Mechanotransductive Activation of the Tumorigenic β-catenin Pathway in Colon Cancer progression

Mechanosensitivity of the β-cat pathway in the mechanical induction of mesoendoderm specification of gastrulating bilaterian embryos

(for a review: *Fernandez-Sanchez et al, Ann Rev Cell Dev Biol 2015*)

Tumour growth pressure: mechanical activation of the tumorigenic pathway in healthy neighbouring cells?

Instituts thématiques

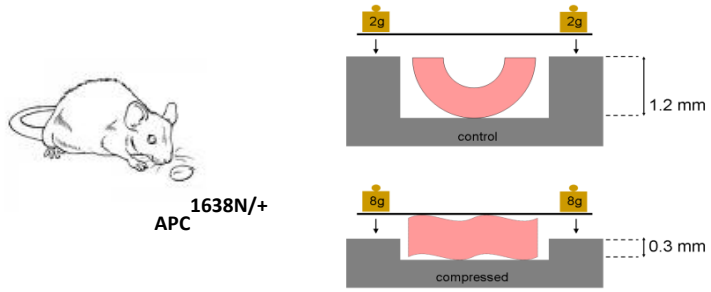
Inserm

Institut national de la santé et de la recherche médicale

UMR168

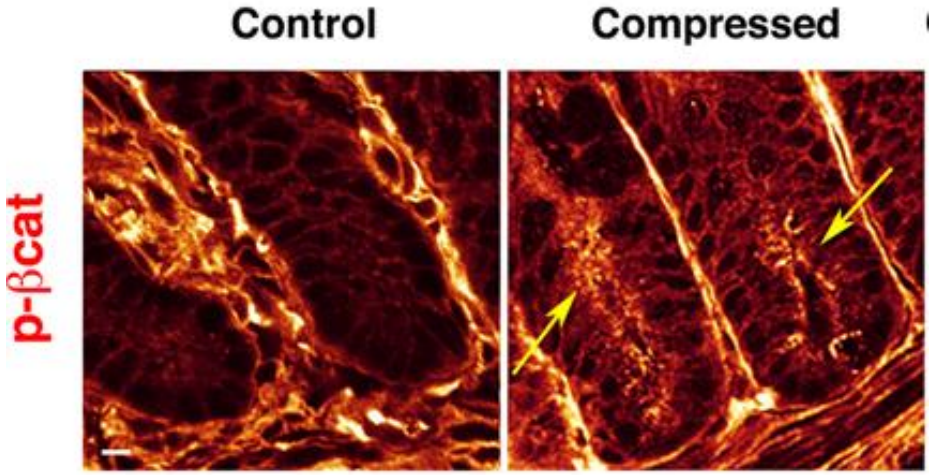
β-cat dependent mechanical induction of oncogenes expression *ex-vivo*

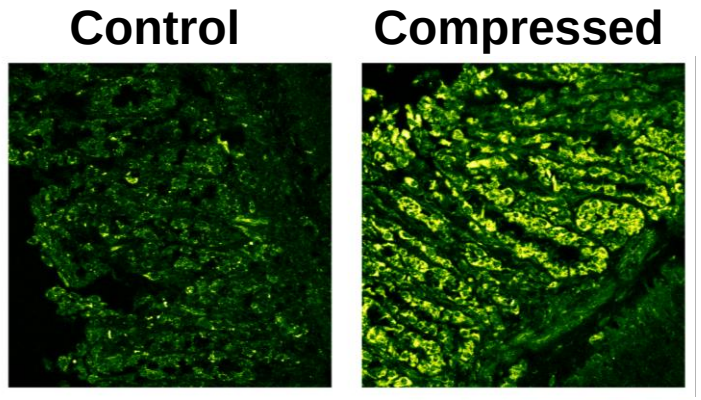
Ex vivo **mechanical compression of the distal colon**



