biochem J 2011

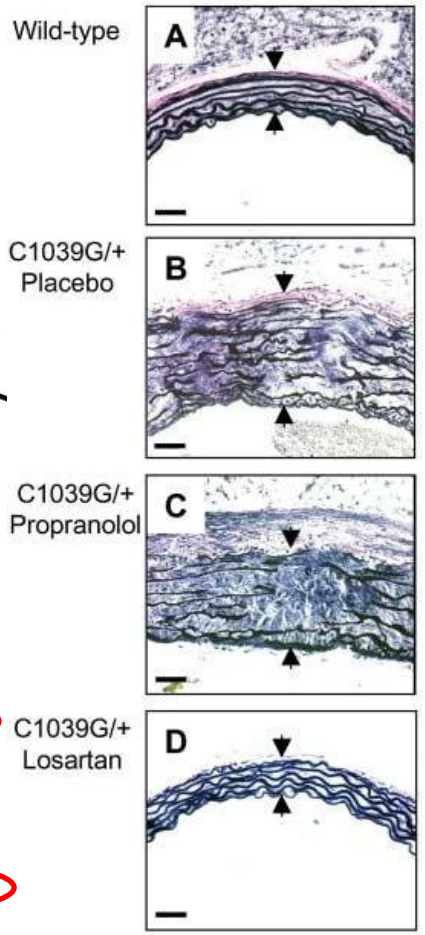
Increased TGF-β and ERK1/2 Activity in Pathogenesis of Aortic Disease in Fibrillin-1 $^{Cys->Gly/+}$ Mutant Mouse



