



150 ans de la SFP, 5 juillet 2023



La formation de notre intestin: beaucoup de génétique ... et de mécanique (et d'électricité)



Nicolas Chevalier

CNRS Researcher

Laboratoire Matière & Systèmes Complexes

Université de Paris



Université de Paris

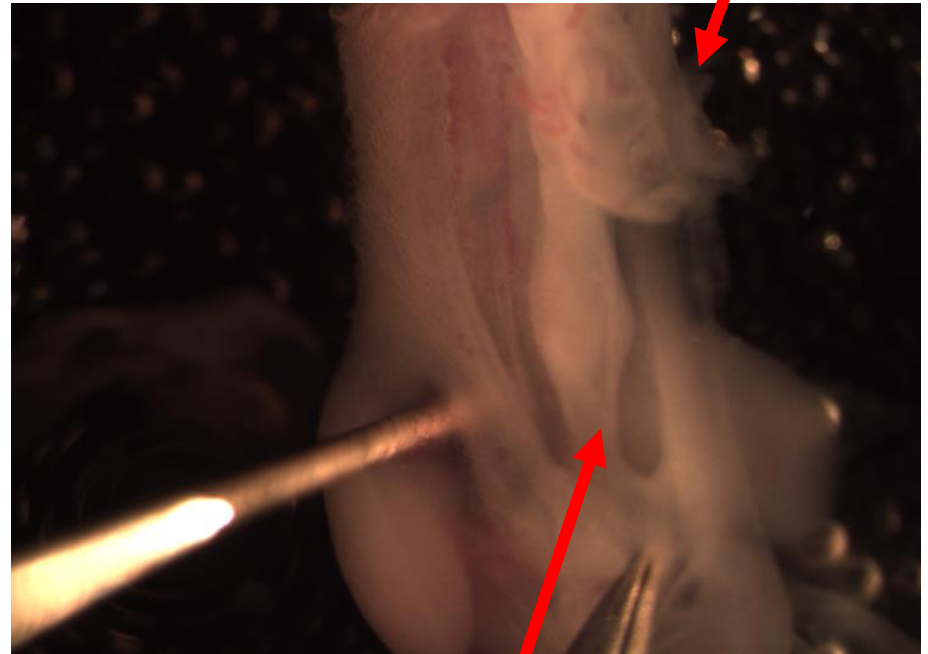
From a sheet to a tube

Epithelium (endoderm)

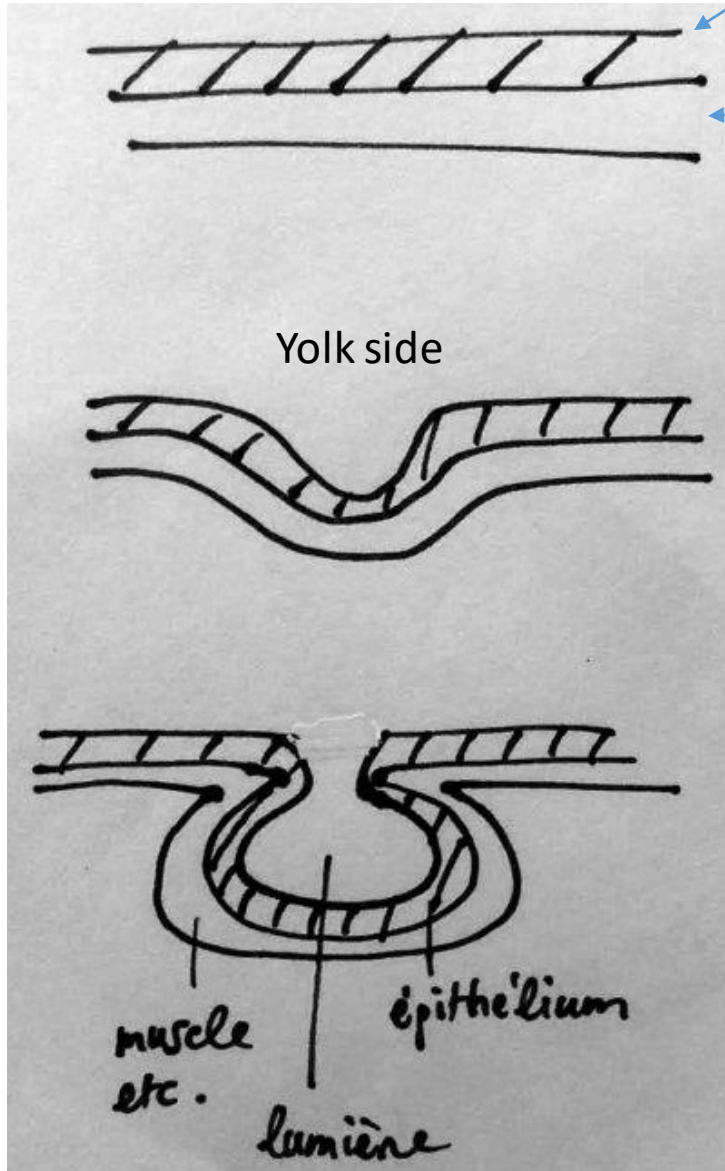
Mesenchyme (mesoderm)

Not completely closed midgut

Chicken E4.5



Colon



Yolk side

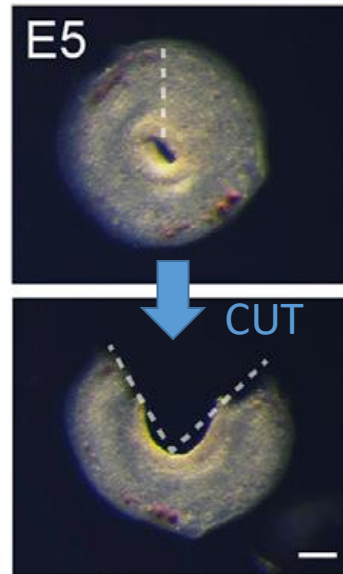
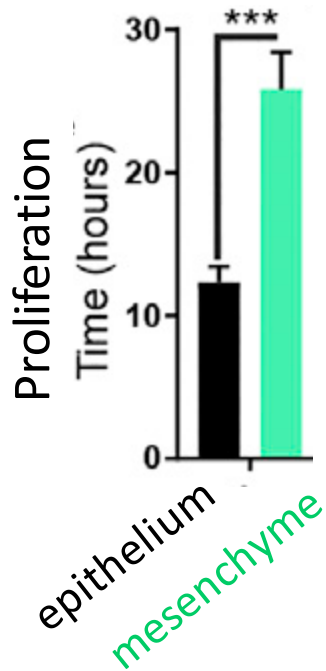
muscle etc.

lumièrè

épithe'lium

A fundamental mechanical orientation phenomenon:

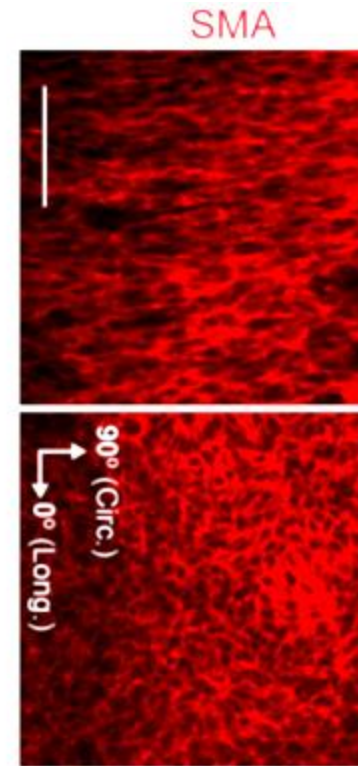
Huycke et al., Cell, 2019



Huycke et al., Cell, 2019

Culture
2 days

Culture
2 days



Huycke et al., Cell, 2019

More
proliferation
of epithelium

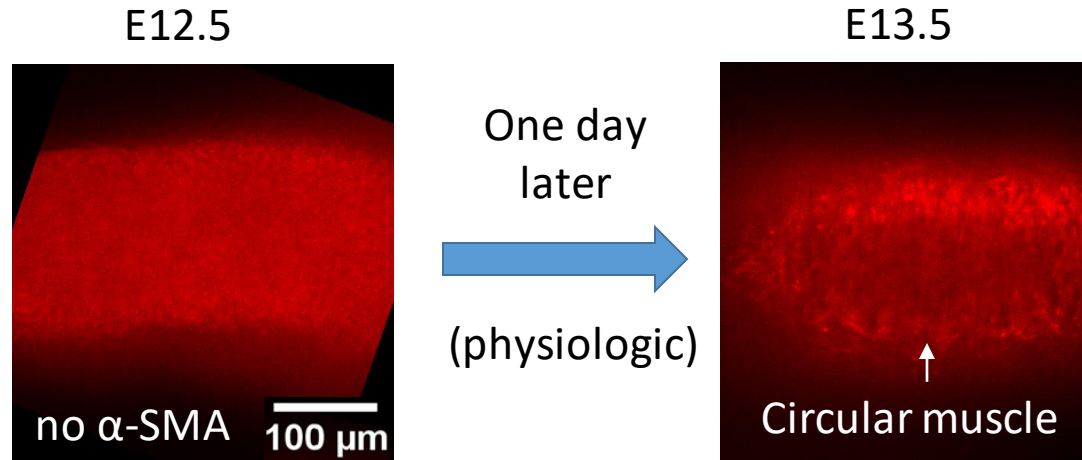


Creates internal
circumferential
stress

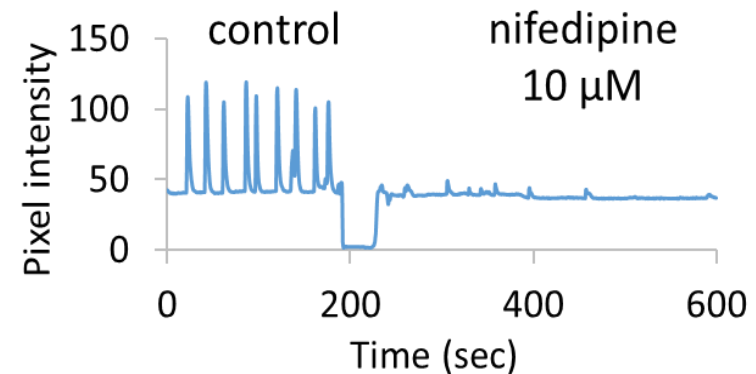
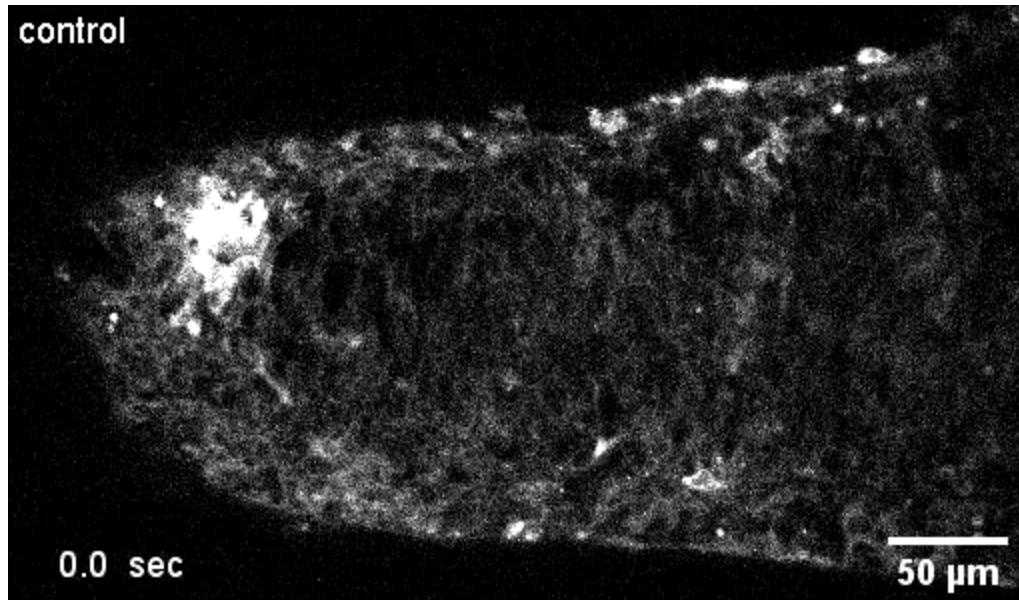


Makes the first
muscle layer
orient circularly

A fundamental bioelectric differentiation phenomenon



But calcium waves present at E12.5 ! (GCamp mouse)

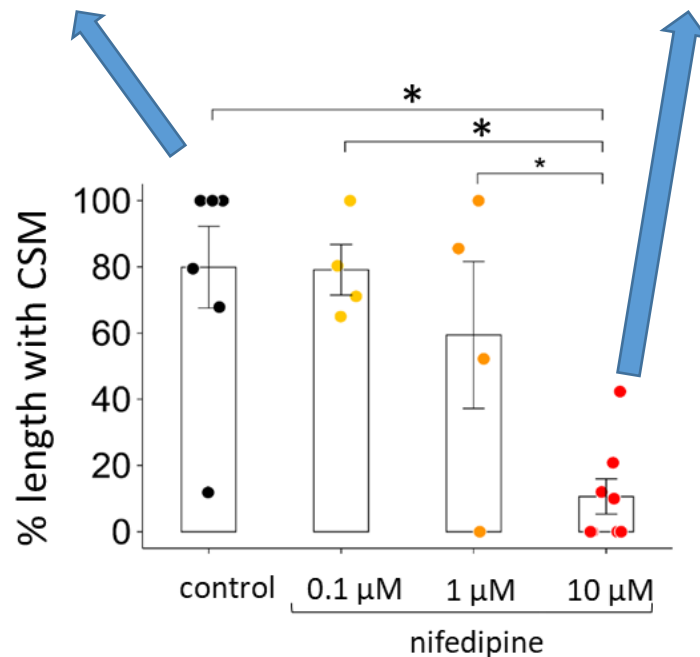
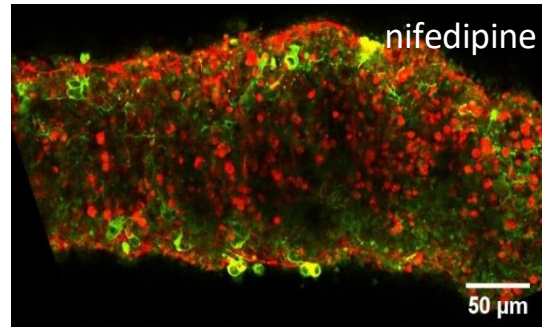
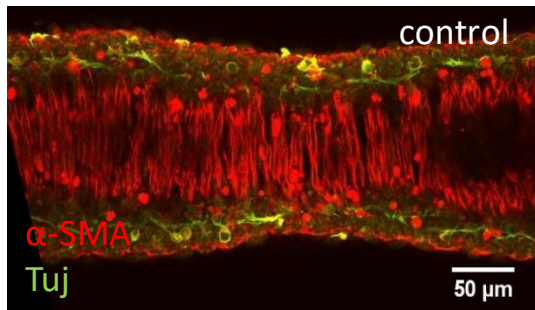