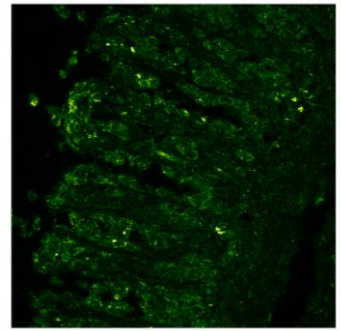
APC$^{1638N/+}$

P = 0.8kPa





c-Myc
(Twist-1)
targets of β-cat

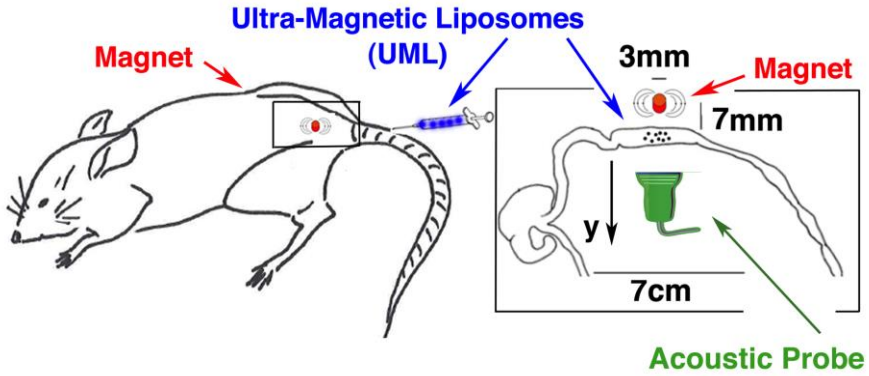


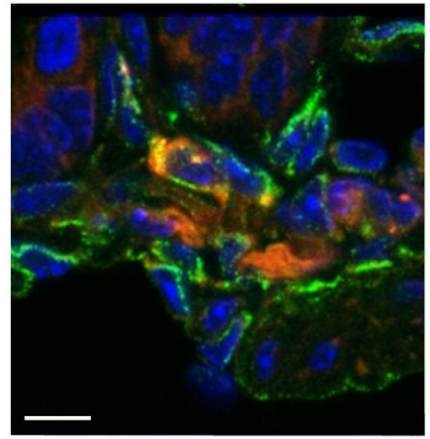
PP1 (inhibitor of Src familly kinases)

