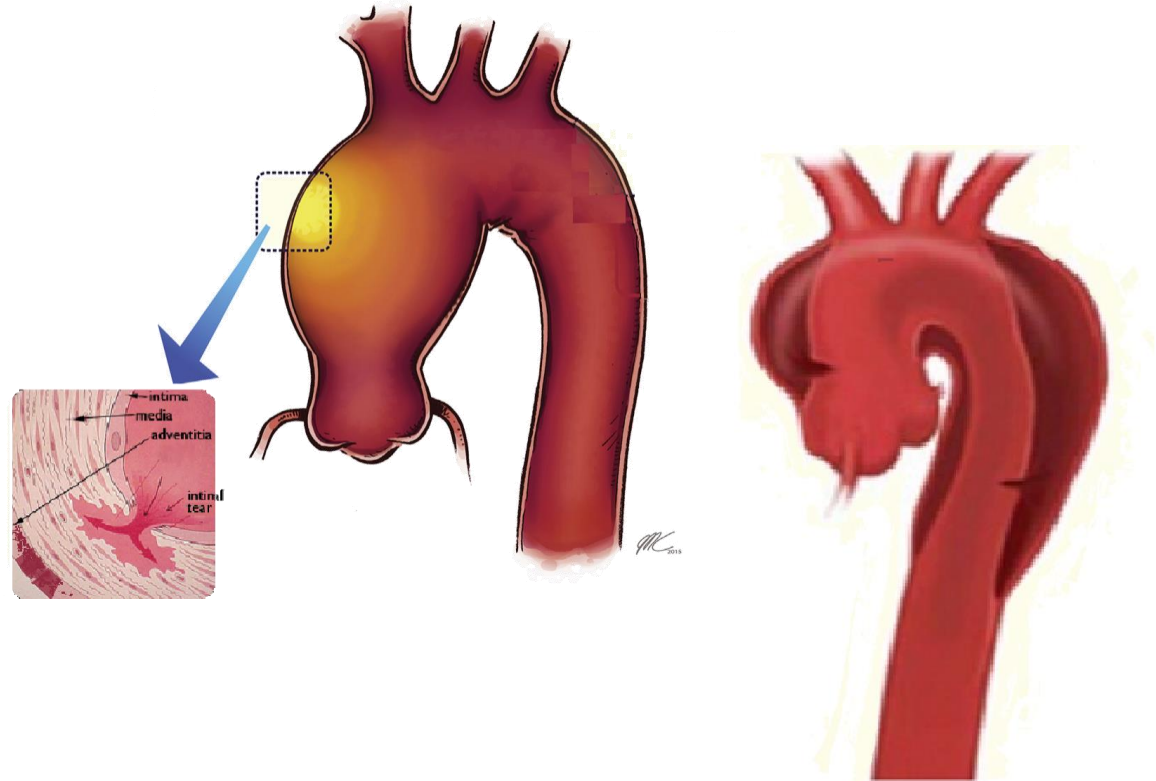
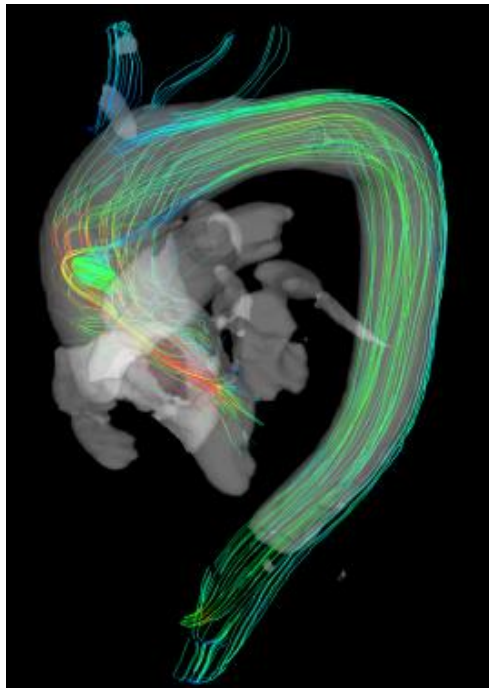


# FROM MECHANOBIOLOGY OF AORTIC SMOOTH MUSCLE CELLS TO IMPROVED PROGNOSIS OF THORACIC AORTIC ANEURYSMS

Stéphane AVRIL



# Aneurysms and Dissections of the aorta



**== Devastating complications!**

## OBJECTIVES

Our first goal was to develop computer models to assist surgical interventions on aortic aneurysms

2010



# Mechanics can predict health!! It even enables decisions everyday in healthcare combined with AI



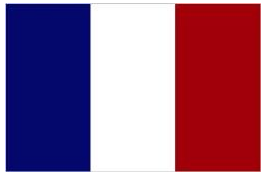
**2014:** FDA allows marketing of HeartFlow vFFR-CT tool for optimal treatment of coronary stenosis

Gaus S, *et al*, JCTT 2013, 7(5):279-88.



**2019:** FEops HEARTguide in silico tool for planning transcatheter aortic valve implantation is CE-marked

El Faquir N, *et al* Int J Cardiovasc Imaging 2019



**2014:** Sim&Cure

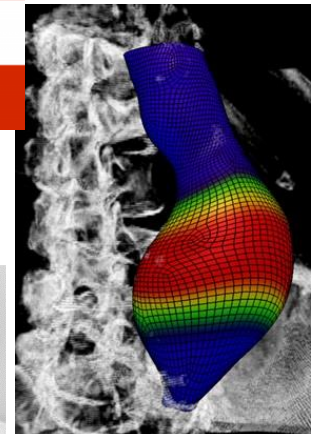


**2017:** Predisurge

Derycke, *et al* Circulation Imaging 2021



Vascops



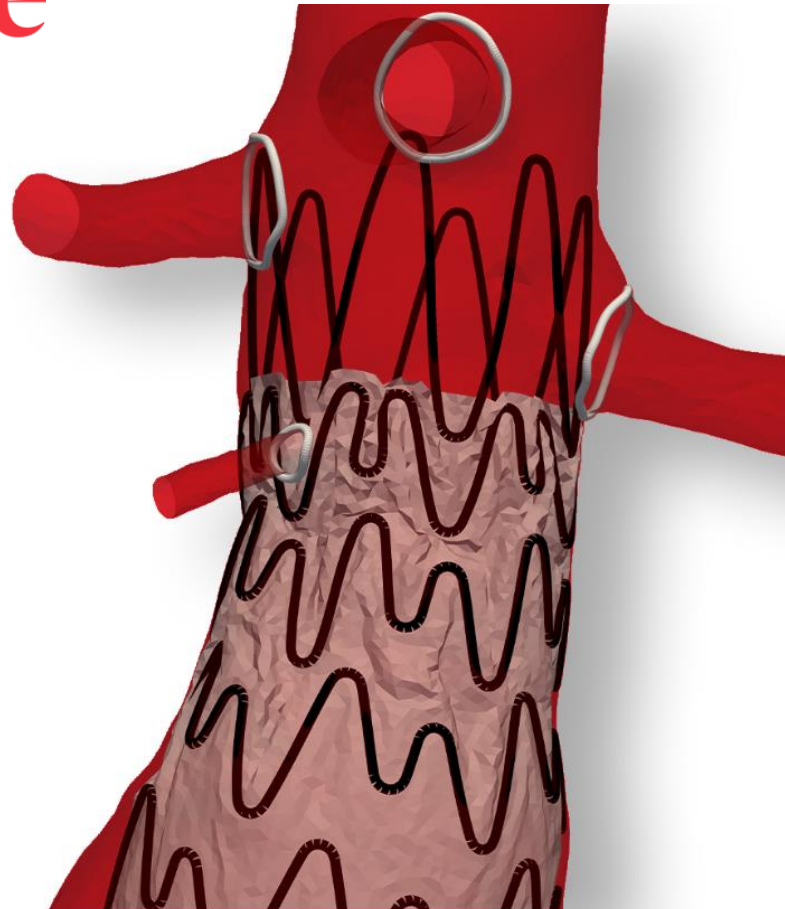
... even in aortic aneurysms

# PrediSurge

Changing patients lives  
with digital twin technology

Predictive Simulation  
for Cardiovascular Intervention

LEARN MORE



## OBJECTIVES

Our next goal was to develop  
patient-specific computer models of  
aneurysm growth...

2010

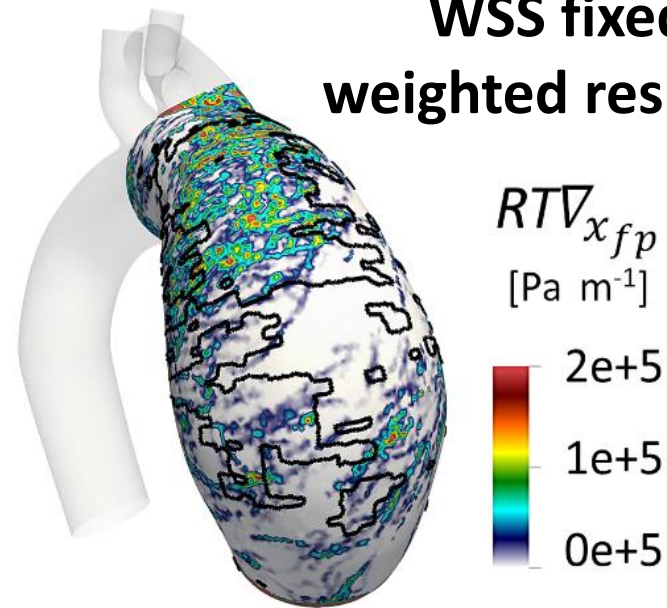
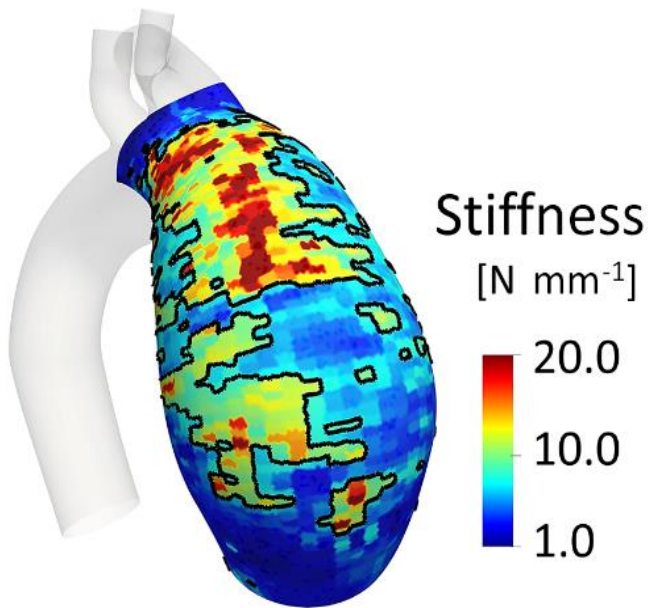
2015