*N. Chevalier, L. Zig, A. Gomis et al.,
under review 2023*

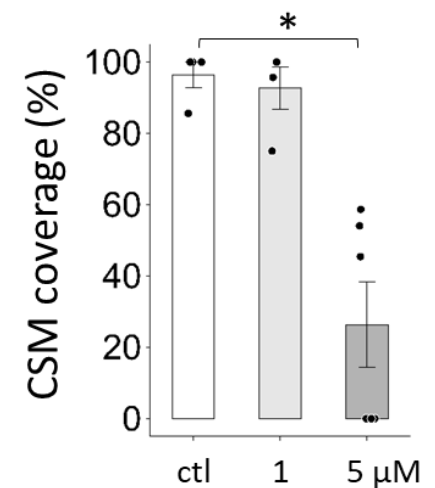
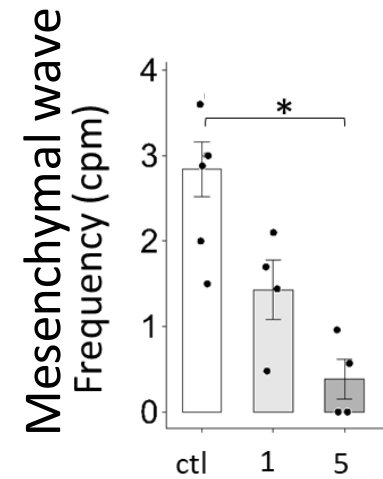
Mesenchymal waves trigger smooth muscle differentiation