In situ ex-vivo: Joanne Whitehead et al, HFSPJ 2008

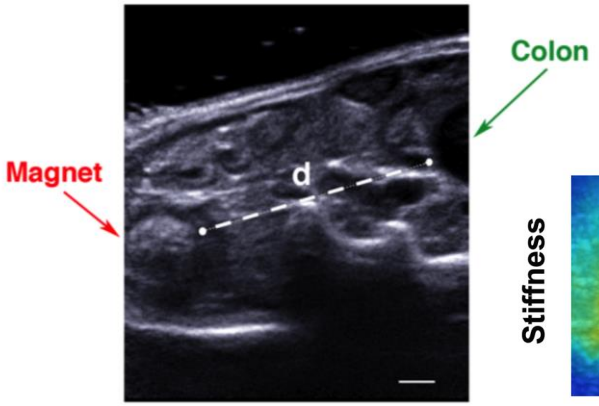
institutCurie

Magnetic loading to mimic tumour growth pressure *in vivo*

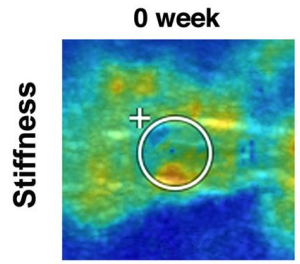




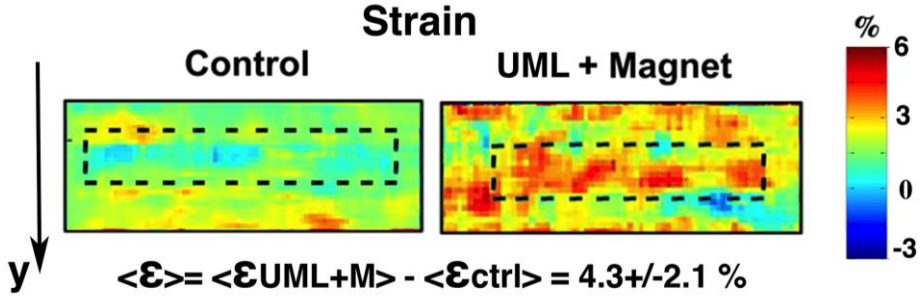
Magnetic Liposomes



<d> = 7+-1 mm



<E>=31.9+/-4.4 kPa

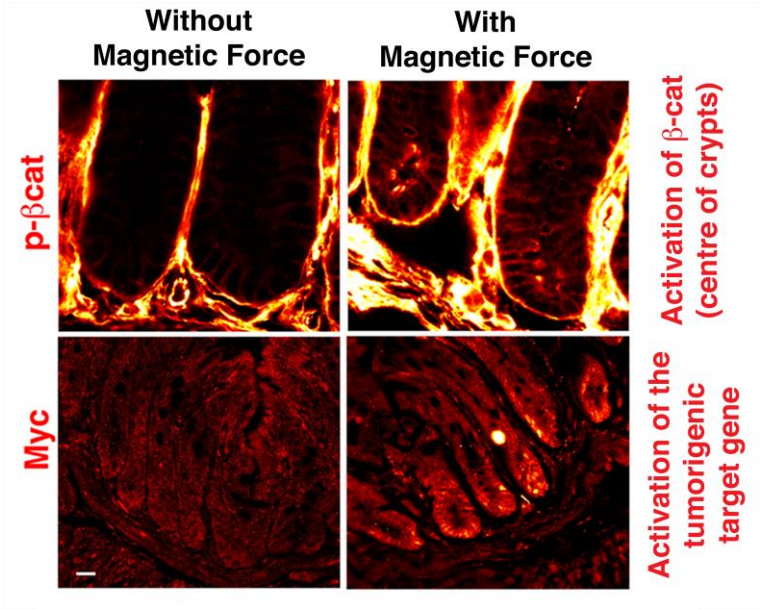


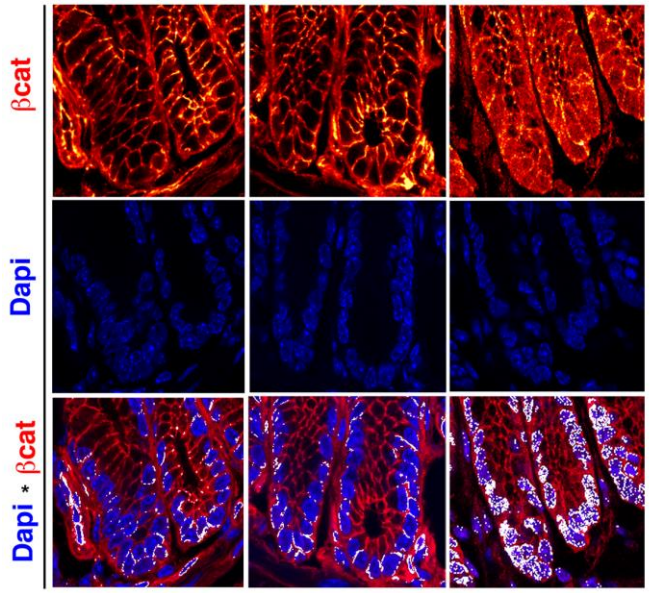
<ε>= <εUML+M> - <εctrl> = 4.3+/-2.1 %

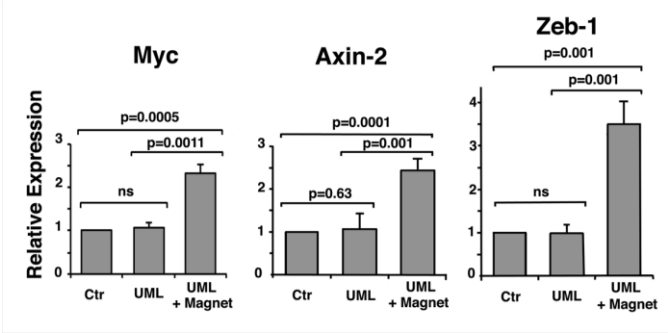
P= 1.2kPa mean value
(tumour growth pressure: 1kPa)