Habashi et al Science 2006





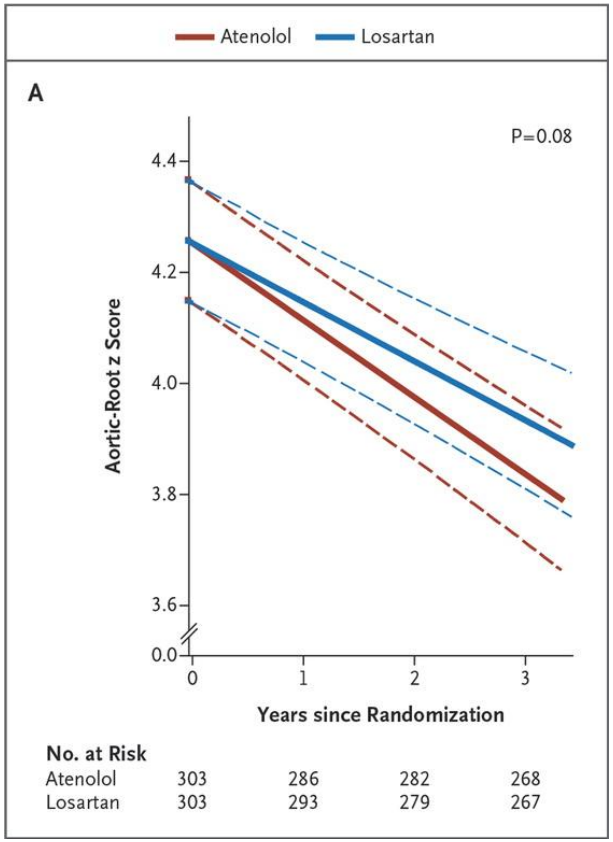


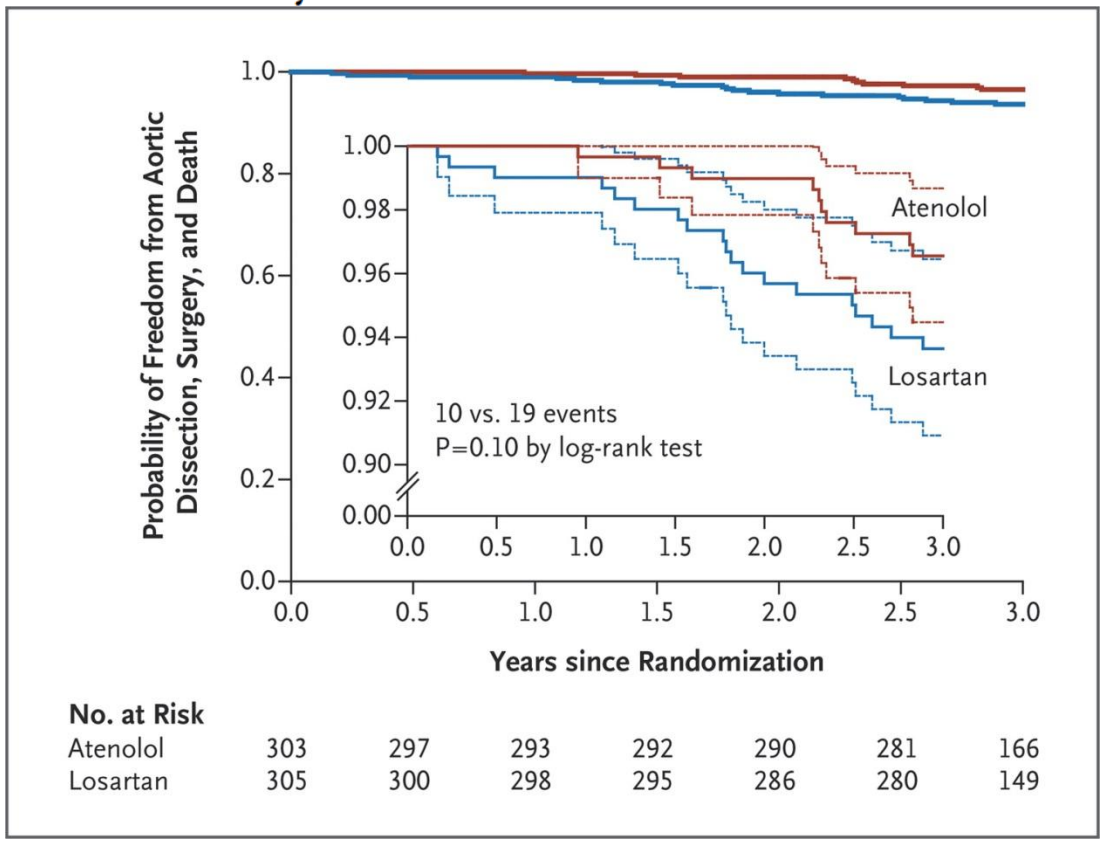
Dietz et al. Science 2011

The NEW ENGLAND JOURNAL of MEDICINE

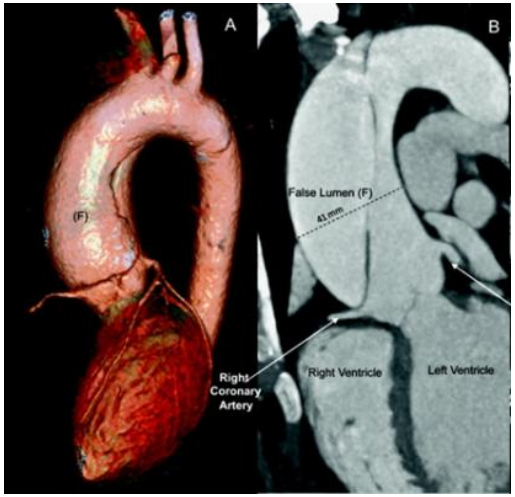
ESTABLISHED IN 1812 NOVEMBER 27, 2014 VOL. 371 NO. 22

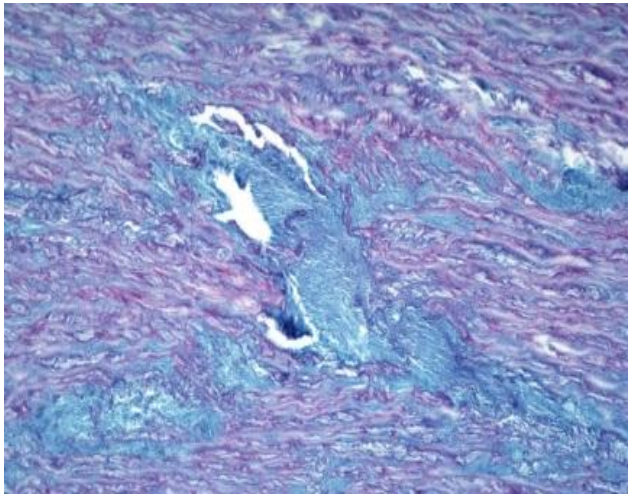
Atenolol versus Losartan in Children and Young Adults with Marfan's Syndrome





Clinical Challenges in Marfan Syndrome





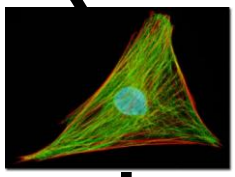
- Medical management limited. Beta blockade +/- surgery slow progression (30-70% aneurysm recurrence)
- Pathology from mouse models
  - Fibrillin-1 mutation -> TGF-β1 signalling??
- Location of disease?

Marfan Syndrome: Disease Modelling

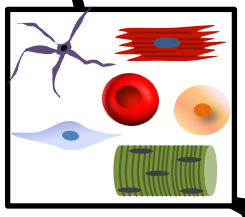
Shinya Yamanaka

Disease mechanisms
Drug screening

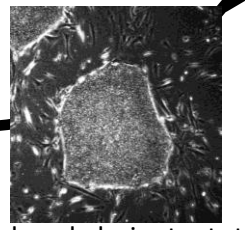
Skin
fibroblast



Oct4 KLF4 Myc Sox2



Vascular cells
Cardiomyocytes
Neurons
etc



Induced pluripotent stem cell
(iPSC)

(PDGF-BB + TGF-β1)

Neuroectoderm → NE-SMC

Lateral plate mesoderm → LM-SMC

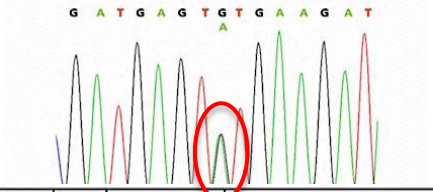
Paraxial mesoderm → PM-SMC

Cheung et al Nature Biotechnol 2012

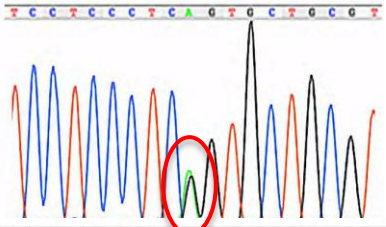
Abnormal Fibrillin-1 Deposition & Distribution in Marfan iPSC-SMC