Nifedipine: L-type Ca^{2+} channel antagonist

E12.5 cultured for 2 days

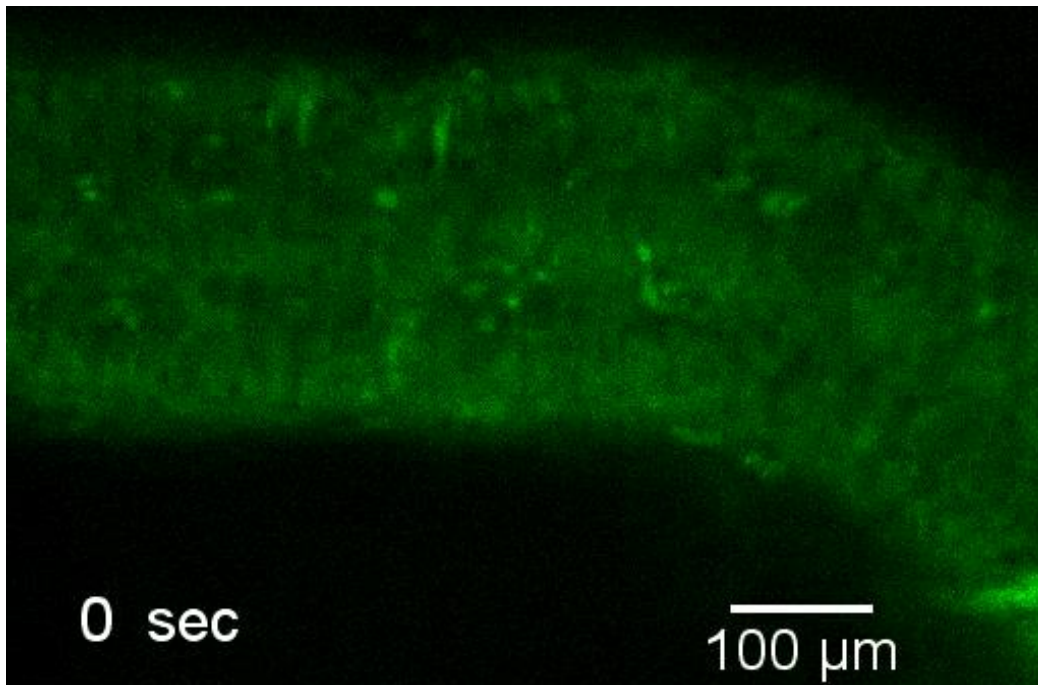


Similar result with **ML-7** :
MLCK inhibitor

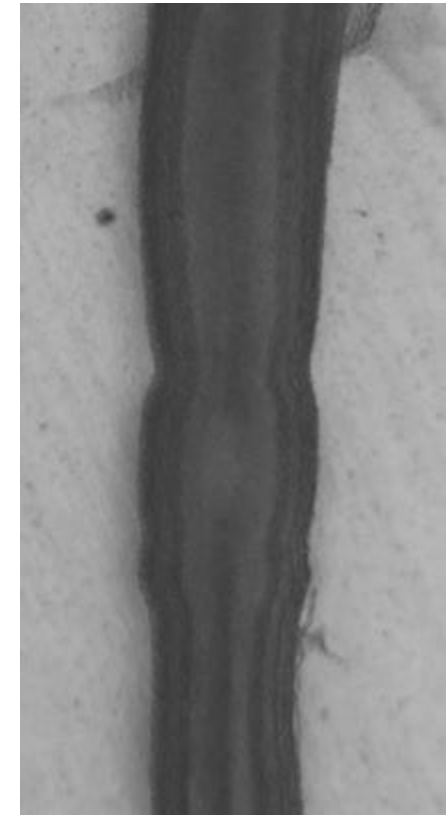


The calcium waves induce peristalsis after muscle differentiation

Intracellular **calcium imaging** at E15.5



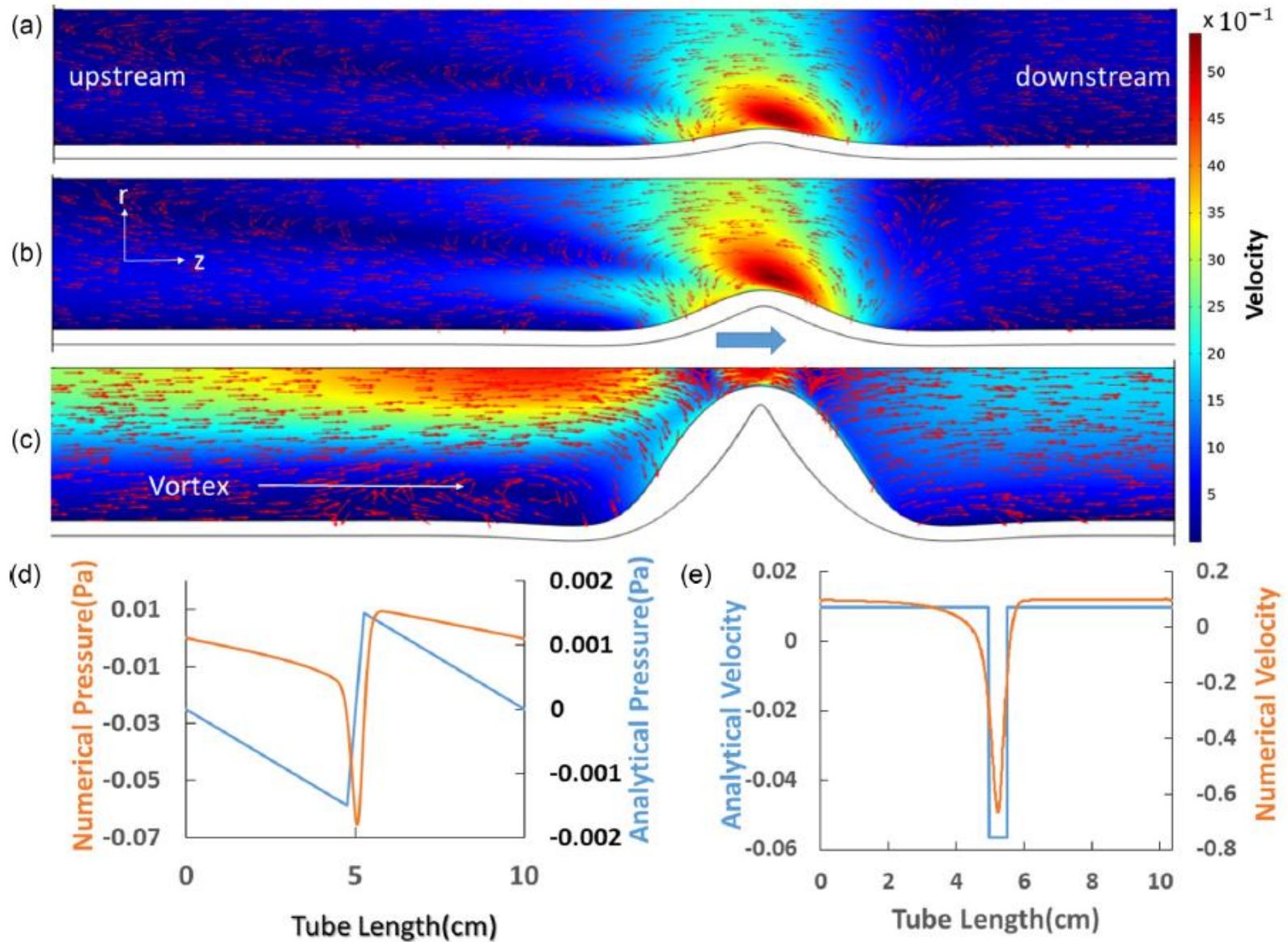
Mechanosensitive



Pinch → two counterpropagating waves

Hydrodynamics of peristalsis

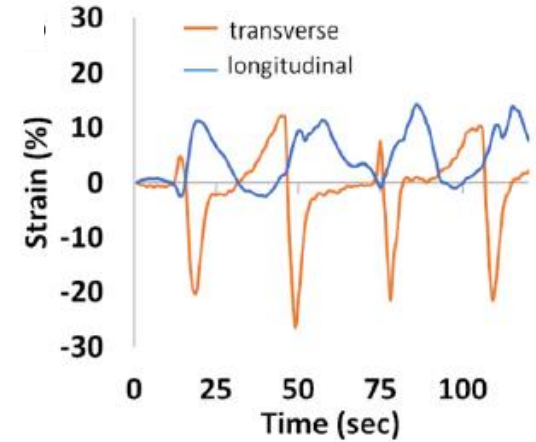
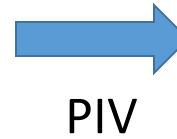
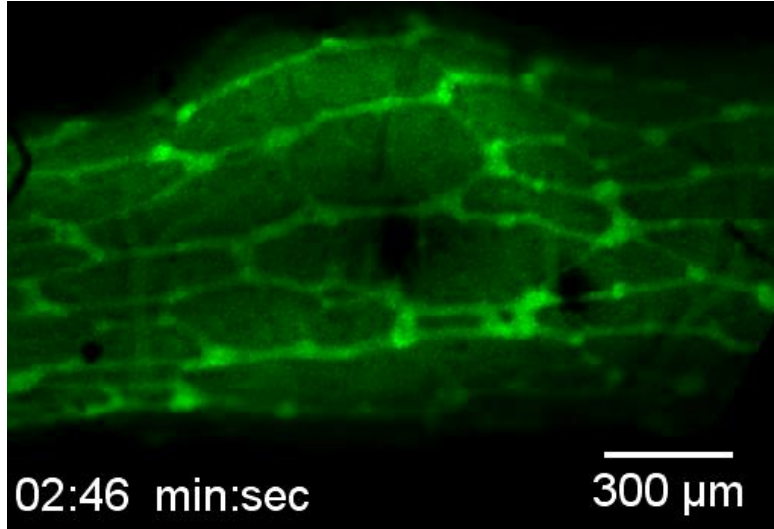
R. Amedzrovi & N.Chevalier,
Phys. Rev. Fluids, 2022



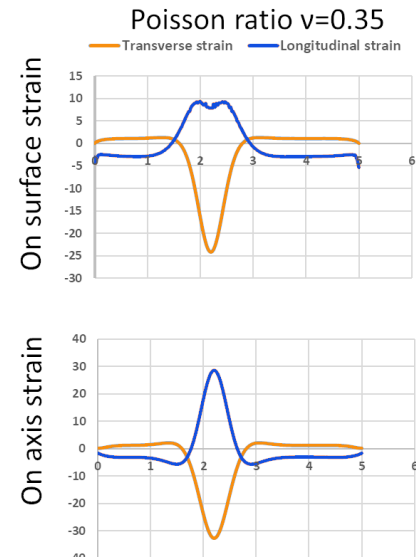
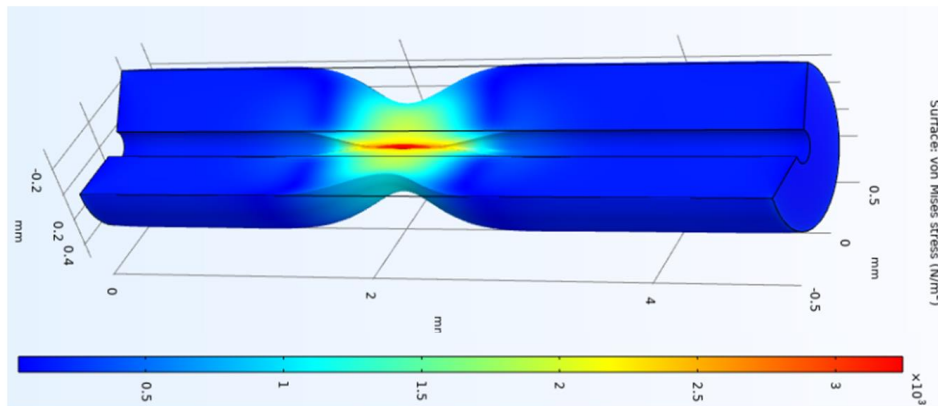
Circular contractions induce longitudinal stretch

N.R.Chevalier et al.,
Front. Cell. Dev. Biol., 2021

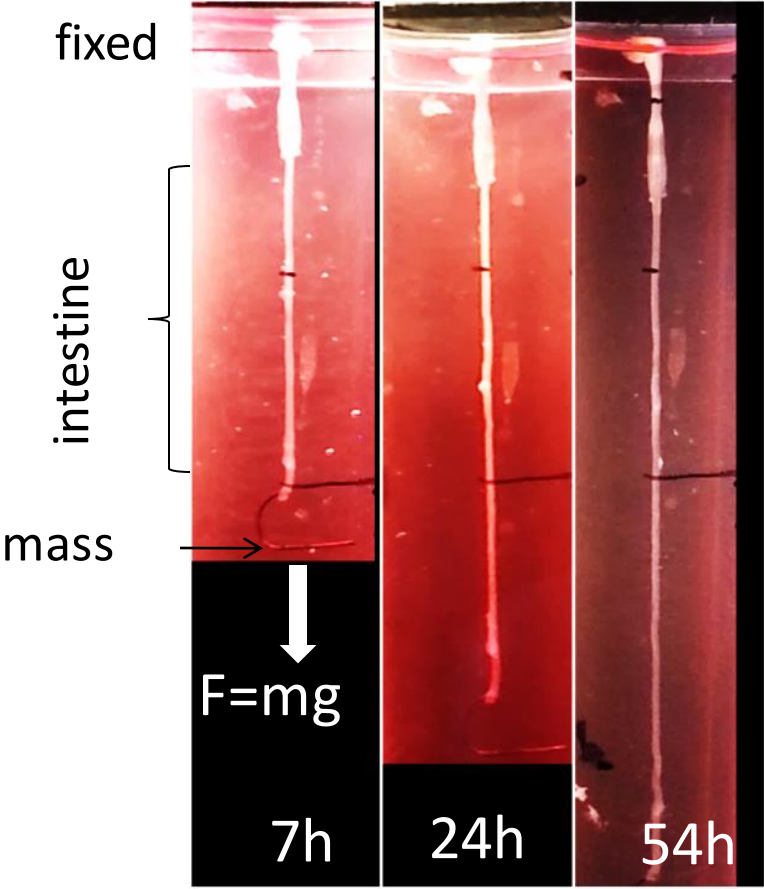
FITC tagged enteric nervous system (4-di-2-asp)