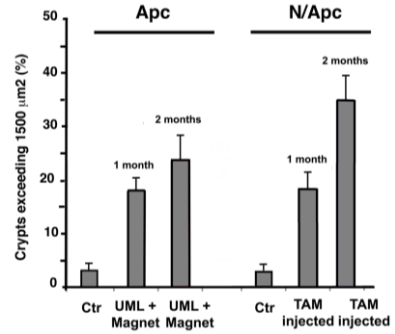
institutCurie

Mechanical induction of oncogenesis by tumour growth pressure *in vivo*





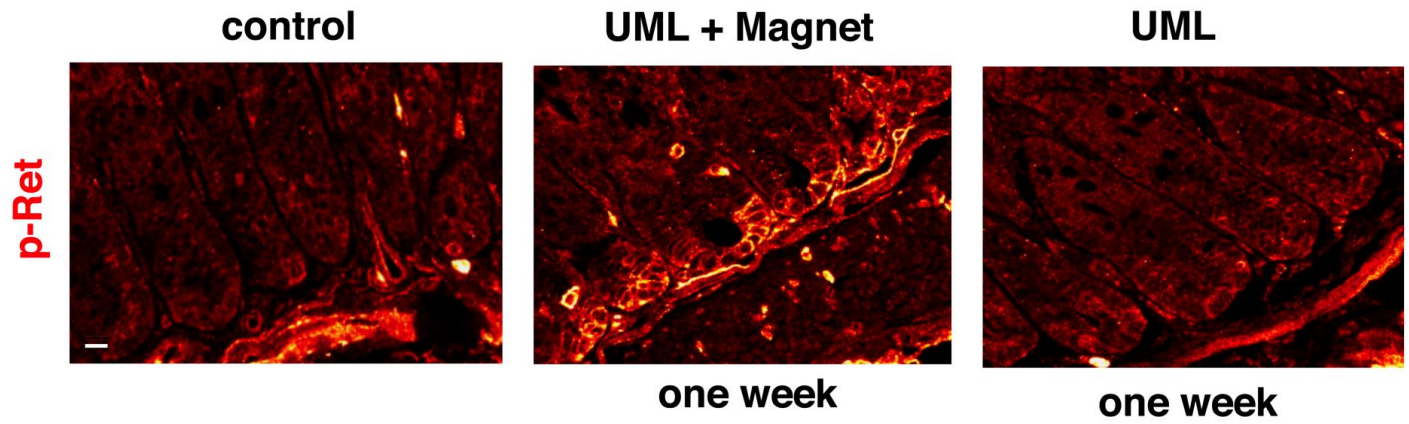


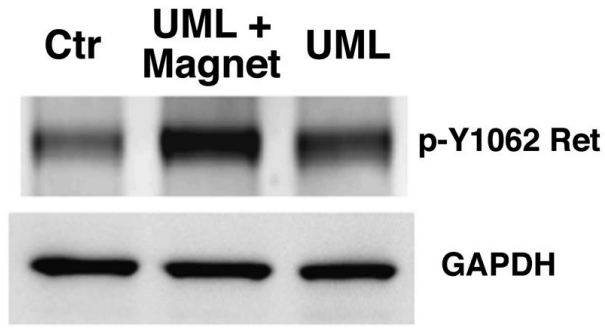


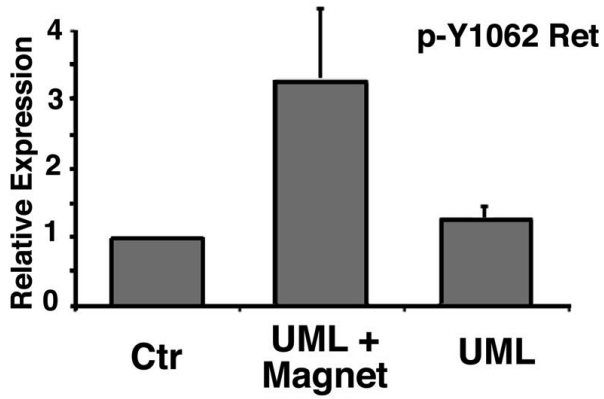
institutCurie

Mechanical activation of the src-familly kinase Ret