Alex Granata

Mis-sense mutations

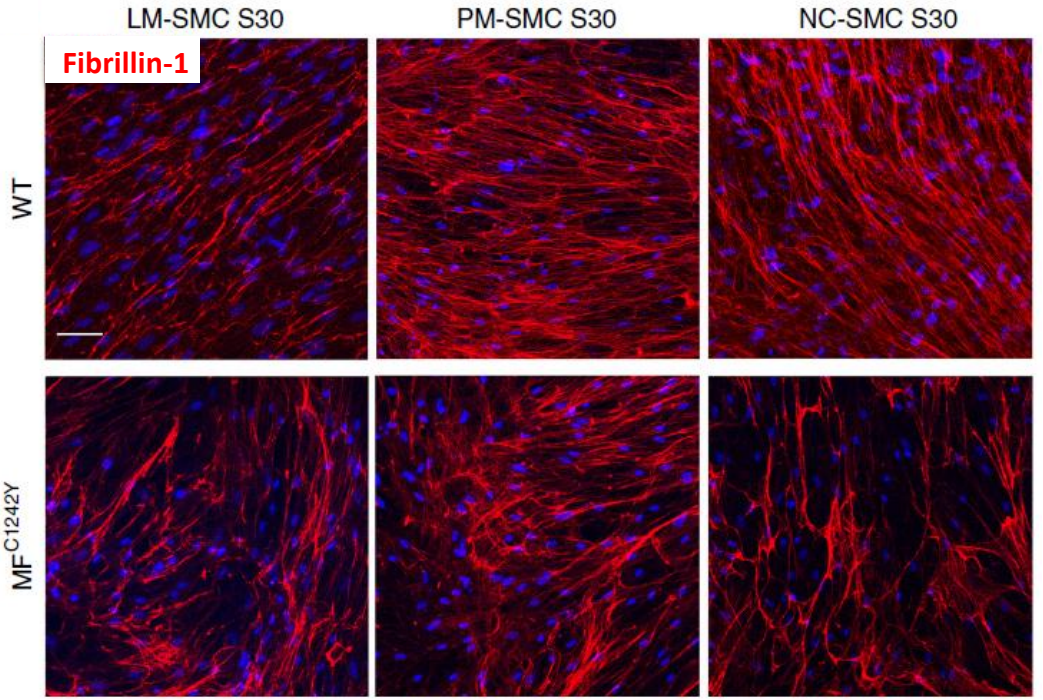


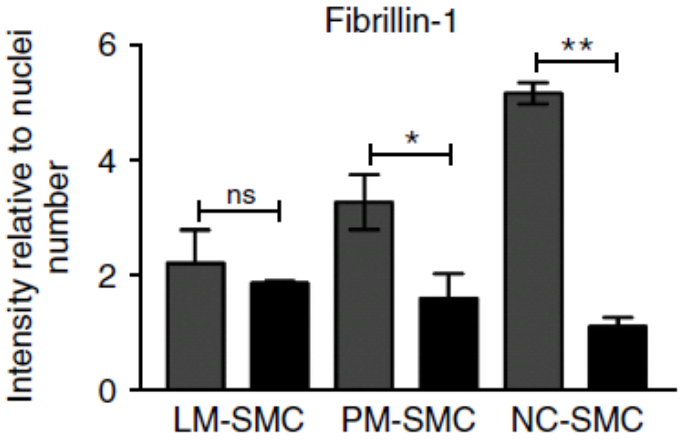
name	sex	age	mutation	remarks
MF^{C1242Y}	M	6	3725G>A	ascending aortic aneurysm



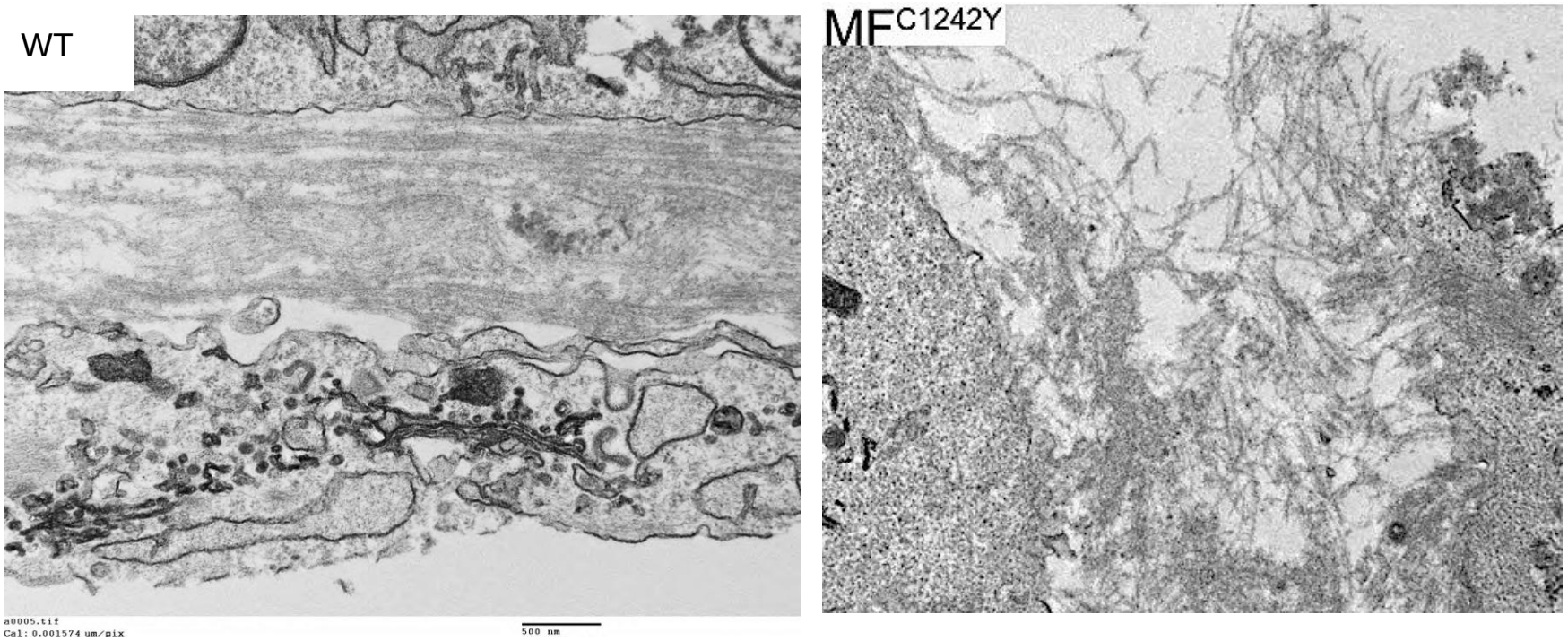
name	sex	age	mutation	remarks
MF^{G880S}	F	31	2638G>A	ascending aortic aneurysm