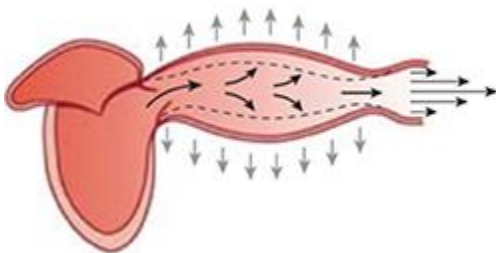


# Local stiffening related to locally altered hemodynamics

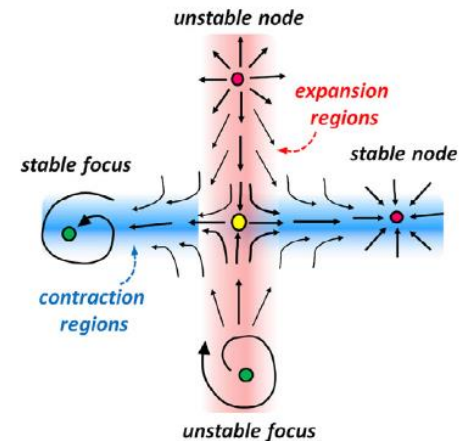
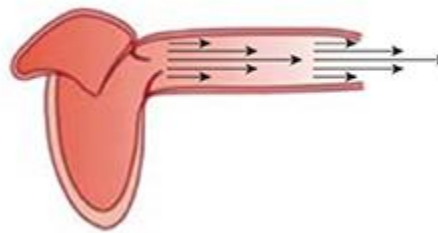
WSS fixed points  
weighted residence time



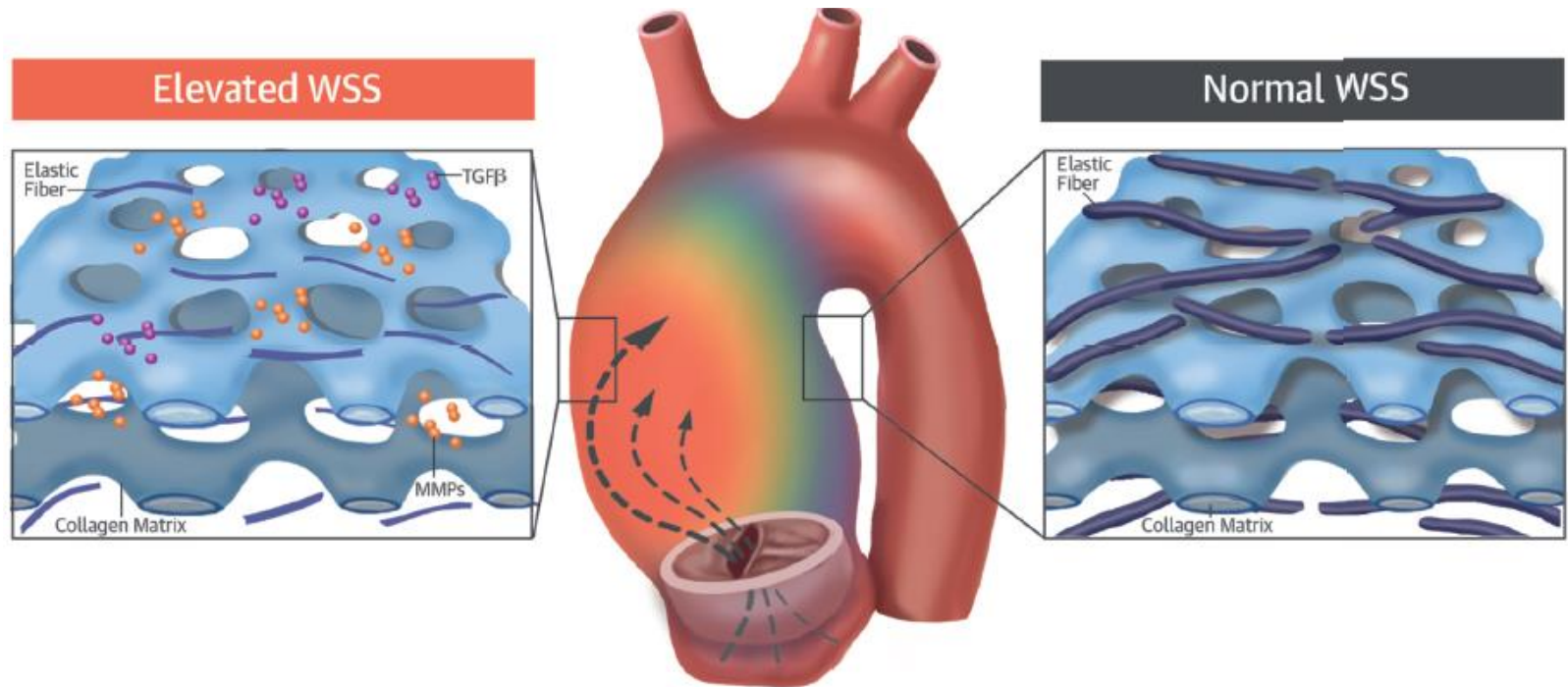
Elastic arteries



Stiff arteries



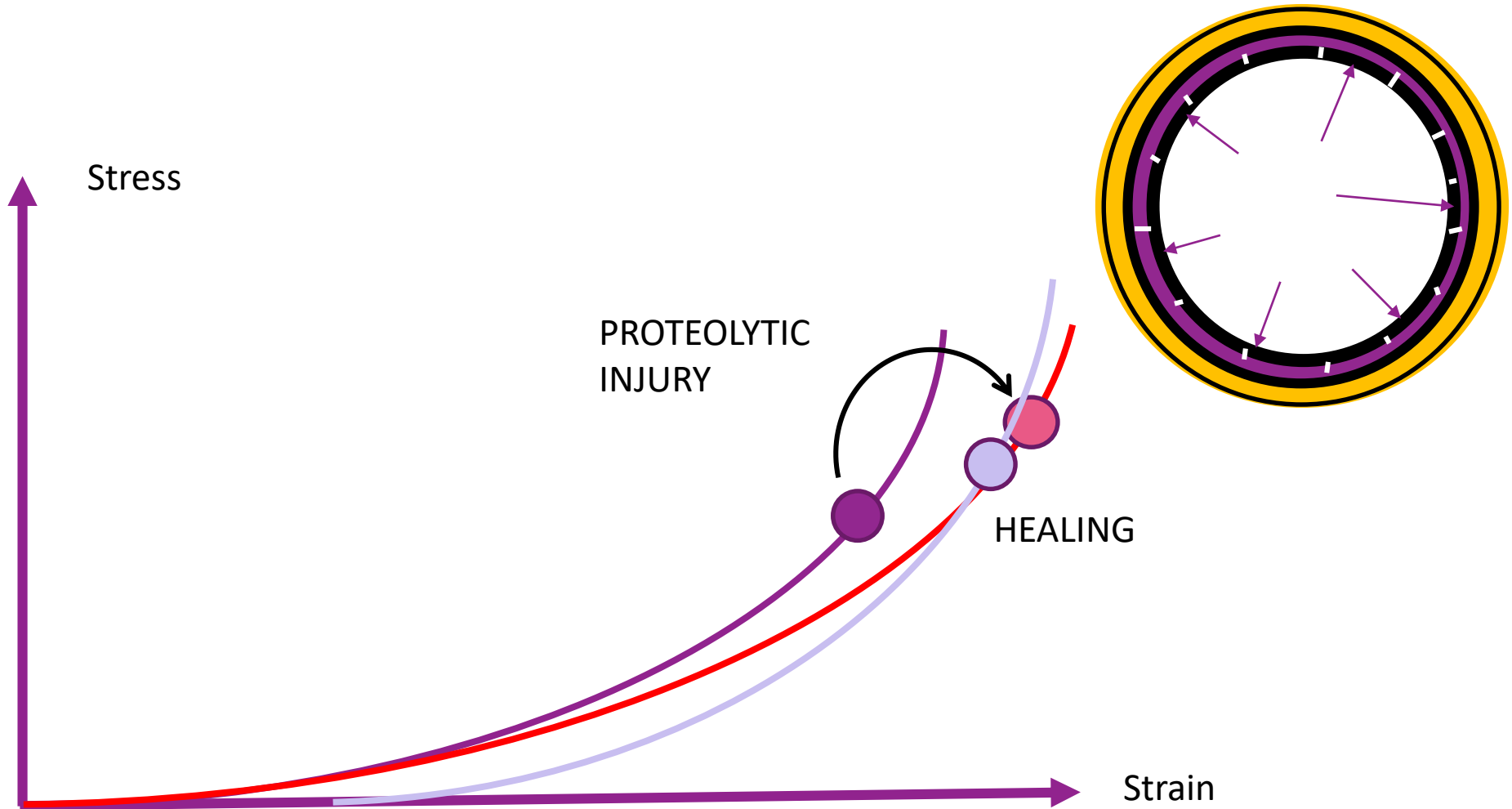
# Local proteolytic injury precedes mechanobiological adaptation

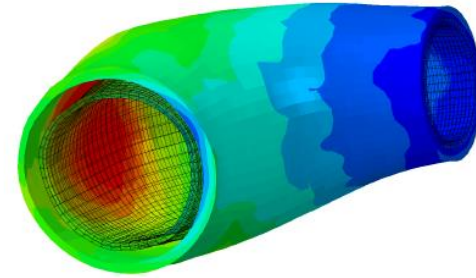


Guzzardi et al, JACC (2014), Condemi et al, IEEE TBME (2019)



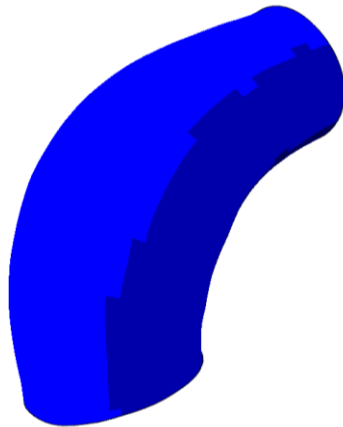
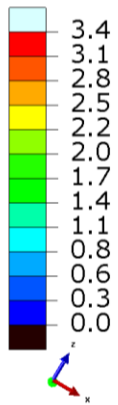
# Mechanical model