Y1062 phosphorylation by tumour growth pressure

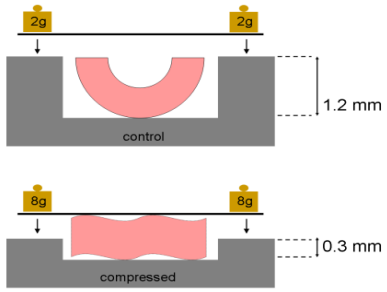


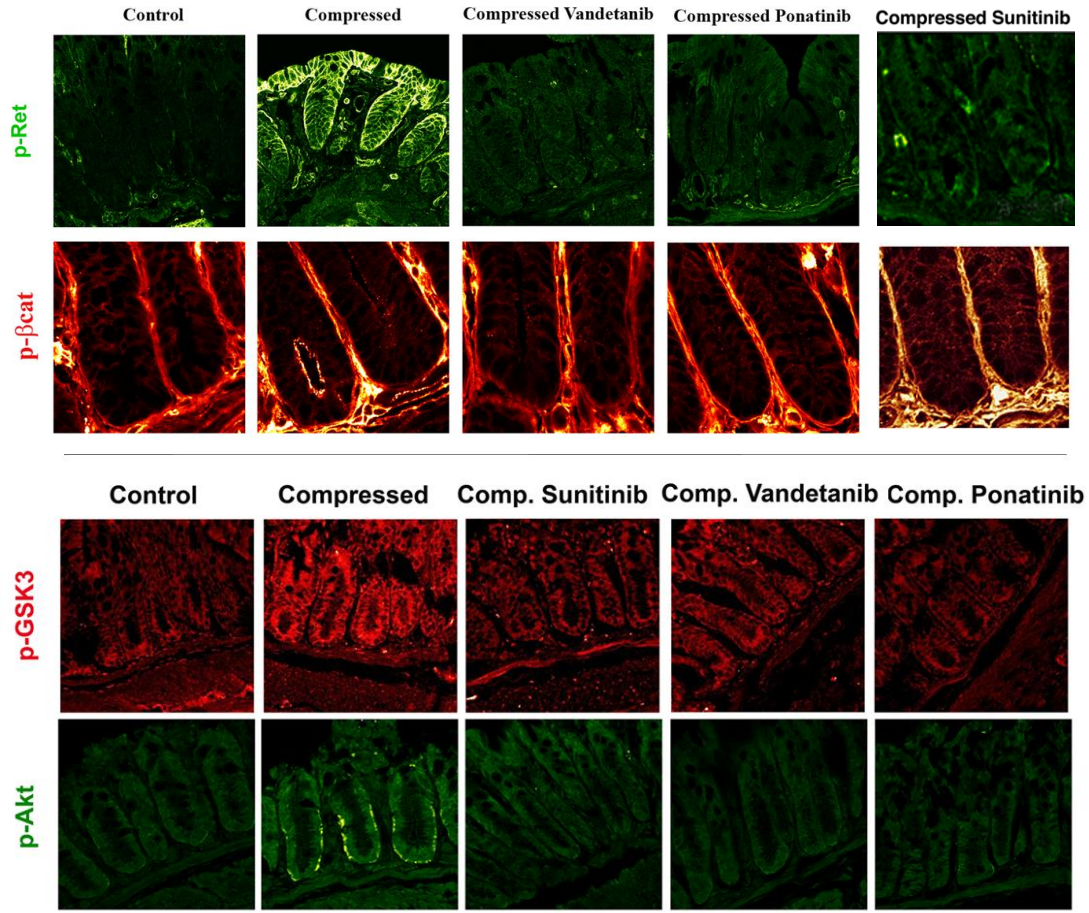




institutCurie

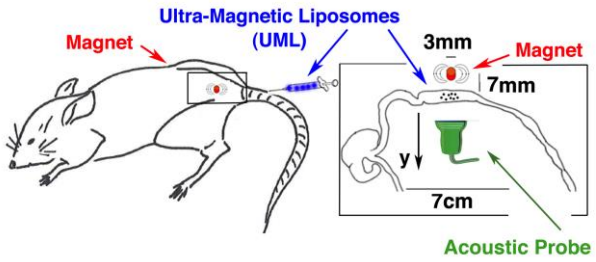
Mechanical induction of p-Y654-βcat and p-Ser9-GSK3 are p-Y1062-Ret dependent *ex-vivo*