Granata et al Nature Genetics 2017



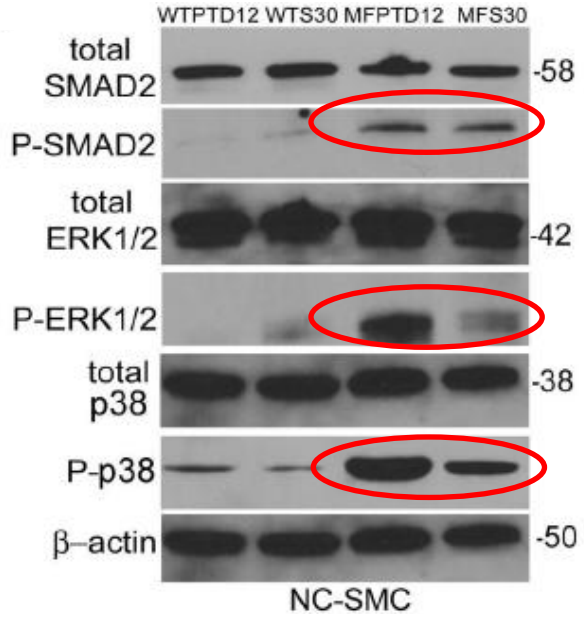


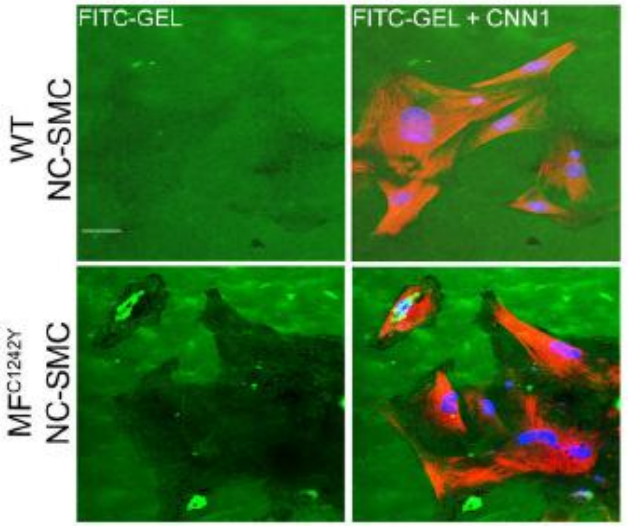
Abnormal Fibrillin-1 Deposition & Distribution in Marfan iPSC-SMC