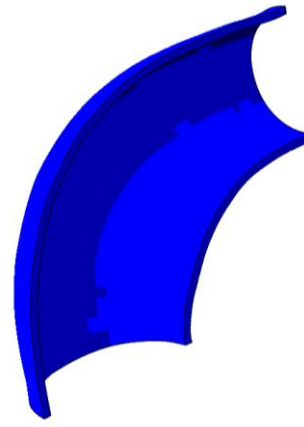
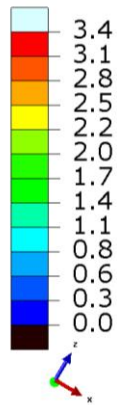


# Computer model of aneurysm growth

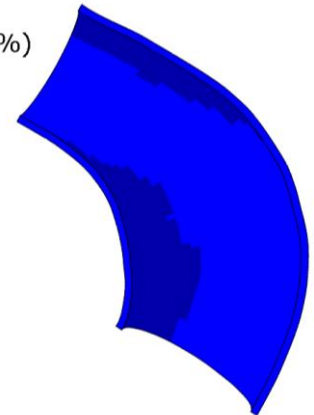
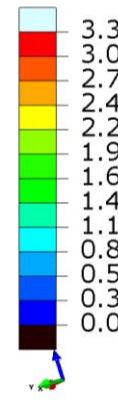
SDV69  
(Avg: 75%)



SDV69  
(Avg: 75%)



SDV69  
(Avg: 75%)



Normalized Thickness

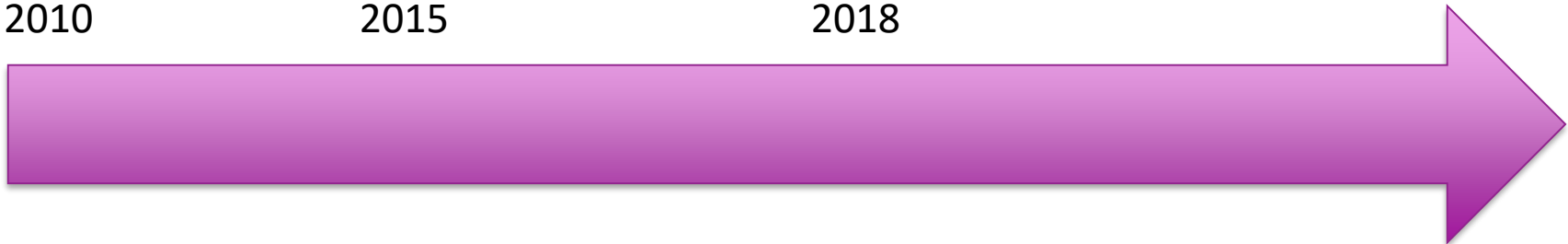
## OBJECTIVES

Our next goal was to integrate more vascular mechanobiology in our computer models of aneurysm growth

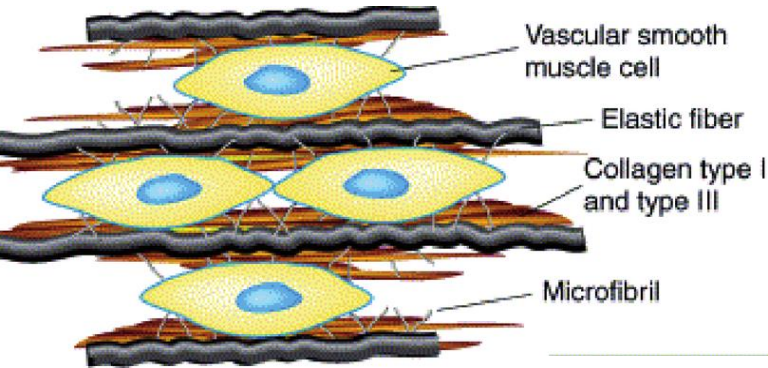
2010

2015

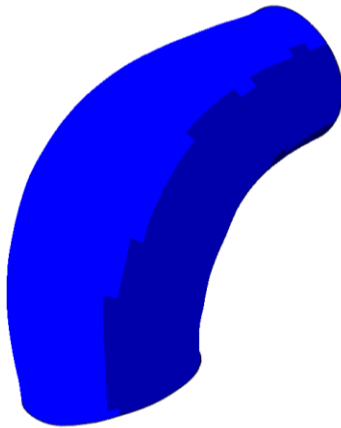
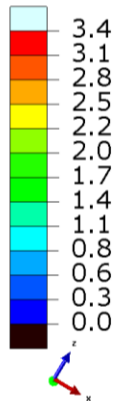
2018



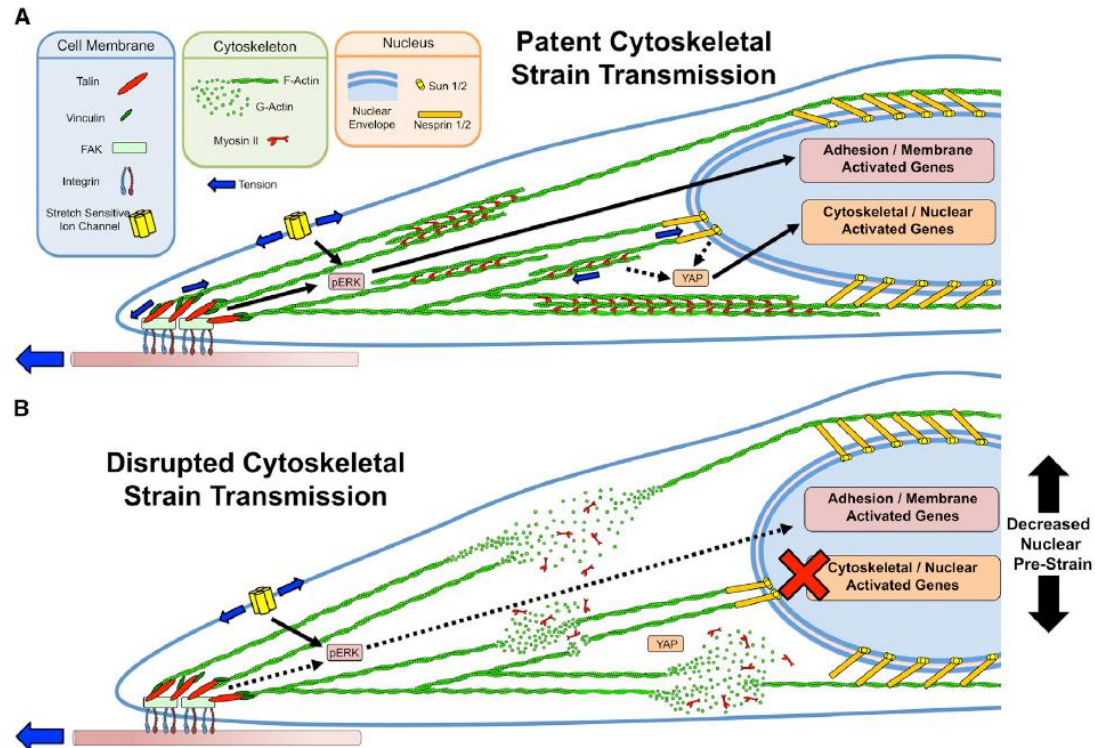
# Major role of smooth muscle cells in mechanoregulation



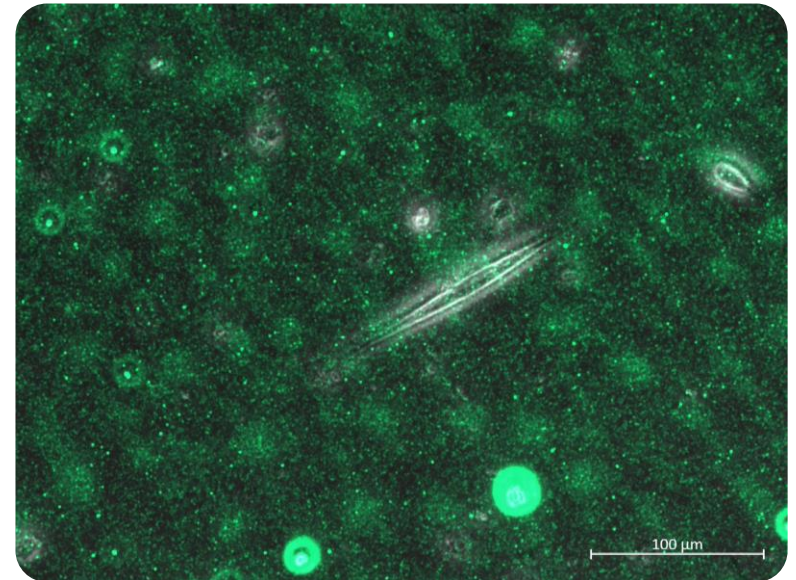
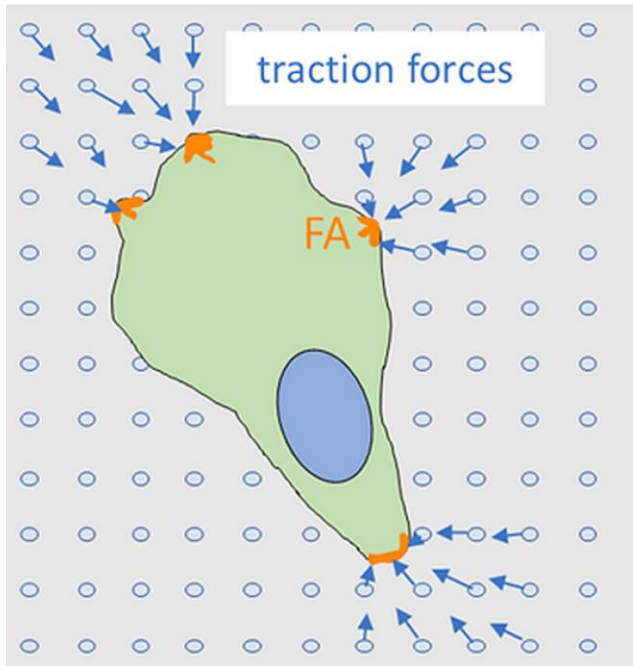
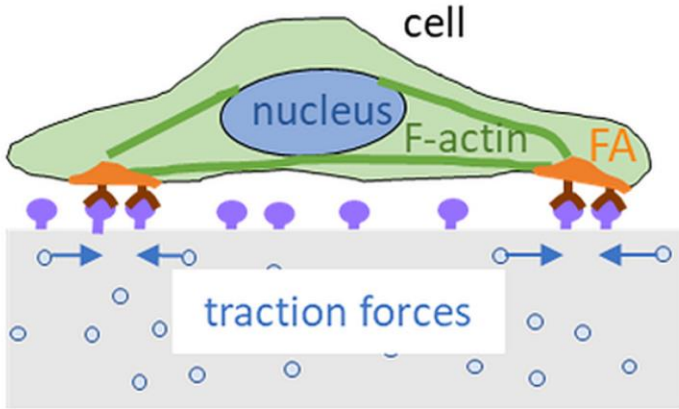
SDV69  
(Avg: 75%)