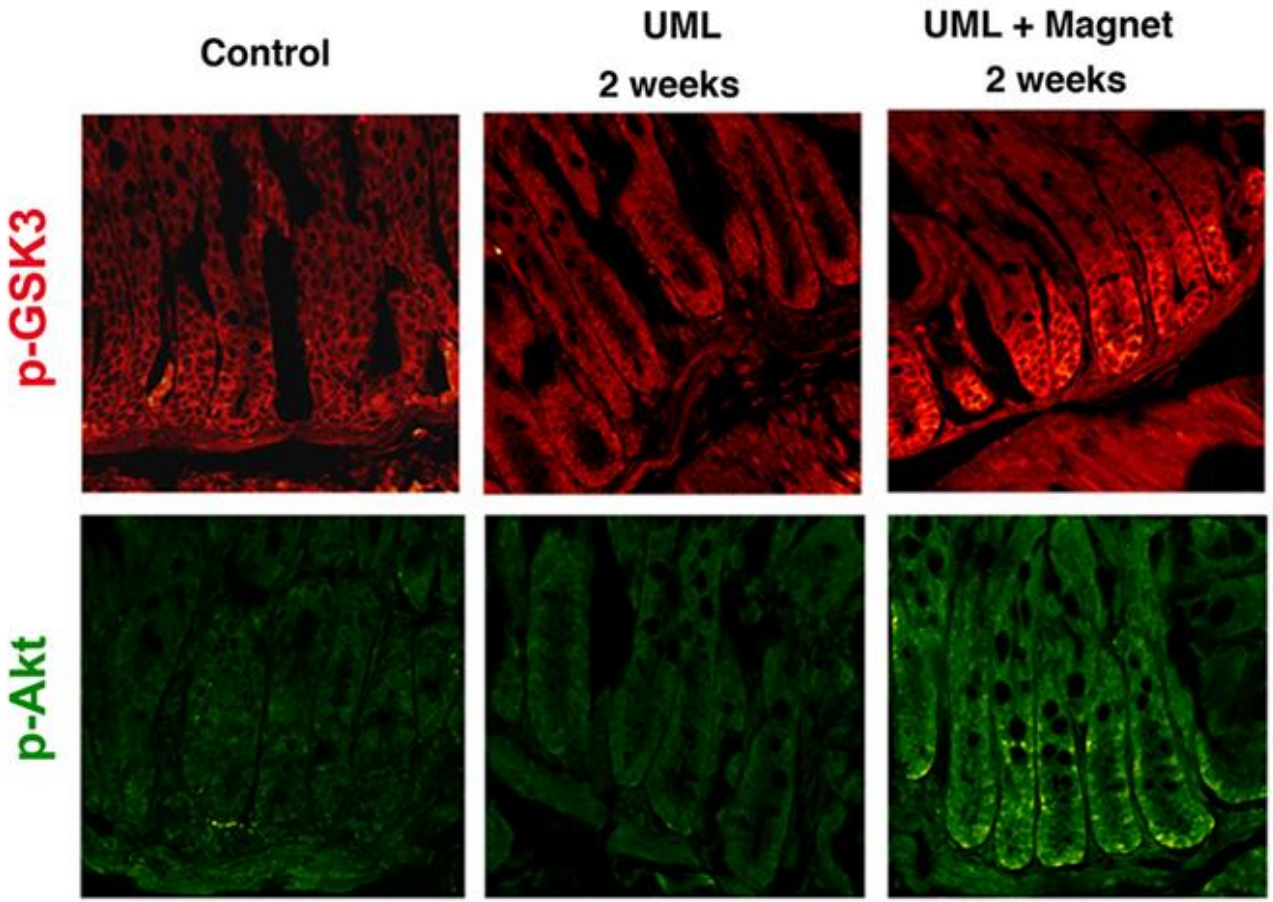




institutCurie

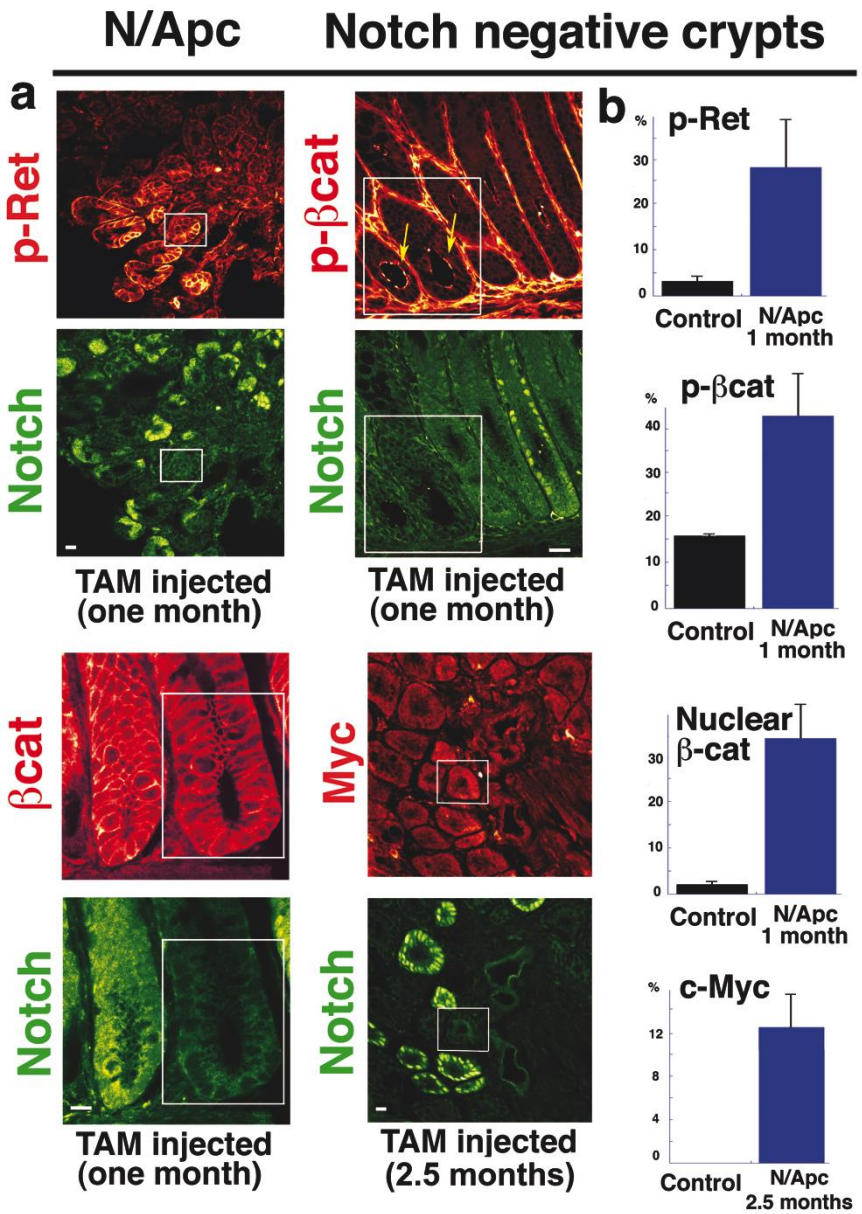
Mechanical induction by tumour growth pressure of p-Ser9-GSK3 *in vivo*