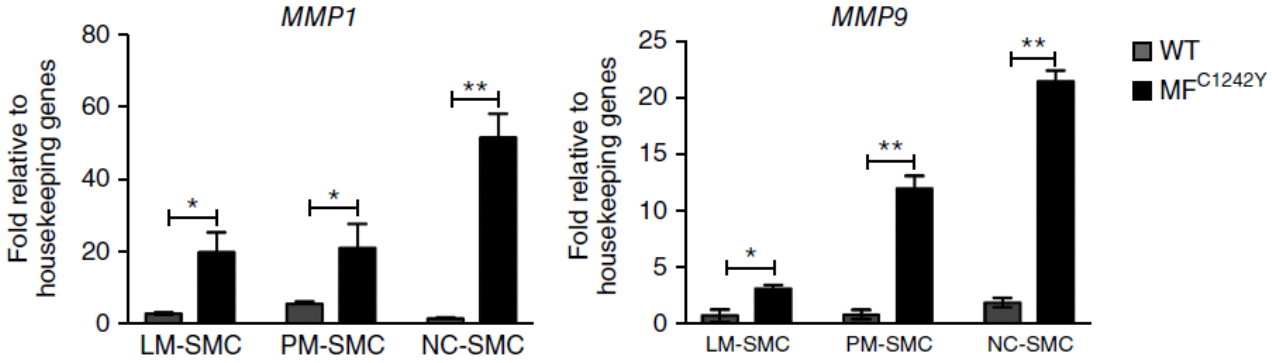


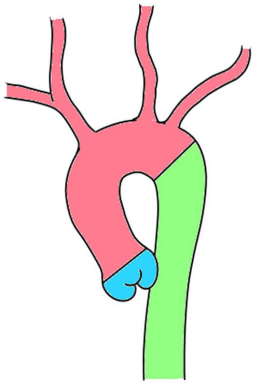
Granata et al Nature Genetics 2017

↑ TGF-β1 & MMP Levels & Activity in MFS iPSC-SMCs









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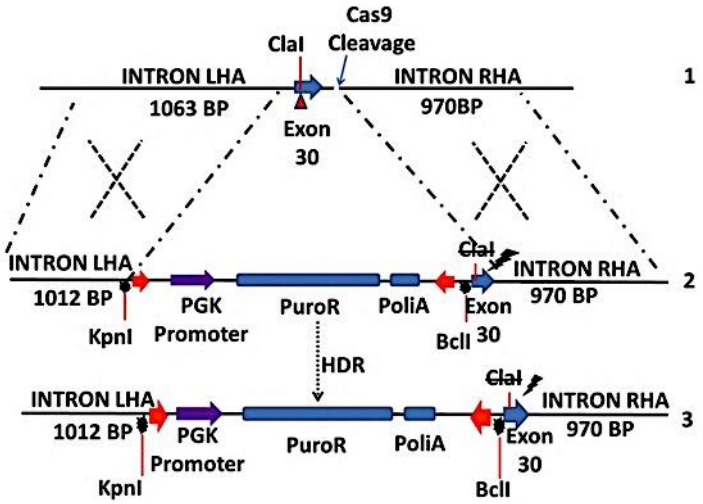
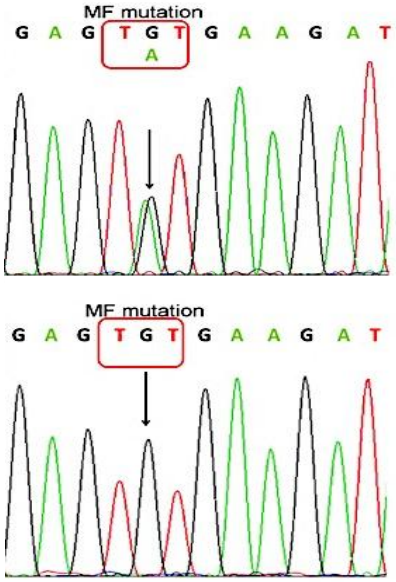
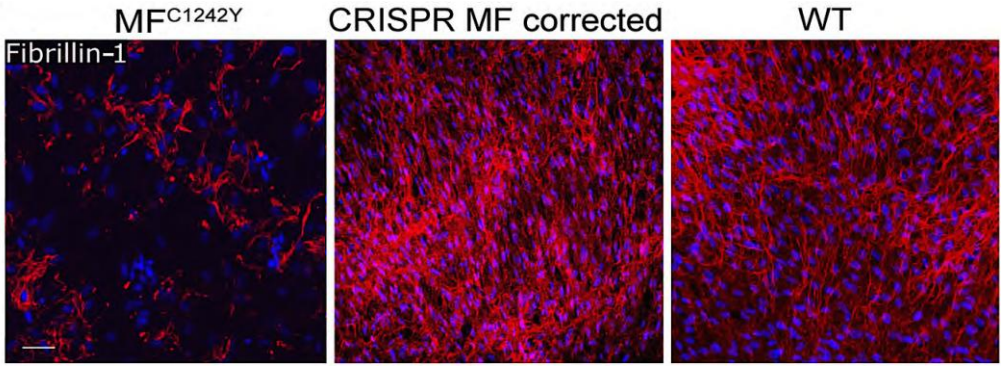
CRISPR/Cas9 Marfan hiPSC correction





Felipe Serrano

Fibrillin-1 deposition



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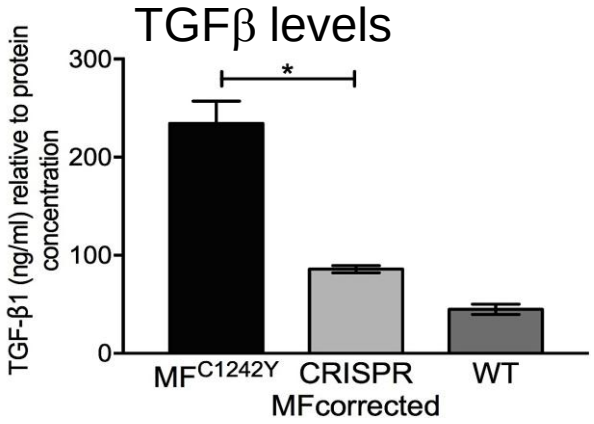
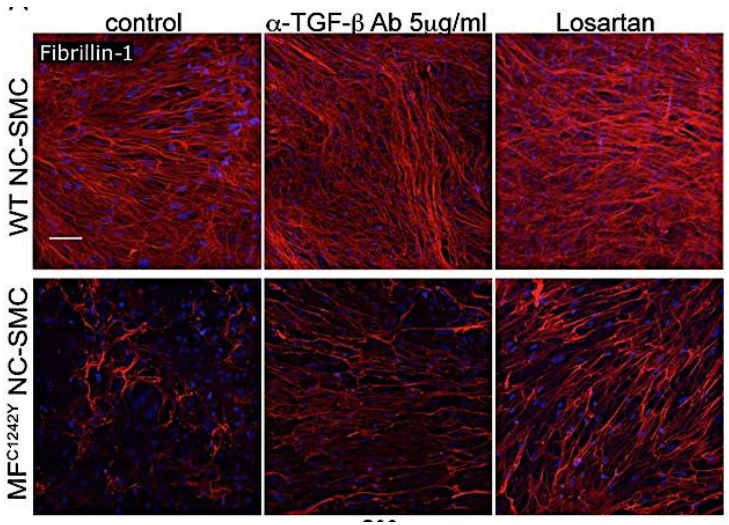
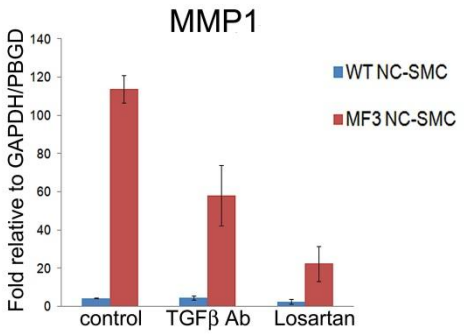
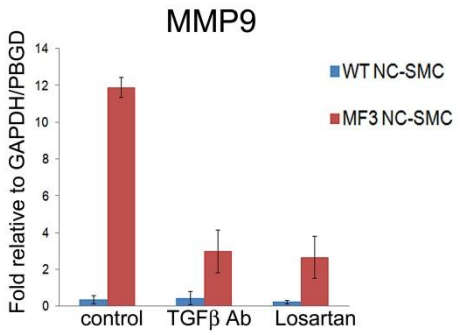
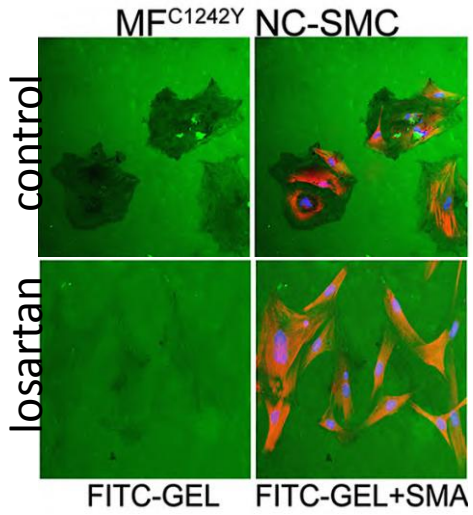