Driscoll et al, Biophysical Journal, 2015

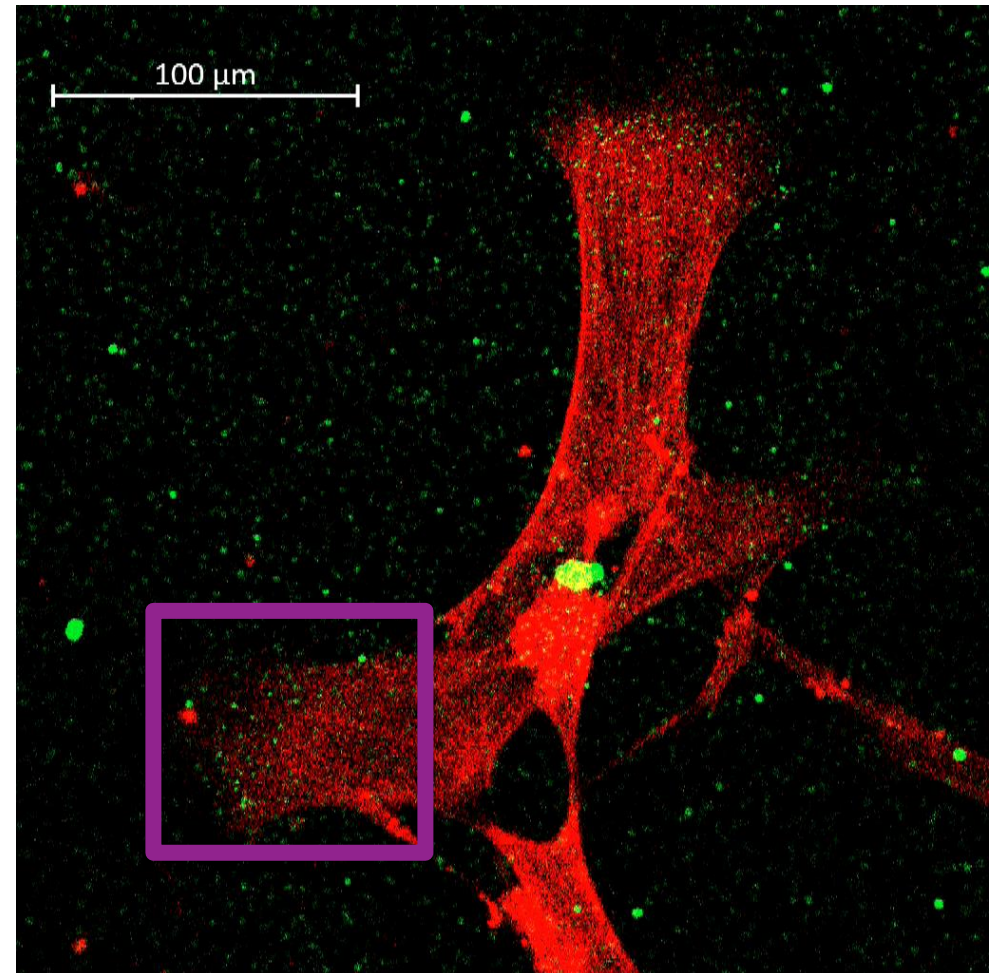
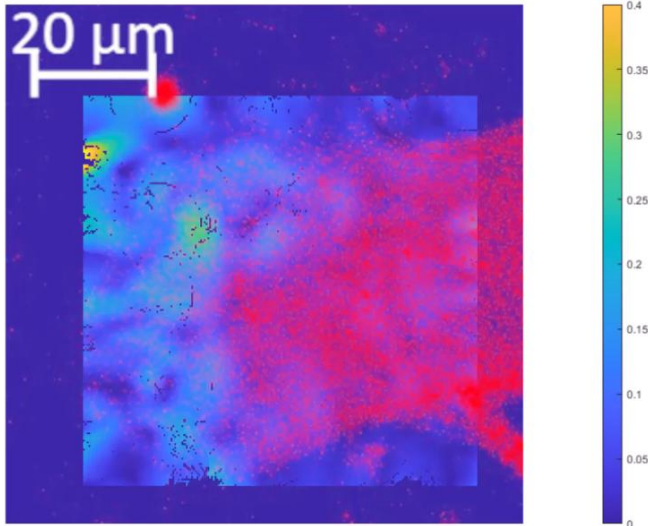


# Possibility to study VSMC mechanics with traction force microscopy





# Mechanobiology of aortic SMCs

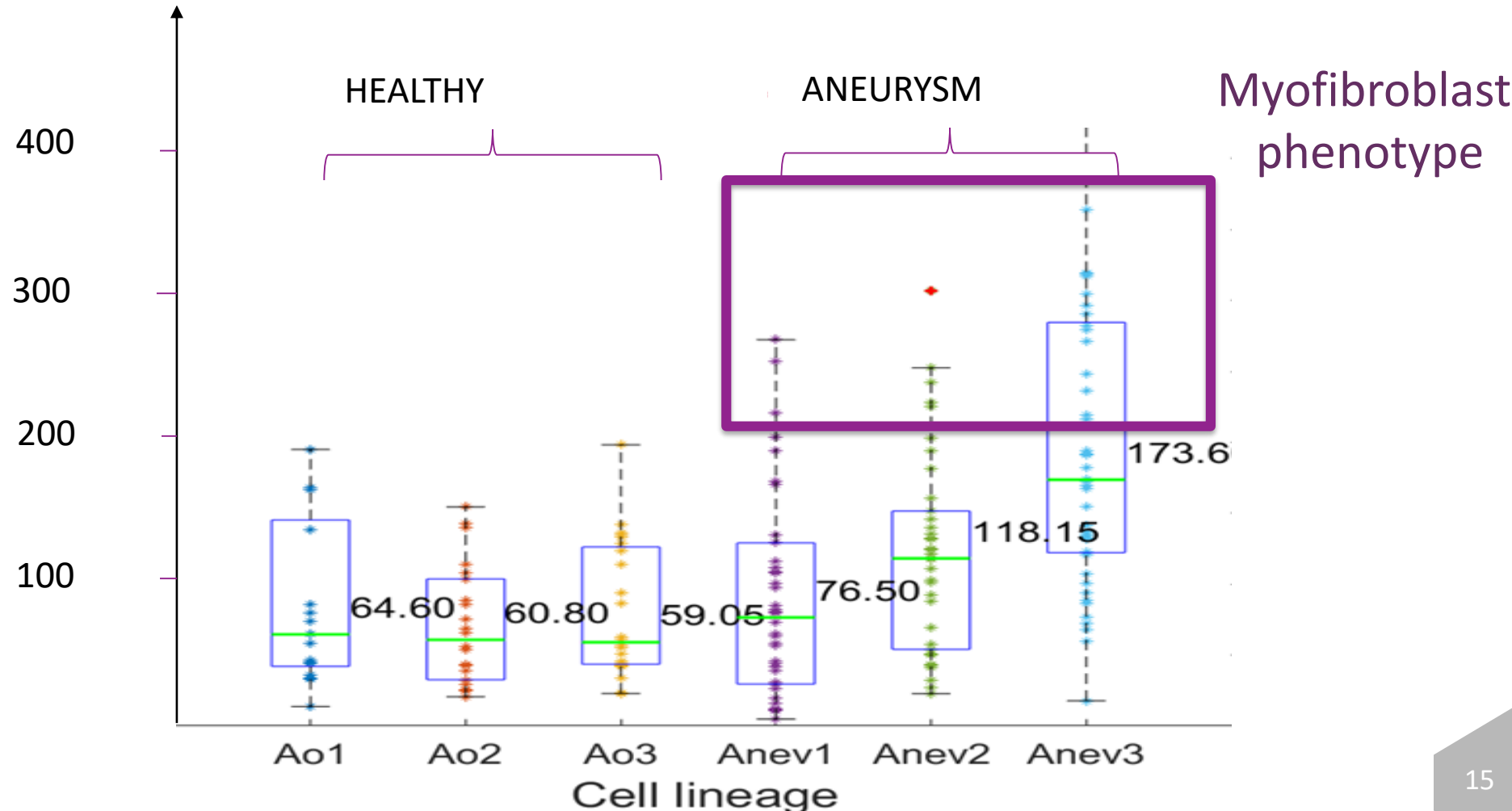


**Confocal microscopy + DIC  
combined with Siractin  
staining on living cells**

# Aneurysmal SMCs express stronger phenotypes

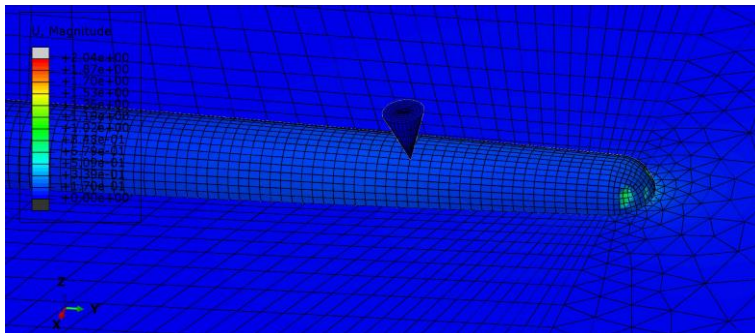
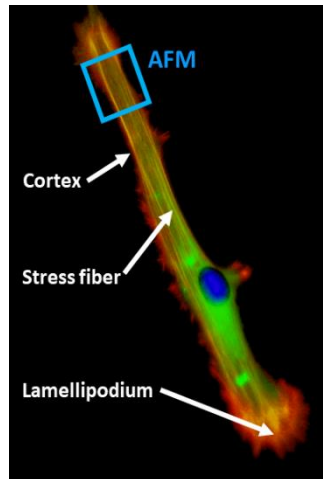
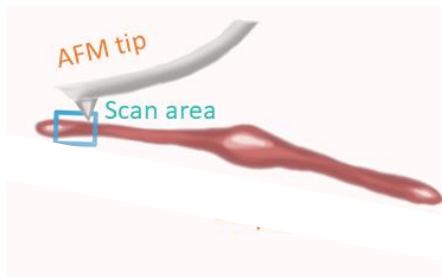
Petit C, Karkhaneh Yousefi AA, Ben Moussa O, Michel JB, Guignandon A, Avril S. Regulation of SMC traction forces in human aortic thoracic aneurysms. *BMMB*. 2021 Apr;20(2):717-731.