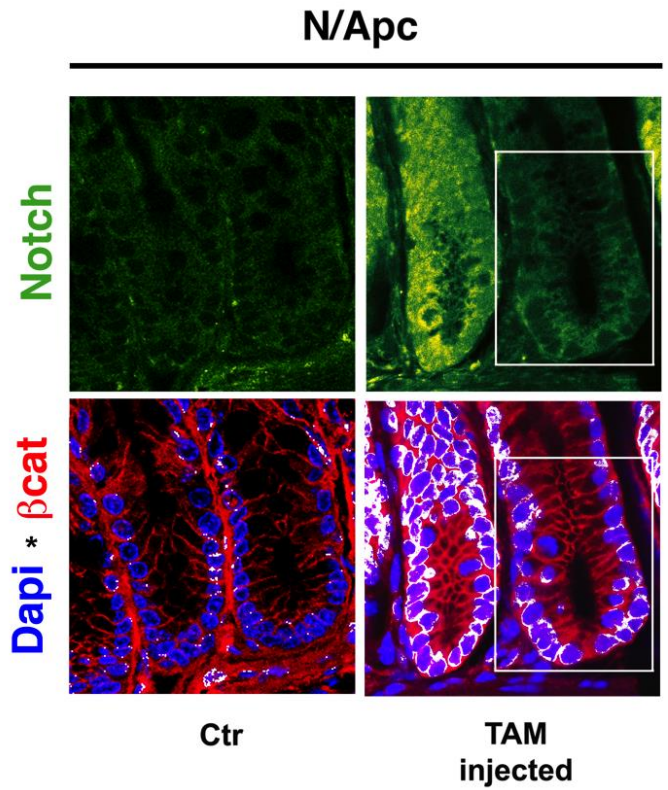




institutCurie

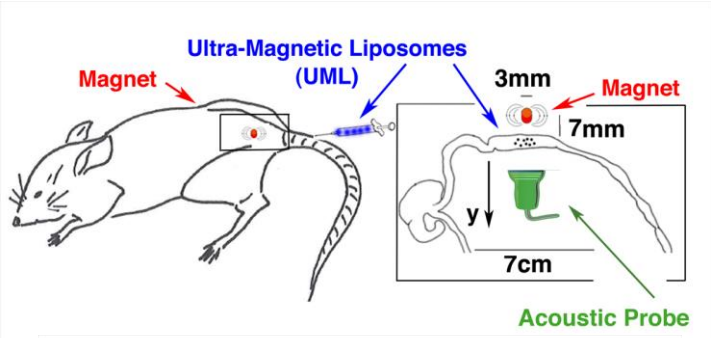
Endogenous hyperproliferative Notch tumour growth pressure activates the β-cat tumorigenic pathway in neighbouring non tumour Notch negative crypts