Partial Rescue of Phenotype with Losartan

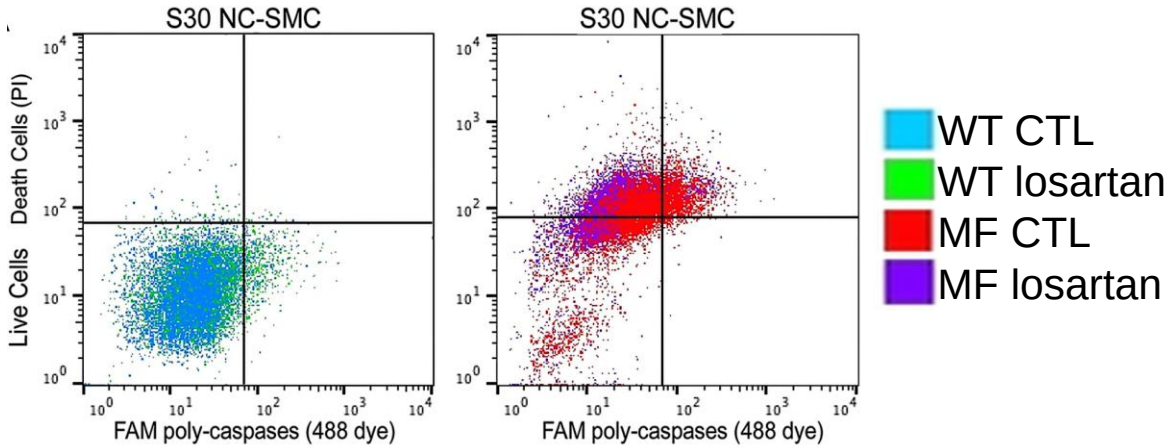




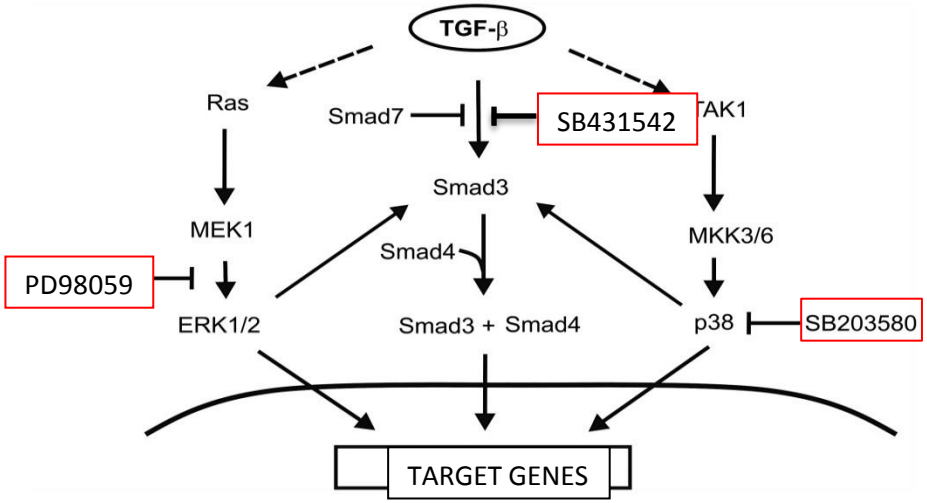


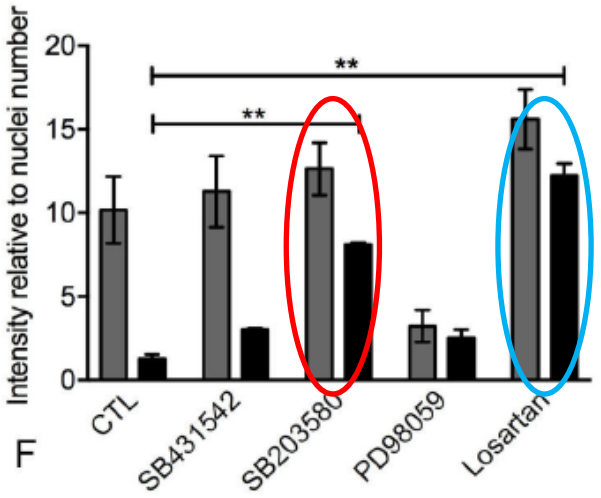


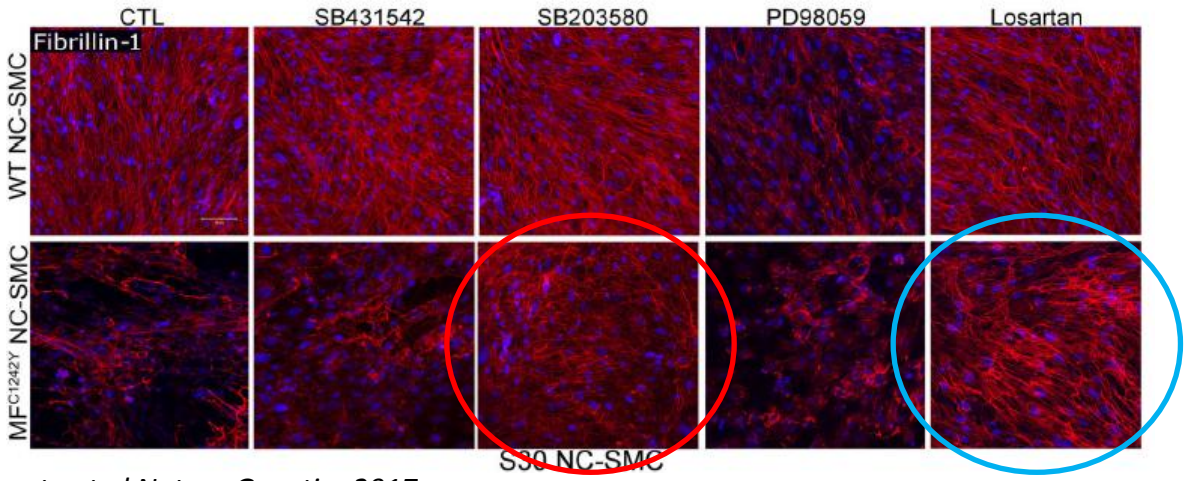
MF cell death

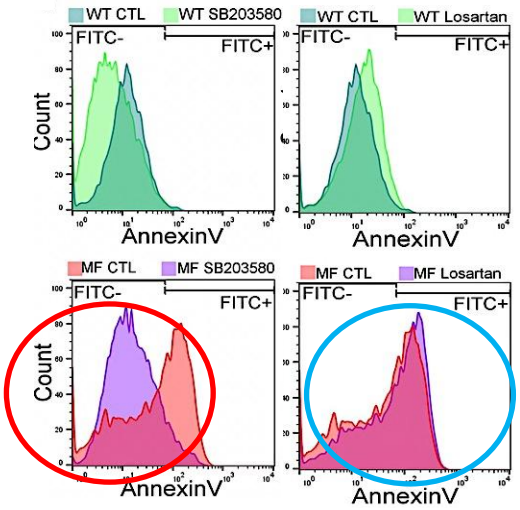