TFM (nN)

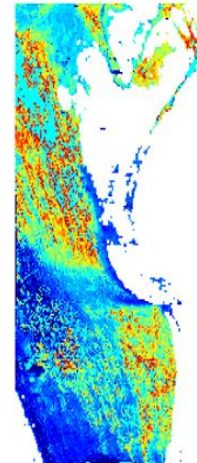


# AFM nanoindentation of the cytoskeleton

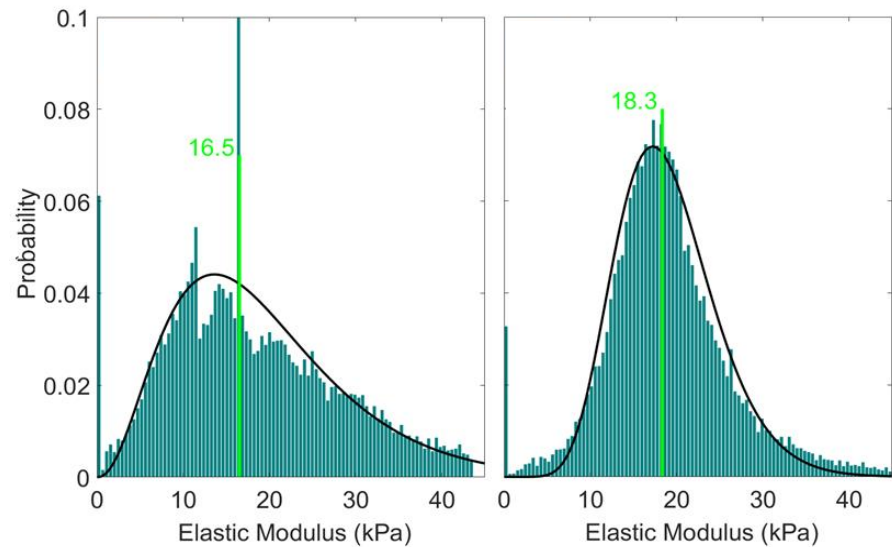
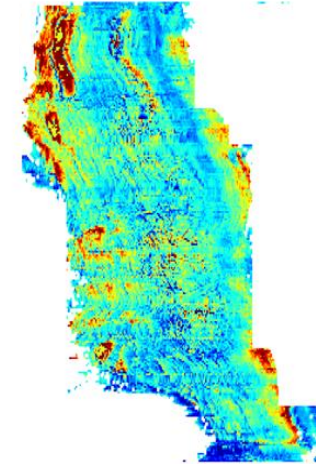
Petit et al, JBME, 2022



HEALTHY

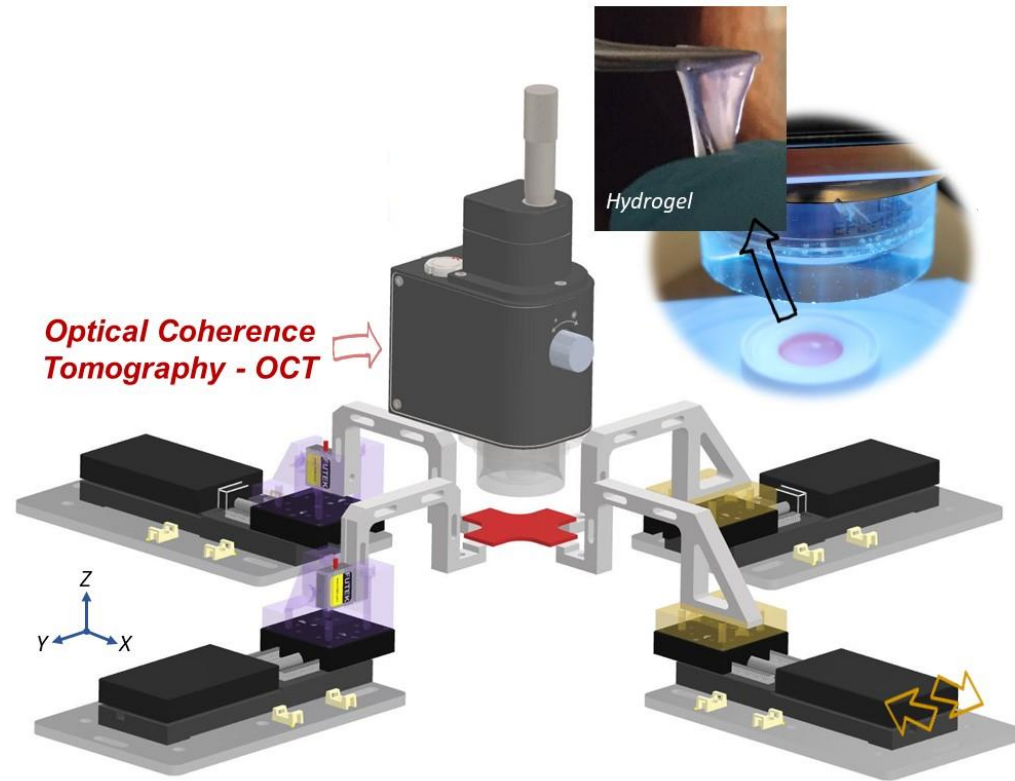
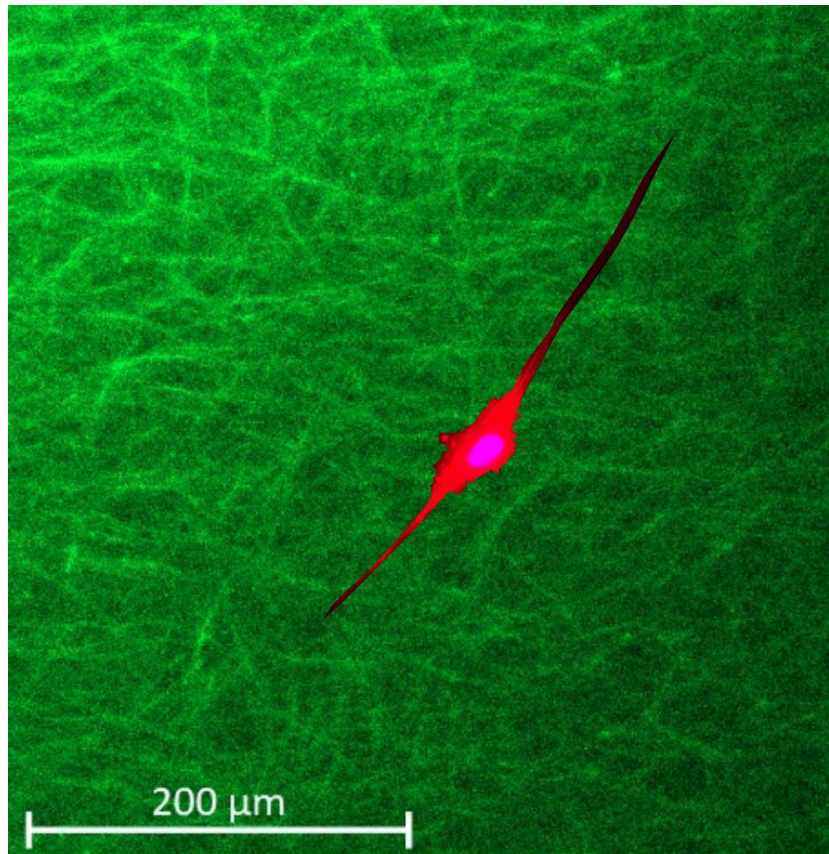


ANEURYSM





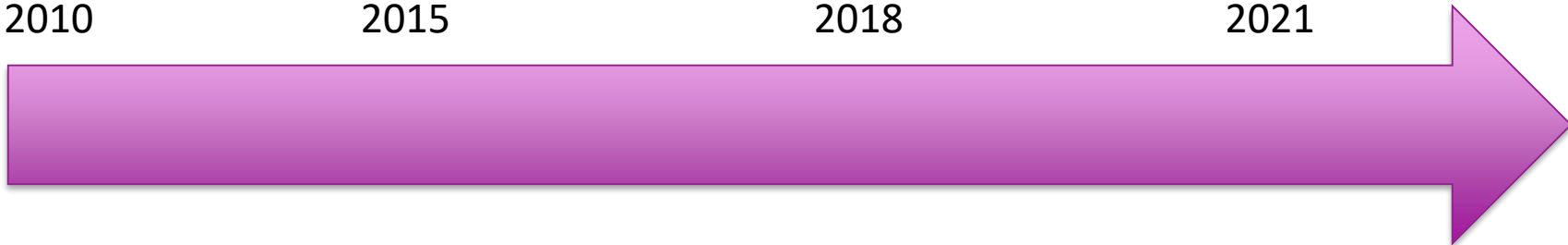
# In progress: 3D TFM in collagen hydrogels



## OBJECTIVES

Our next goal was to decipher the links between phenotypic modulations of SMCs and mechanical stimulations

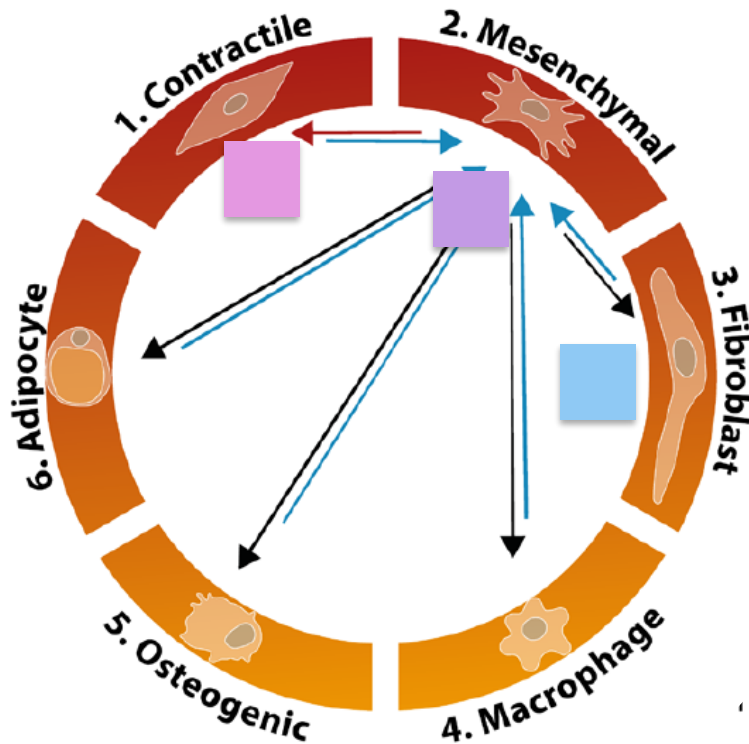
2010                      2015                      2018                      2021





# Variety of aortic SMC phenotypes

Yap et al, ATVB. 2021; 41:2693–2707.