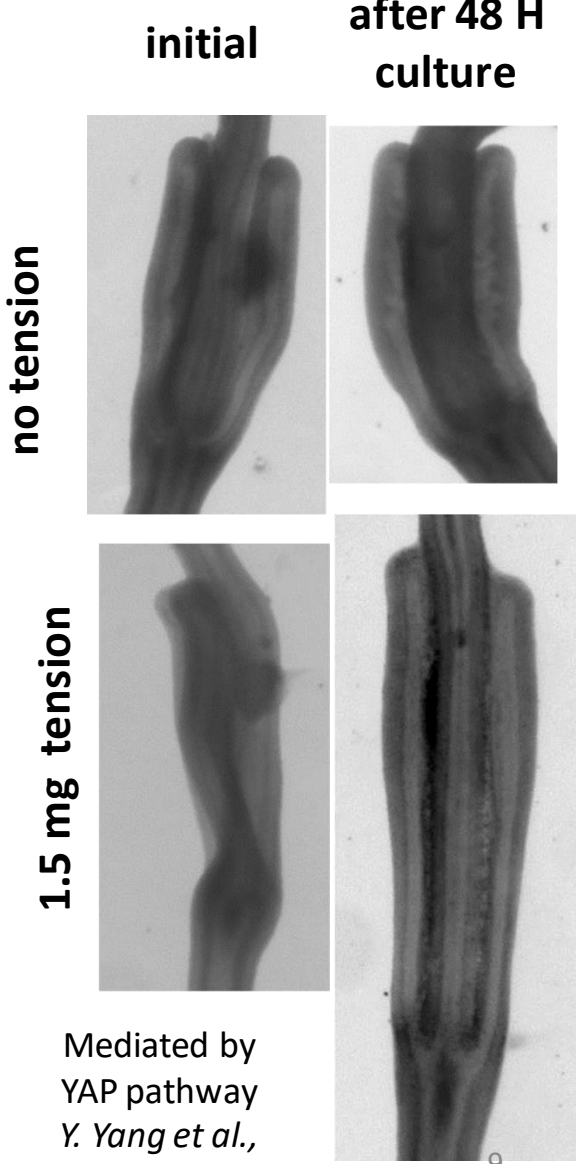
Finite element simulation (PhD Richard Amedzrovi)



Longitudinal stretch makes the gut grow



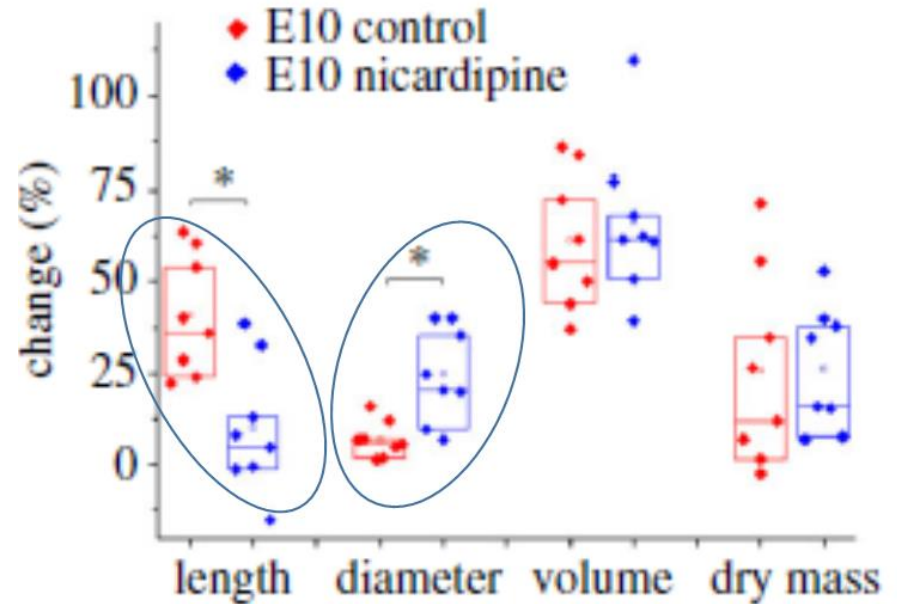
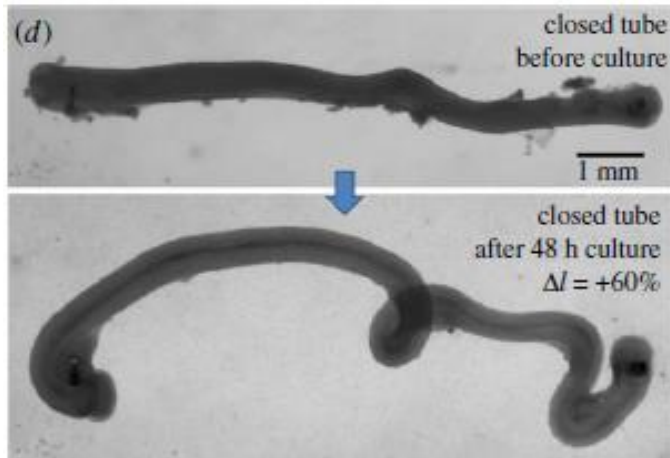
N. Chevalier et al. Sc. Rep., 2018



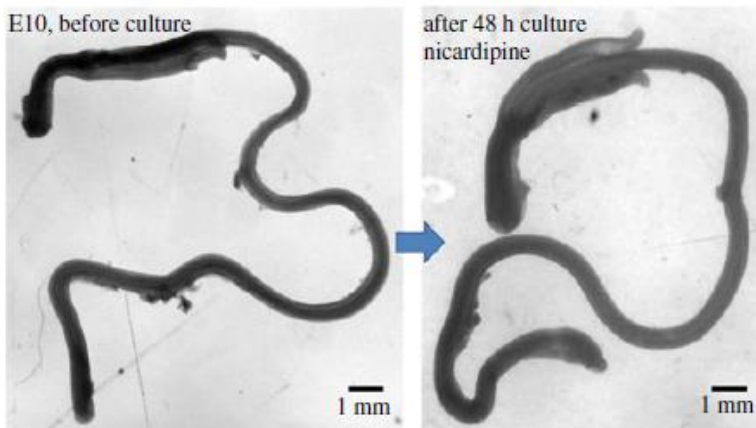
Mediated by YAP pathway
Y. Yang et al., Nat. Com., 2022

Inhibiting contractions stops anisotropic growth

Normal gut growth (2 days in culture)



With nifedipine (no contractions):