Dissecting Specific TGF-β Pathways in Marfans: Key Role for p38









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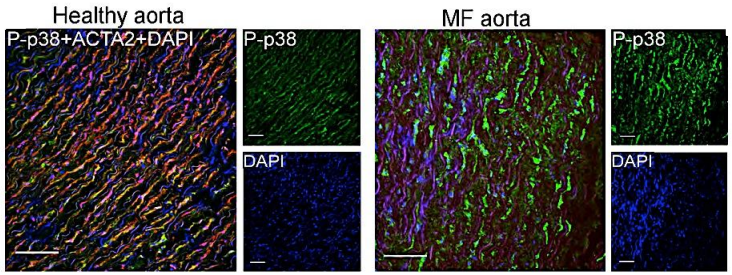
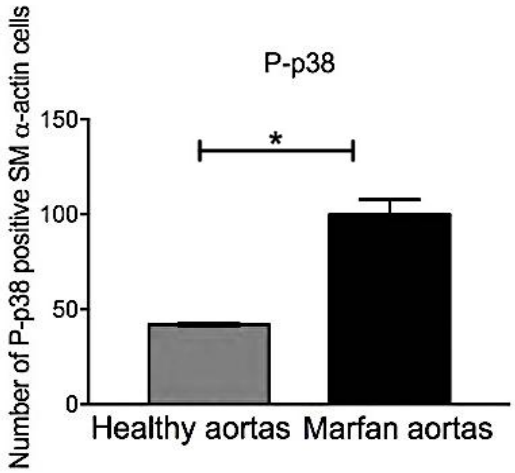
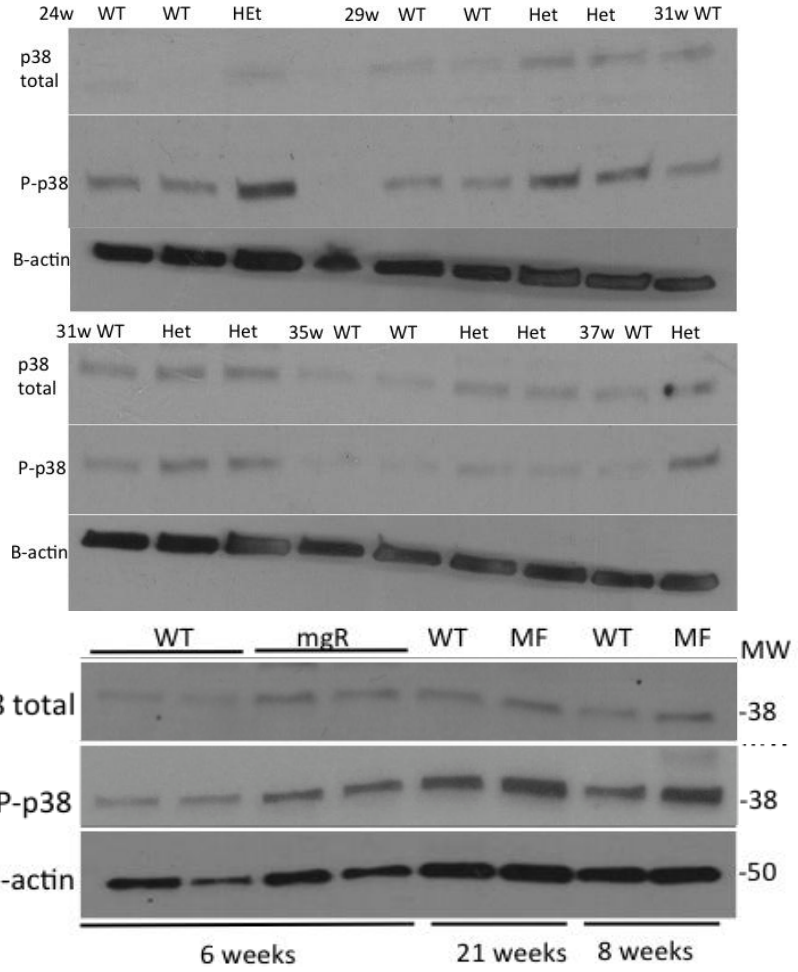
Validation of p38 Activation *in vivo*