TAGLN - transgelin

TNFRSF11B TNF – OPG - osteoprotegerin

SERPINE1 – human plasminogen activator inhibitor 1 (PAI-1)

ACTA2 -  $\alpha$ -SMA

MLCK – myosin light chain kinase

TGFBR1 – Transforming Growth Factor receptor 1

PRKG1 – Protein kinase cGMP-dependent 1

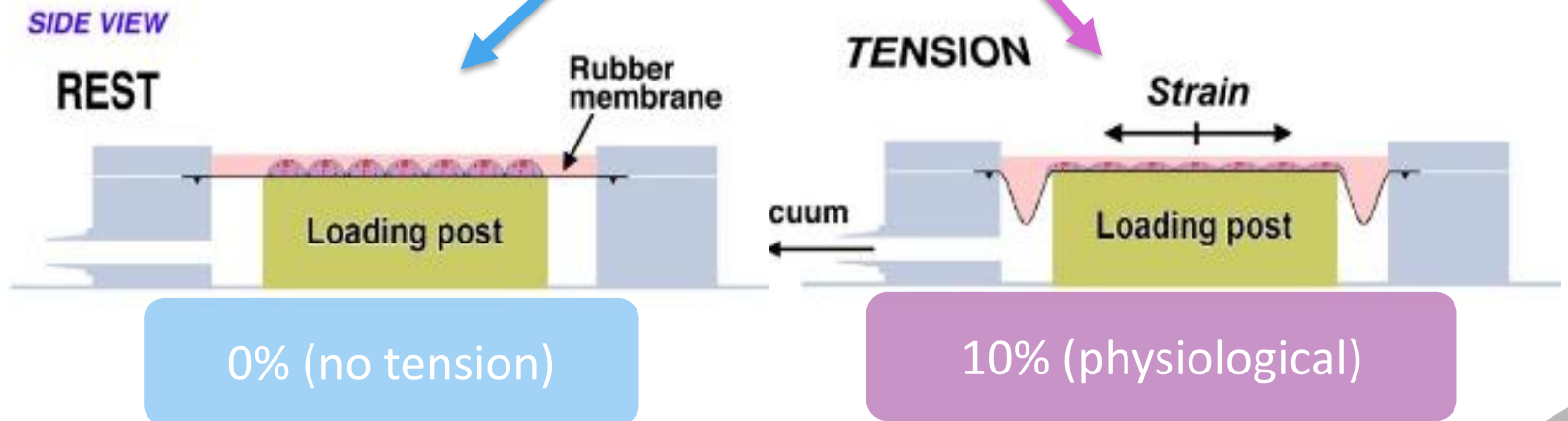
FBN1 - fibrillin 1

COL1A1 – Collagen type 1 $\alpha$ 1

LAMA5 - Laminin

MMP2 – matrix metalloproteinase 2

# Flexcell tension system



# Mechanical stimulation in culture

Commercial lineage : Lonza  
AoSMC, Passage 6-7,  
H, 21 y.o.

Cell culture



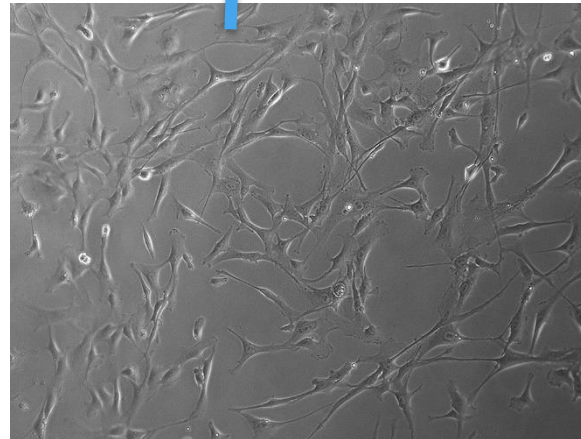
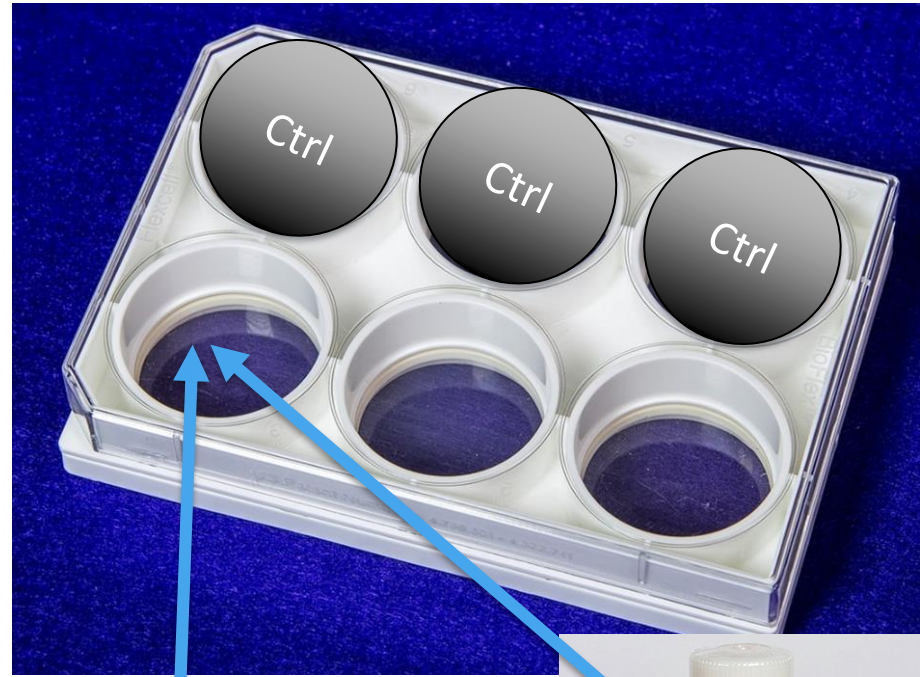
Sample preparation



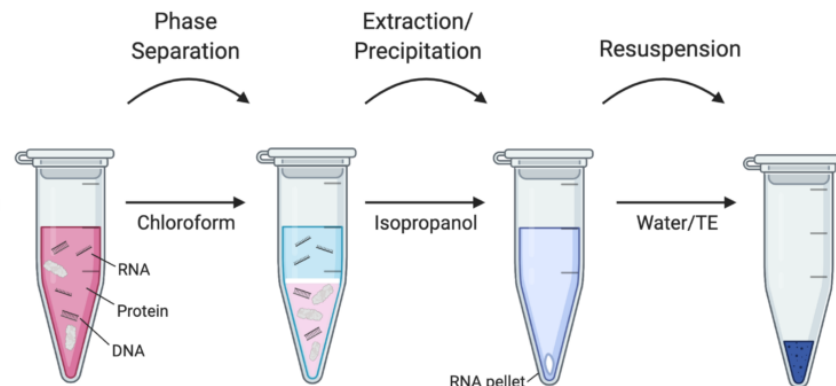
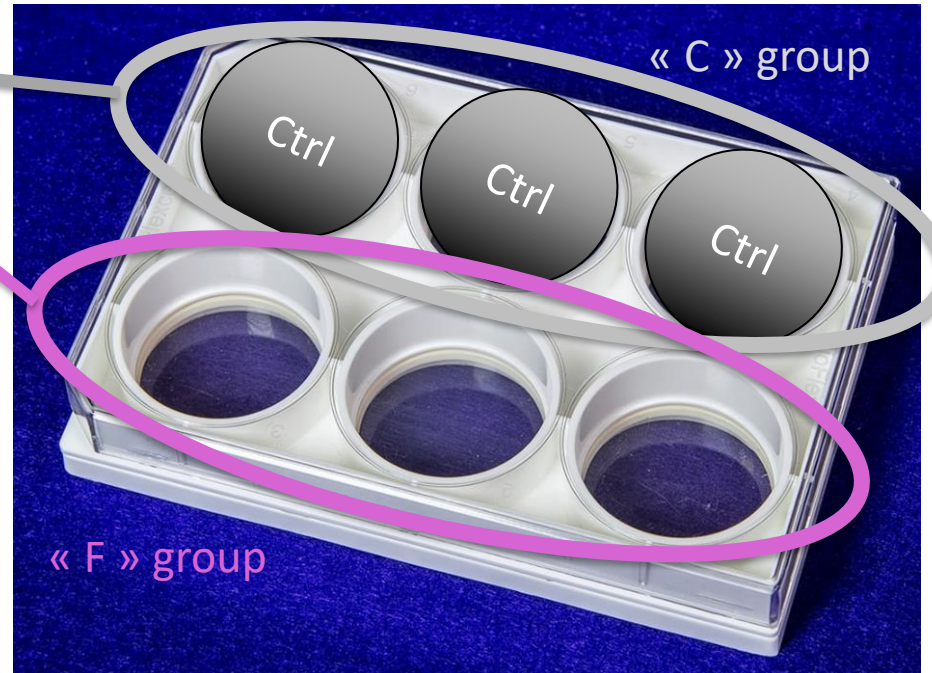
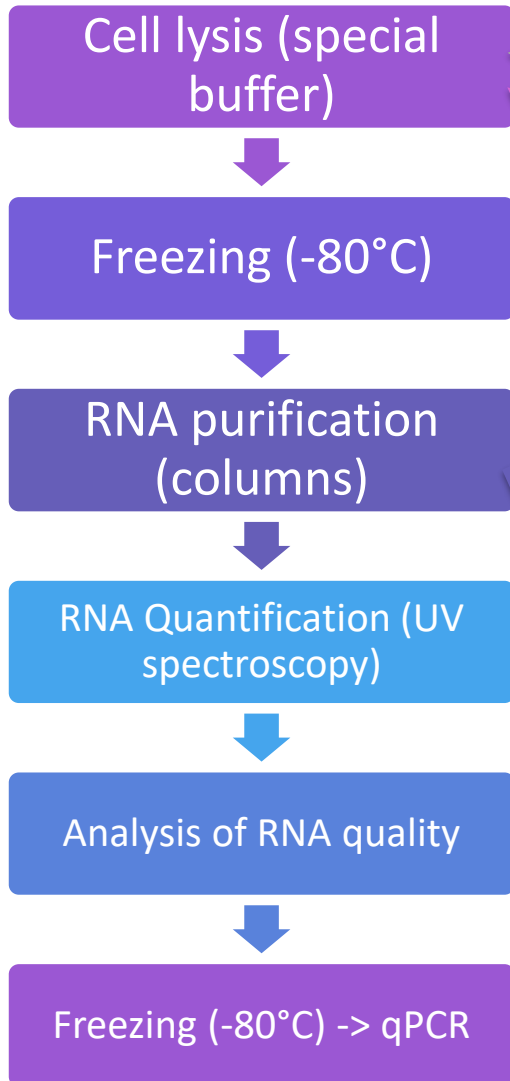
Stimulation in culture  
(24, 48, 72, and 100h)