→ Growth becomes **isotropic** when contractions are inhibited


*D. Khalipina, N. Chevalier et al.,
J. R. Soc. Interface, 2019*

Notre soif de reconnaissance enfin assouvie

The New York Times

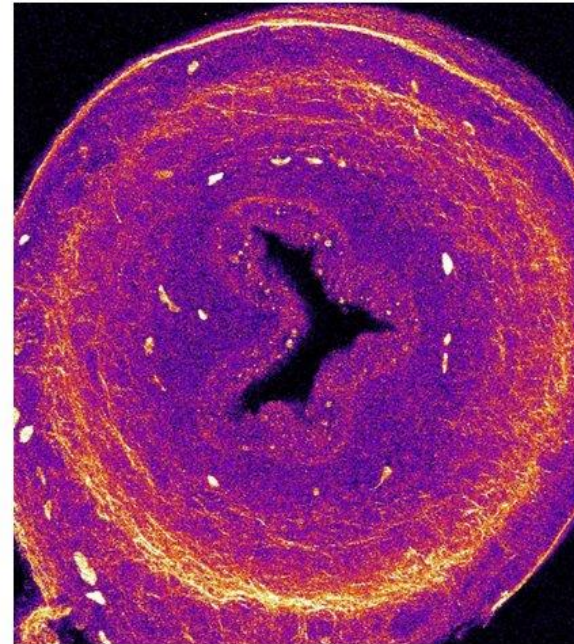
The Twitch That Helps Your Intestines Grow

Pulsing movements in an embryo are crucial to helping intestines grow into the wonder tube that it is, a study finds.

 Give this article



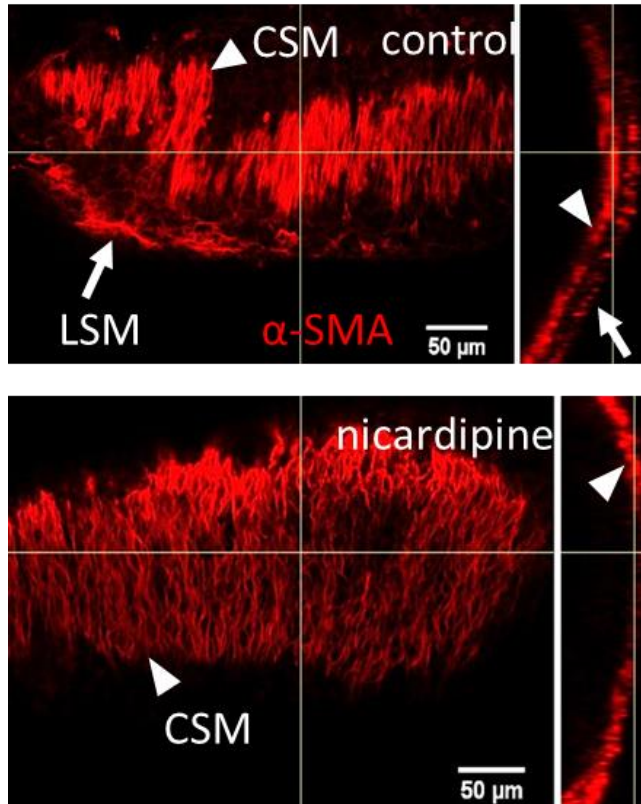
 1



A side view of a 9-day-old embryonic chicken gut. Nicolas Chevalier/CNRS/Université de Paris & Thomas Guillbert/IMAG'IC Facility Institut Cochin

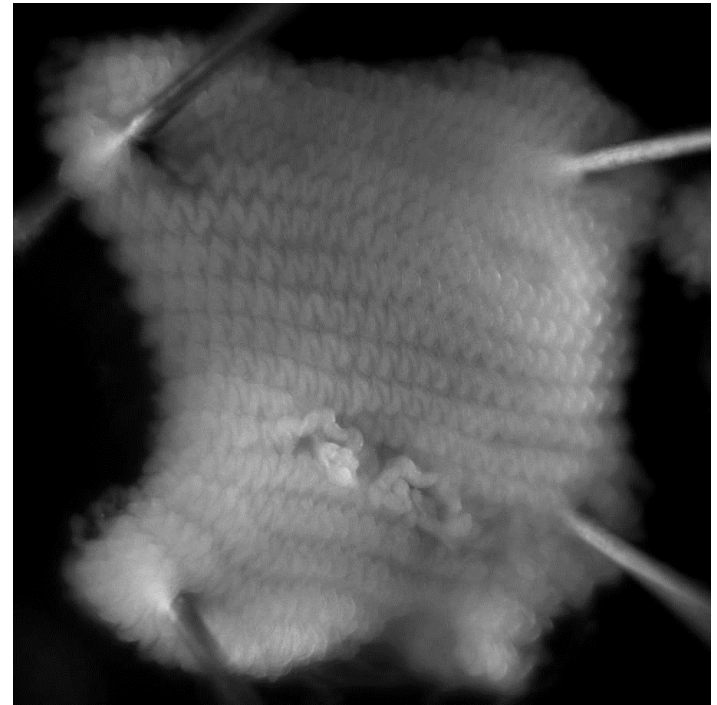
By [Veronique Greenwood](#)

Longitudinal stretch orients the next muscle layer longitudinally



2 independent oscillators:

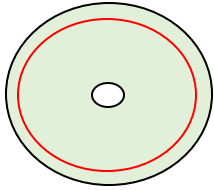
Circular (50 mHz)



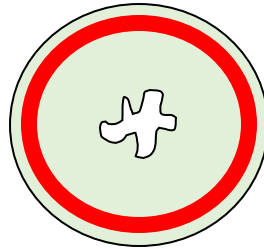
Longitudinal (5 mHz)

Muscle contractions direct epithelial villi formation

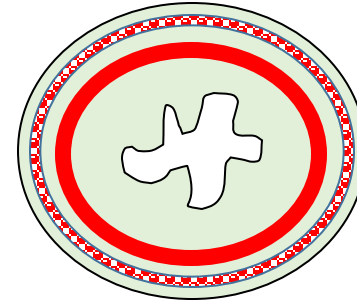
No muscle



Circular muscle



Circular & longitudinal muscle

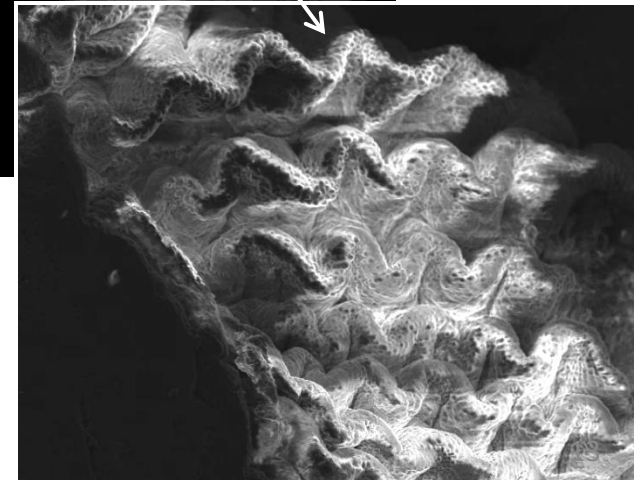
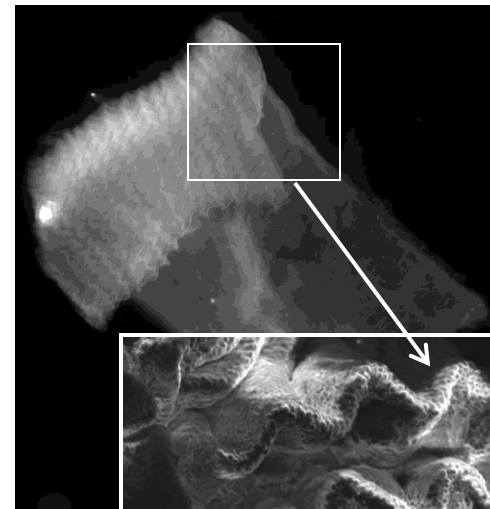