Patient-derived tissue



Marfan mice

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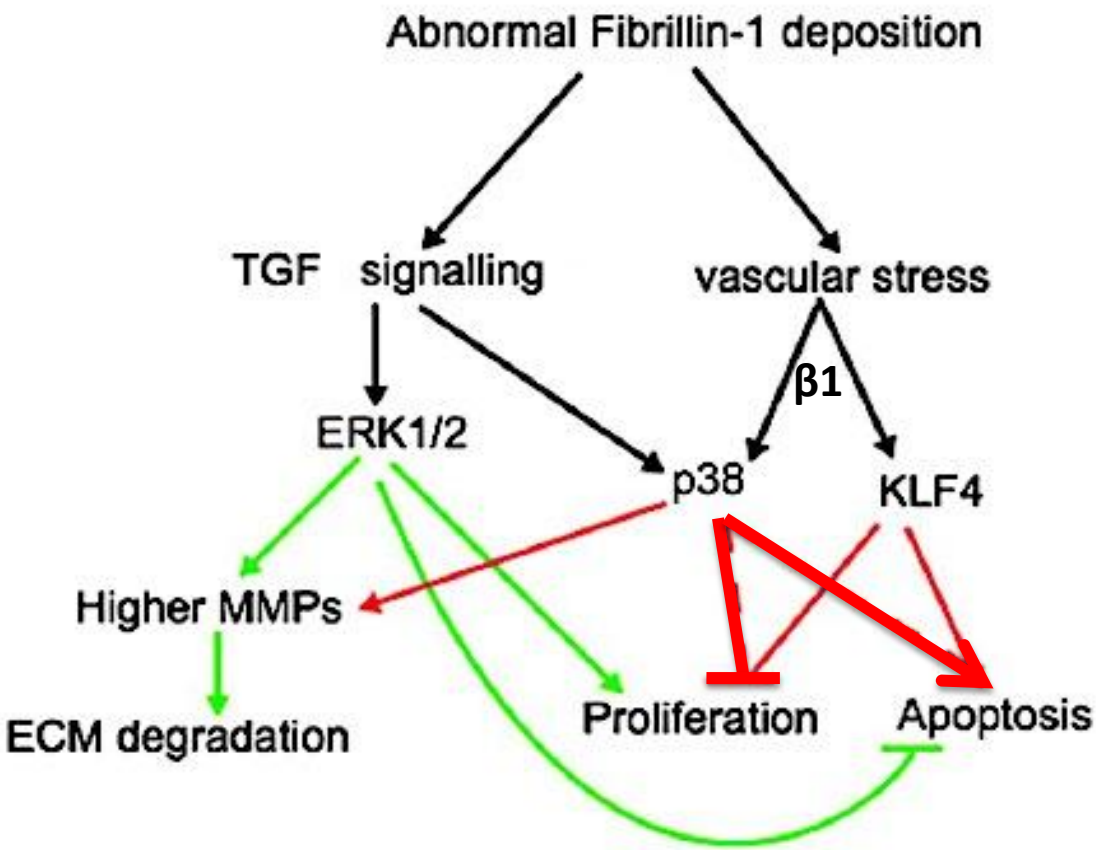
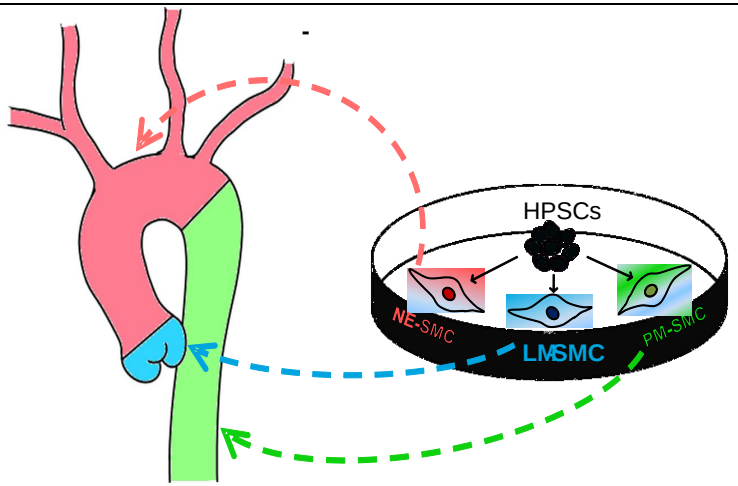
p38: a Novel Therapeutic Target in Marfans



SMC Origin and Disease: Summary

1. Developmental origin may influence SMC behaviour & disease development

2. Developmental origin – specific SMC can be modelled in vitro using hESC/hiPSC



3. Embryonic origin affects HoxA9/NFkB: predisposes to atherosclerosis susceptibility

4. Disease in a dish: the power of in vitro modelling & importance of the right kind of SMC

5. SMC lineage matters!

Acknowledgements

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NHS National Institute for Health Research

wellcome trust

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SMC Origin and Disease: Summary

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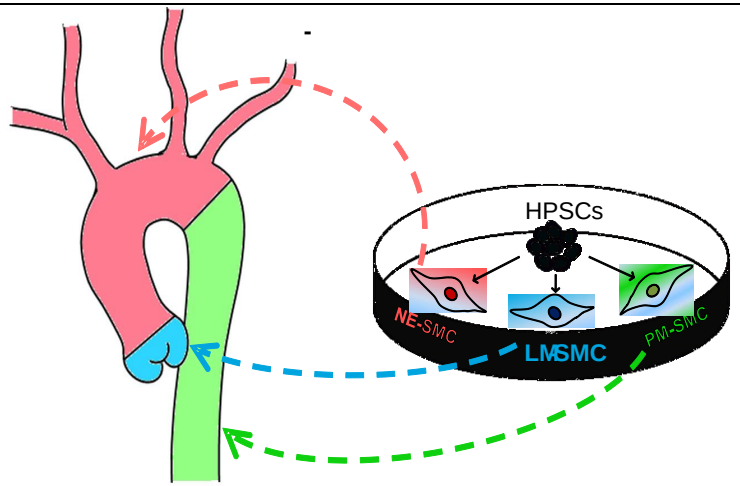

3. Embryonic origin affects HoxA9/NFkB: predisposes to atherosclerosis susceptibility

4. Disease in a dish - the importance of the right kind of SMC & many other aortic diseases

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