RNA extraction + qRT-PCR



# RNA extraction & sequencing



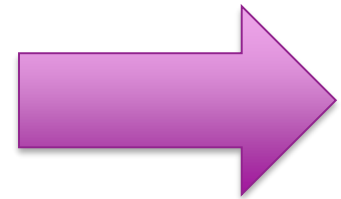
Genes of ECM remodeling are upregulated after 2 days only in controls, not in stimulated SMCs

Col1a1
FBN1
TAGLN
MLCK
PRKG1
MMP2
OPG



No mechanical stimulation

Col1a1
FBN1
TAGLN
MLCK
PRKG1
MMP2
OPG



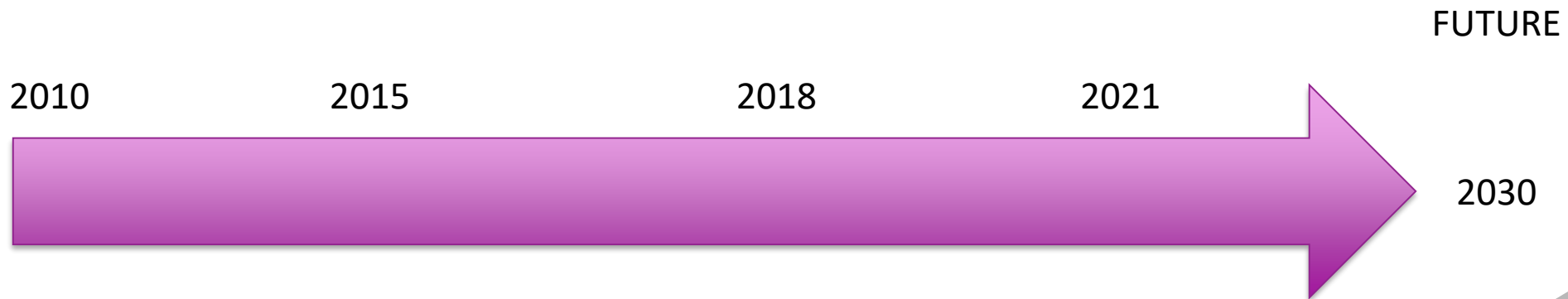
With mechanical stimulation

**Mechanical stimulation prevent SMCs to remodel their ECM.**

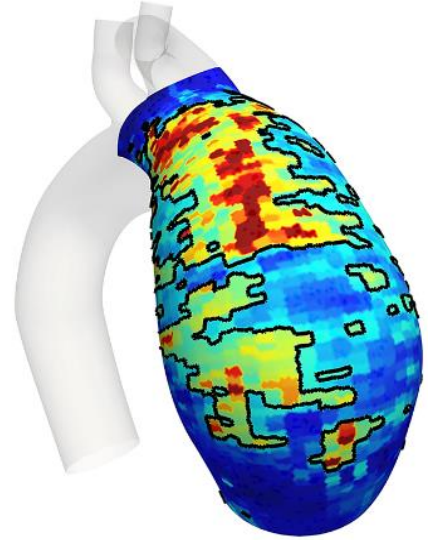


## PERSPECTIVES

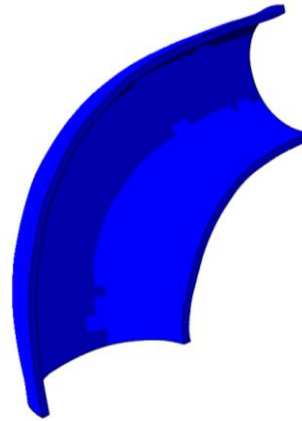
Our goal in the future is to develop digital twins



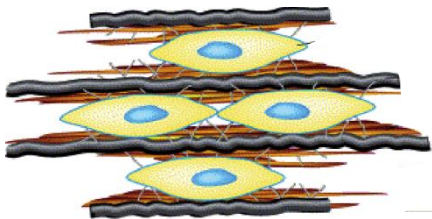
# TOWARDS DIGITAL TWINS



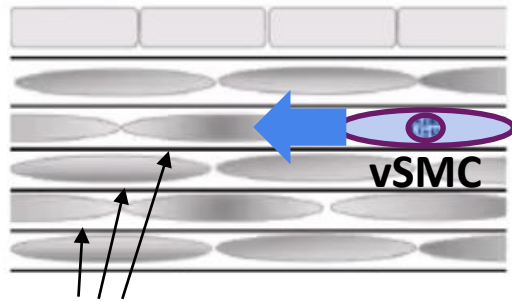
Monitoring immuno-mechanical  
stimulations



Predicting tissue remodelling,  
deformations, stresses and stiffness

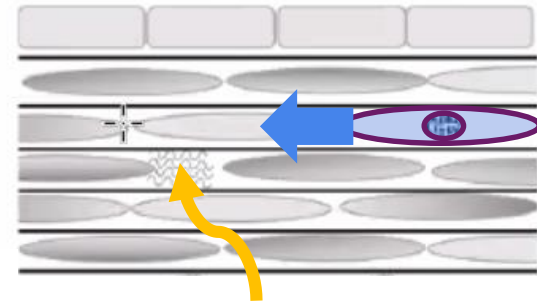


# DIGITAL TWINS TRACKING MECHANO-ADAPTATION



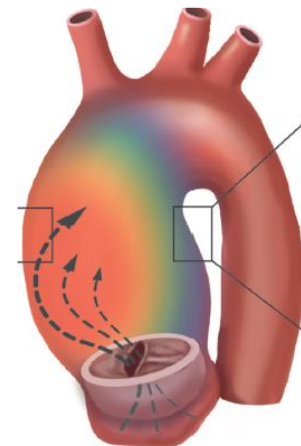
Elastic  
lamella

HOMEOSTASIS

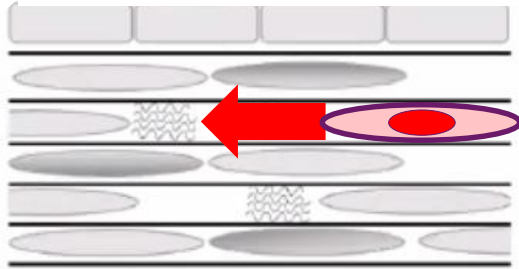


ECM REMODELLING

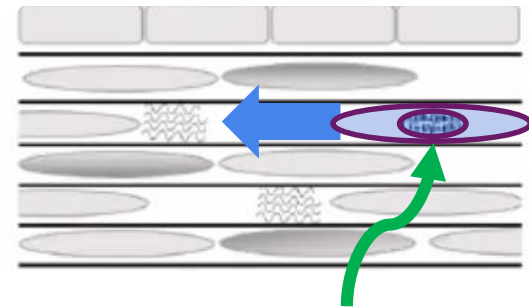
Cell-to-cell crosstalk



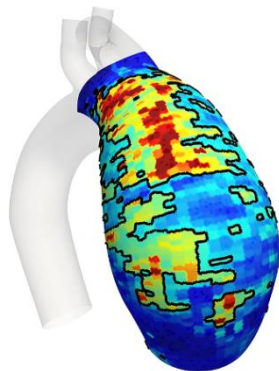
# DIGITAL TWINS ANTICIPATING AORTIC WALL DEGENERATION



**ILL-STRESSED vSMC**



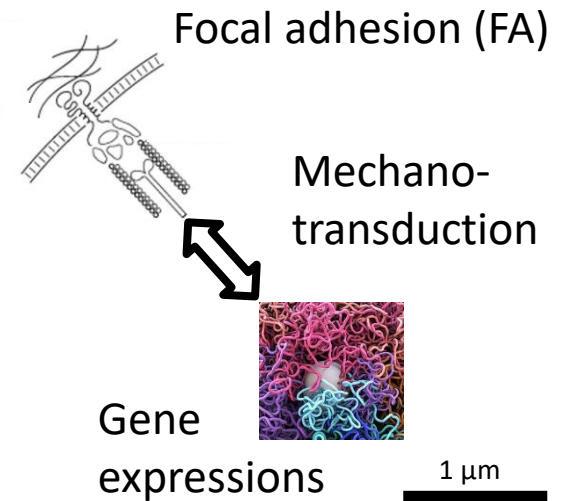
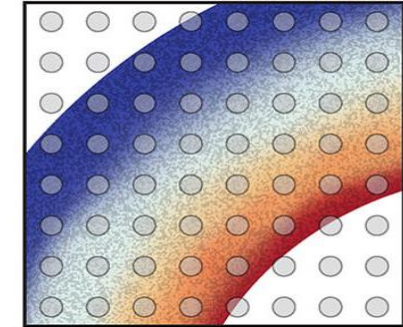
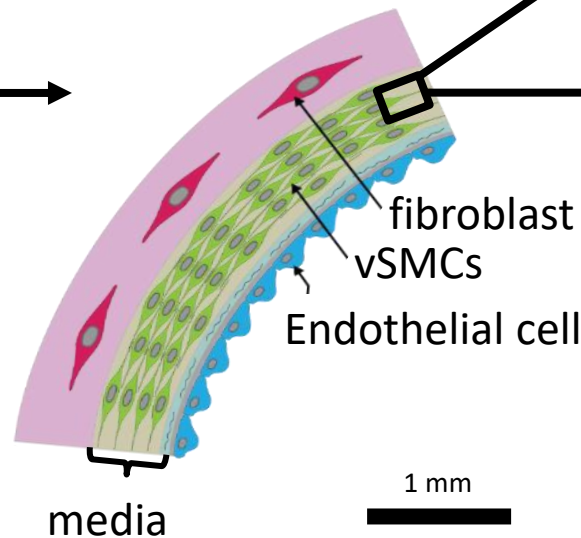
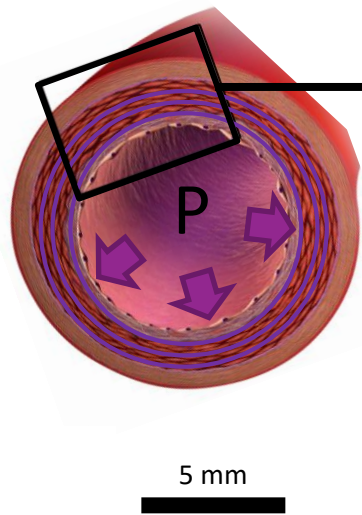
**MOLECULAR TREATMENT**