E6: flat epithelium

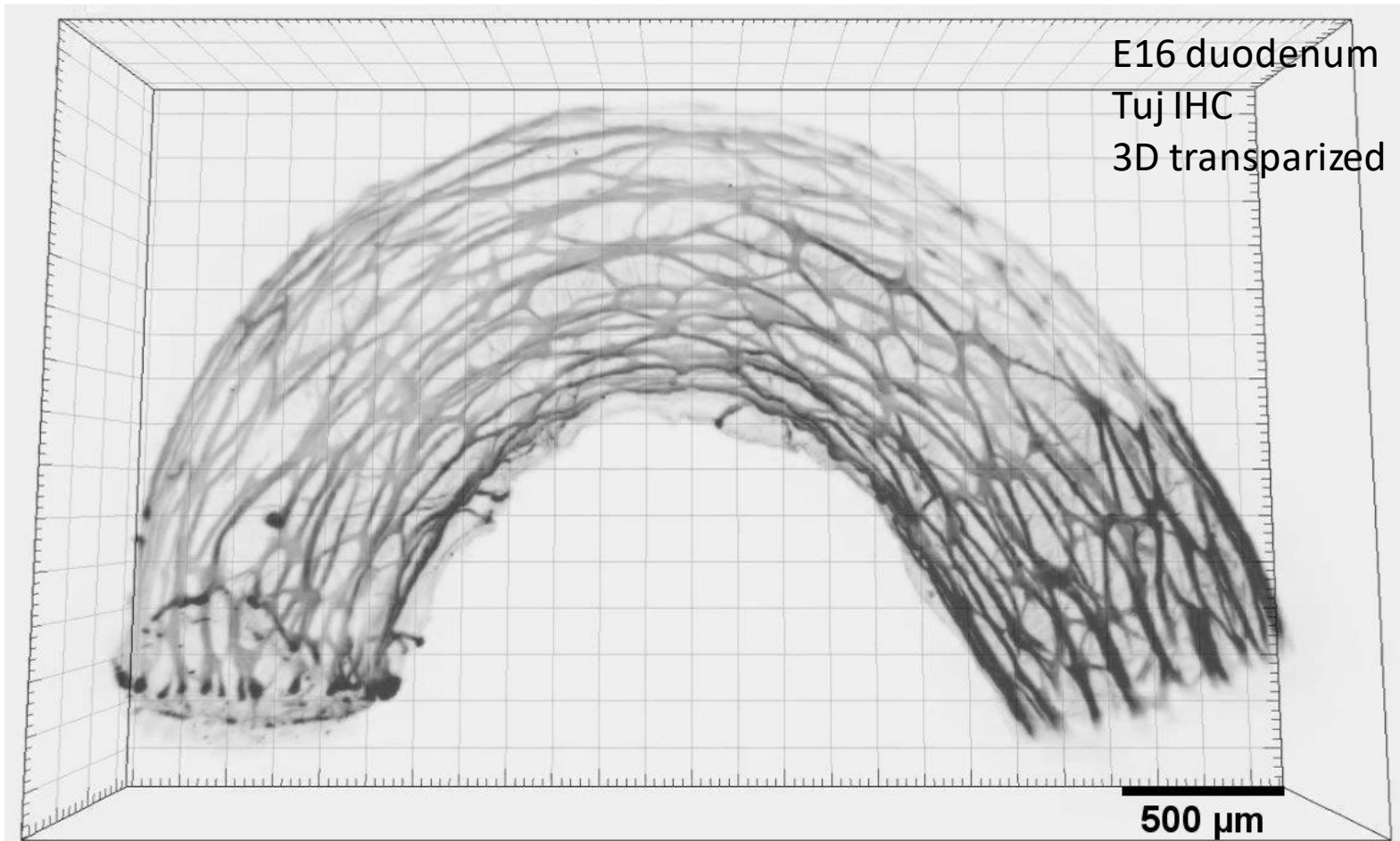


Shyer et al., Science, 2013

Hilton W. "The morphology and development of intestinal folds and villi in vertebrates." 1902

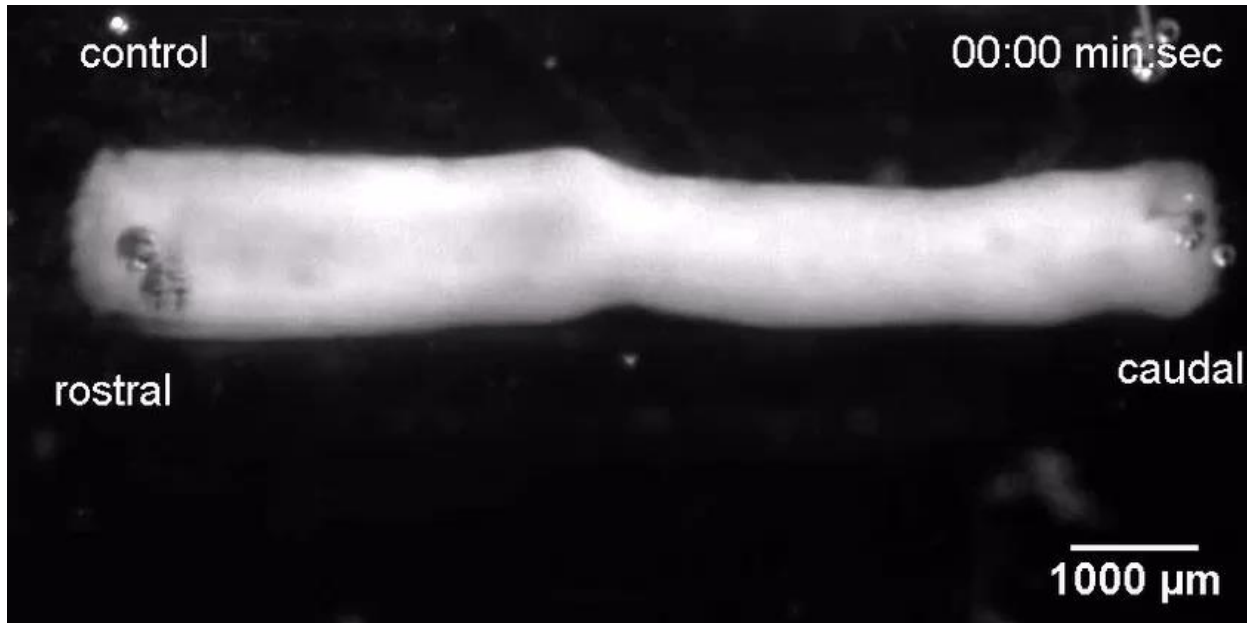


Finally the « second brain » becomes active:
the enteric nervous system



N.R. Chevalier et al., « Embryogenesis of the Peristaltic Reflex », J. Physiol 2019