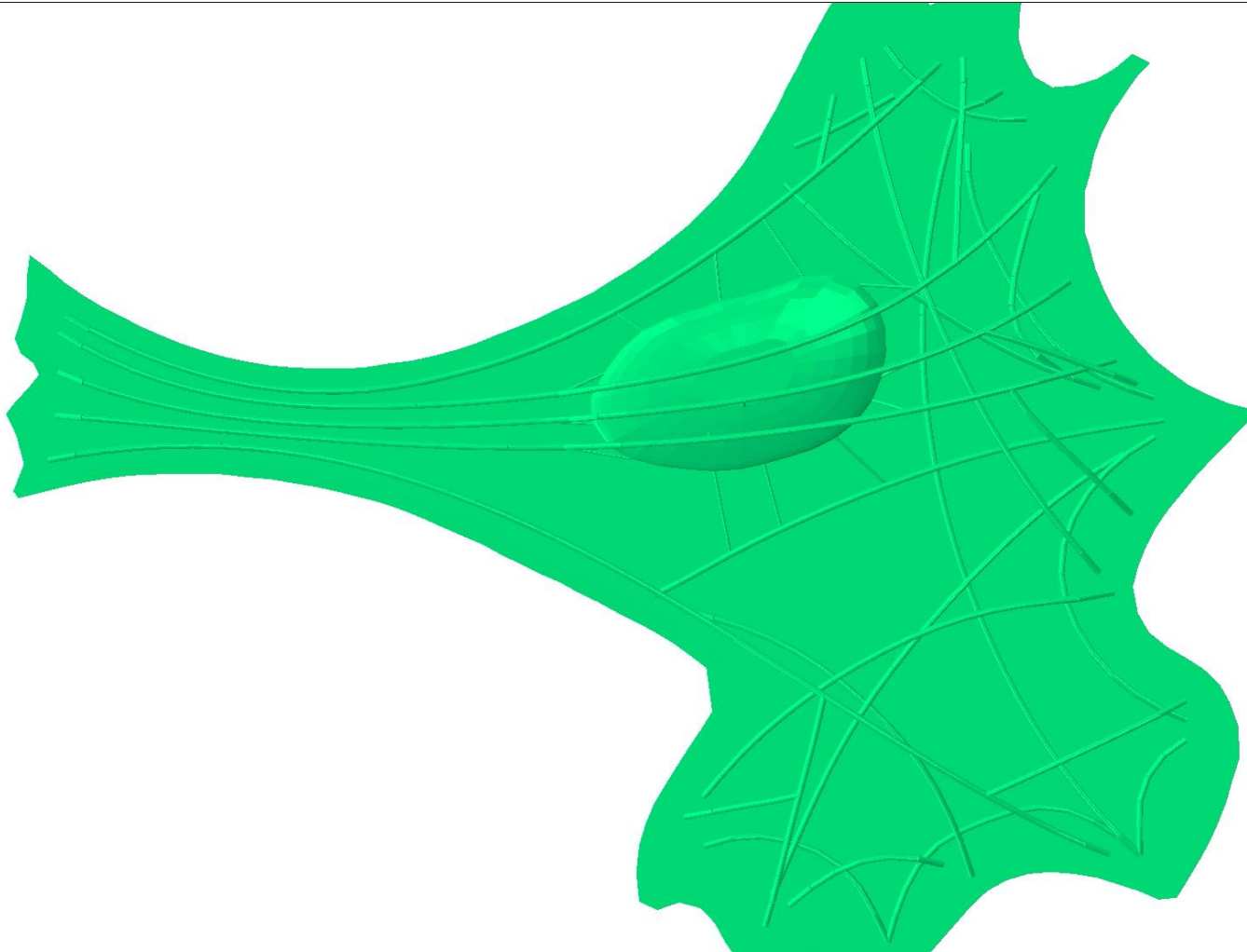
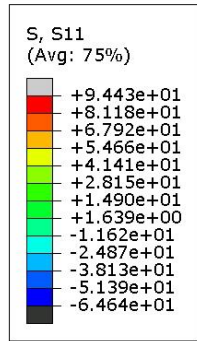


# MULTISCALE DIGITAL TWINS

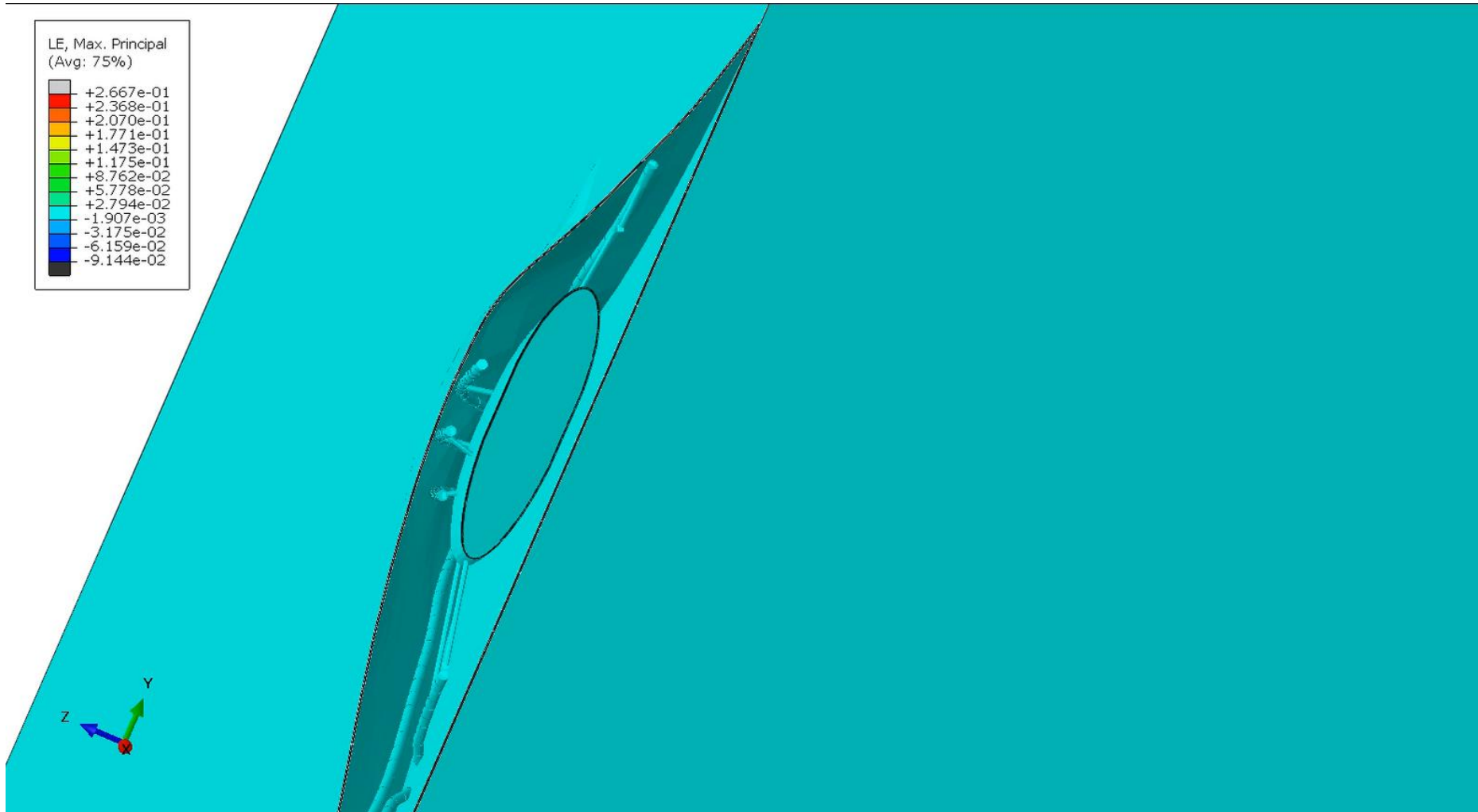
## SPATIAL TRANSCRIPTOMICS & PROTEOMICS



# Computer model of SMCs

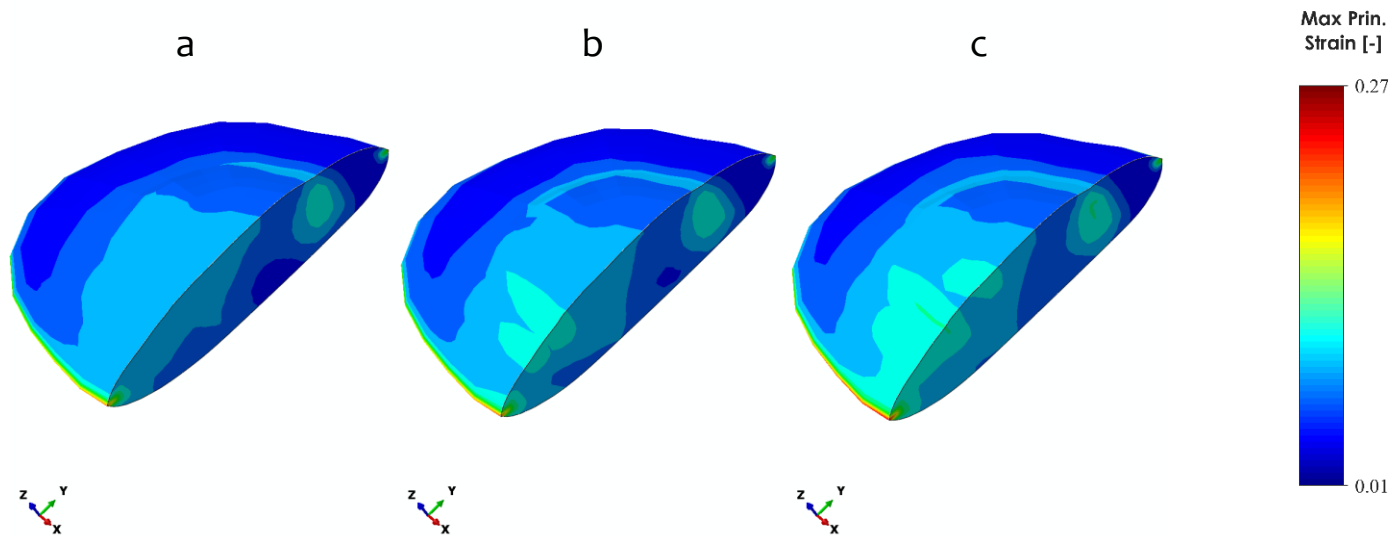


# Computer model of SMCs



## Strain map in the cell nucleus

---



Distribution of the maximum principal strain in half of the nucleus for substrates with Young's moduli of 2 kPa (a), 4 kPa (b), and 8 kPa (c).



Prof Stéphane Avril, [avril@emse.fr](mailto:avril@emse.fr), @StphaneAvril1

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