Neural action on motility in one video



Inhibitory neural action

Neurons « calm down »
spontaneous contractions
by secretion of NO

Longitudinal-circular contraction coupling

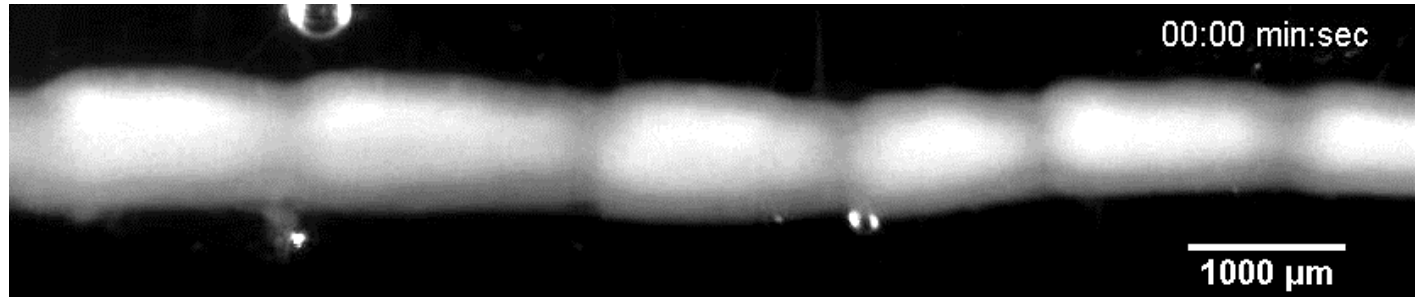
So the two muscles
work antagonistically
(like biceps-triceps)

New polarized motor pattern

Neurons give the
gut a mouth-to-
anus direction

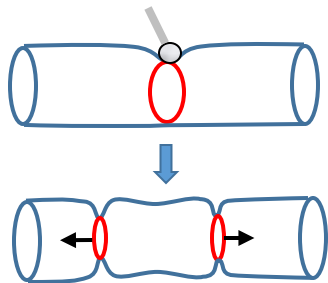
Nerves **polarize** the response to mechanical stimulation

E16 -
active
nervous
system

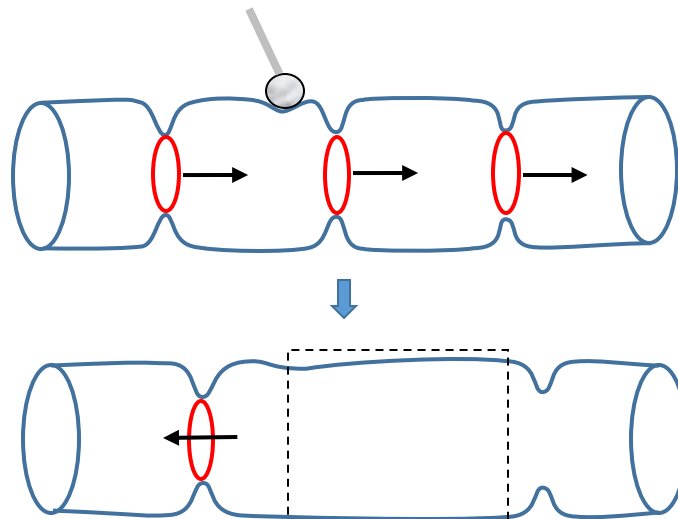


Fetal neurogenic

Embryonic myogenic

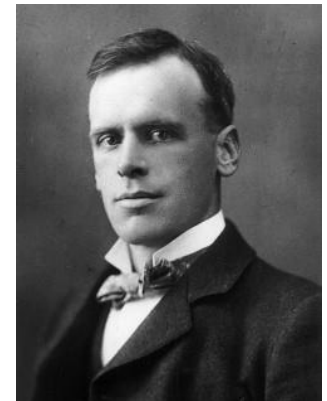


2 contractile
waves



contraction inhibition

« **Law of the intestine** »
(Starling, 1899)



→ directed bolus
transport

Now the chicken may hatch and eat ... and you may have questions

Contributors to the work presented:

- Richard J. Amedzrovi (PhD)
- Anthony Gomis (BTS intern)
- Lucas Langlois (BTS intern)
- Nicolas Dacher (BTS intern)
- Yusuke Kaga (M2 intern)
- Diana Khalipina (M2 intern)
- Léna Zig (IR CNRS)
- Vincent Fleury (DR CNRS)

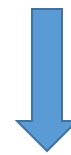
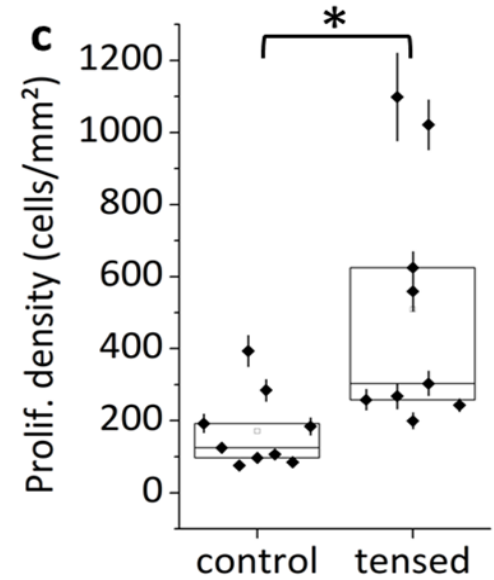
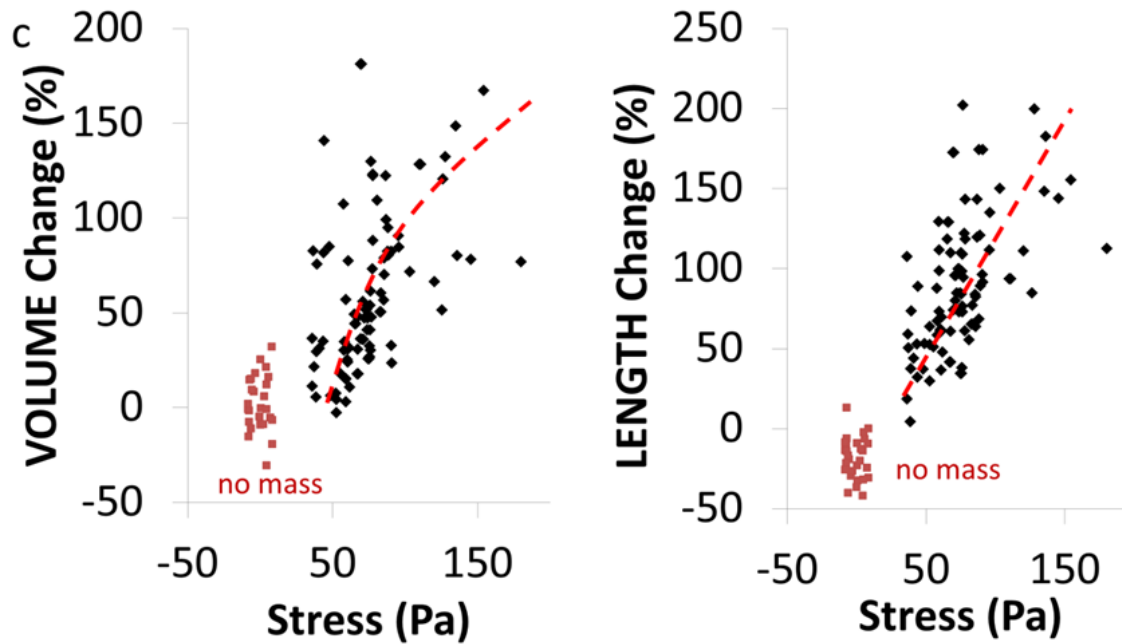
- The animal husbandry staff (IJM)
- Orestis Faklaris (Imagoseine)
- Thomas Guilbert (Imagic)
- Sylvie Dufour (INSERM)
- Sandrine Faure (INSERM)
- Pascal de Santa Barbara (INSERM)



nicolas.chevalier@u-paris.fr

<http://nicochevalier.net>

Growth is proportional to mechanical stress



Mediated by
YAP pathway

Y. Yang et al., Nat. Com., 2022