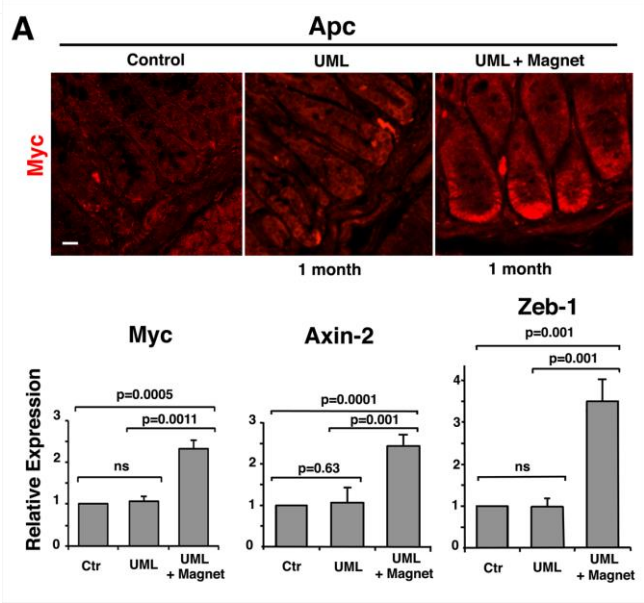




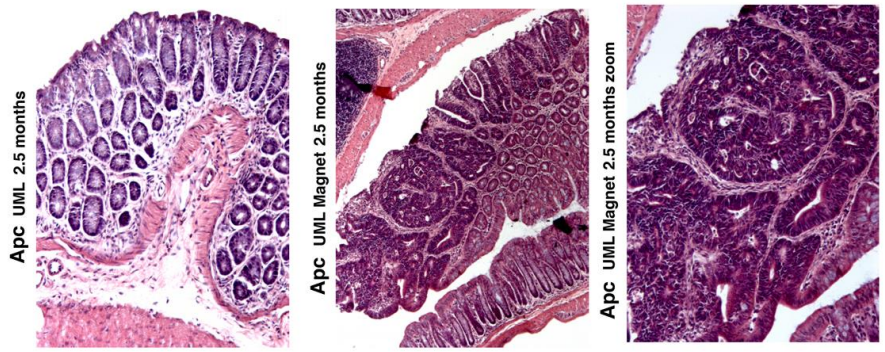
institutCurie

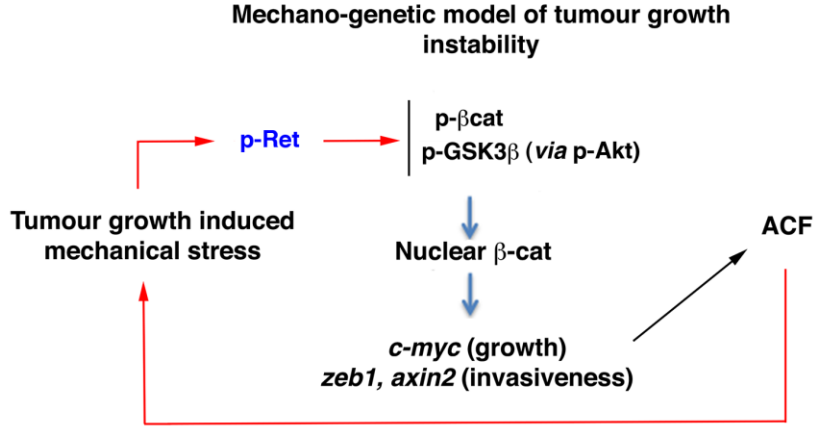
Conclusion - Beta-cat dependent mechanical Induction of Oncogenes Expression in healthy tissues by tumour growth pressure *in vivo*





In APC+/-



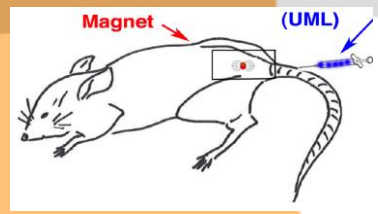


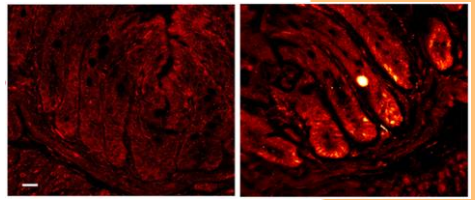
In vivo: Elena Fernandez-Sanchez, Sandrine Barbier et al., Nature, 2015

institutCurie

“Mechano-Cancer” Consortium

Emmanuel Farge’s team
(UMR168 Institut Curie)
Elena Fernandez-Sanchez
Sandrine Barbier
Anne-Christine Brunet
Adrien Bouclet
Thibaut Brnuet
Joanne Whitehead

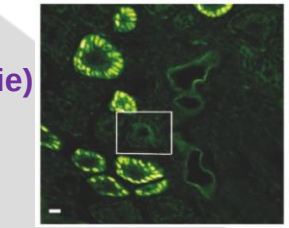




Christine Ménager’s team
(Université Pierre et Marie Curie Physico-Chimie, ESPCI) and Sylviane Lesieur’s team (Université Paris12 Pharma)
Gaelle Bealle
Aude Michel
Hélène Marie

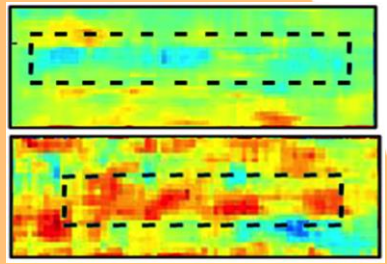
Sylvie Robine’s team
(UMR 144 Institut Curie)
Jeanne Netter

Silvia Fre’s team
(UMR 3215 Institut Curie)
Mathilde Huygue



institutCurie

Plateforms: Animal House’s team, Bioinformatics, Sequencing (Institut Curie)
- Isabelle Grandjean
Virginie Dangles-Marie
Stéphanie Boissel
- Elodie Girard
Nicolas Servant
- Thomas Rio-Frio



Mickael Tanter’s team
(Institut Langevin, ESPCI)
Jean-Luc Gennisson
Heldmuth Latorre-Ossa

Chantal Housset’s team
(Faculté de Médecine, Hopital Saint-Antoine, Inserm)
Colette Rey
Laura Fouassier
Audrey Claperon

Instituts thématiques
Inserm
Institut national de la santé et de la recherche médicale

FONDATION PIERRE-GILLES DE GENNES POUR LA RECHERCHE
PSL RESEARCH UNIVERSITY PARIS
INSTITUT NATIONAL DU CANCER
AGENCE NATIONALE DE LA RECHERCHE ANR
FONDATION RECHERCHE MÉDICALE

phybio
cnrs dépasser les frontières

Mechanics & Genetics of Embryonic and Tumour Development

ANR

–Joanne Whitehead, Sandrine Barbier and Elena Fernandez-Sanchez
–Tumoral Progression / Post-docs IC-Marie Curie, ANR, RTRA FPGDG

–Nicolas Desprat
–Ferromagnetic Injections and Mechano-transcription Post-doc INSERM 2005/2008

–Philippe-Alexandre Pouille, Padra Ahmadi,, Démosthène Mitrosslis, Benjamin Driquez, Willy Supatto, A. Bouclet
–Numerical simulations and experiments
–PhD 2005/2009, Microsoft European Grant

–T. Brunet, Adrien Bouclet, L. Henry, F. Serman
–Zebrafish

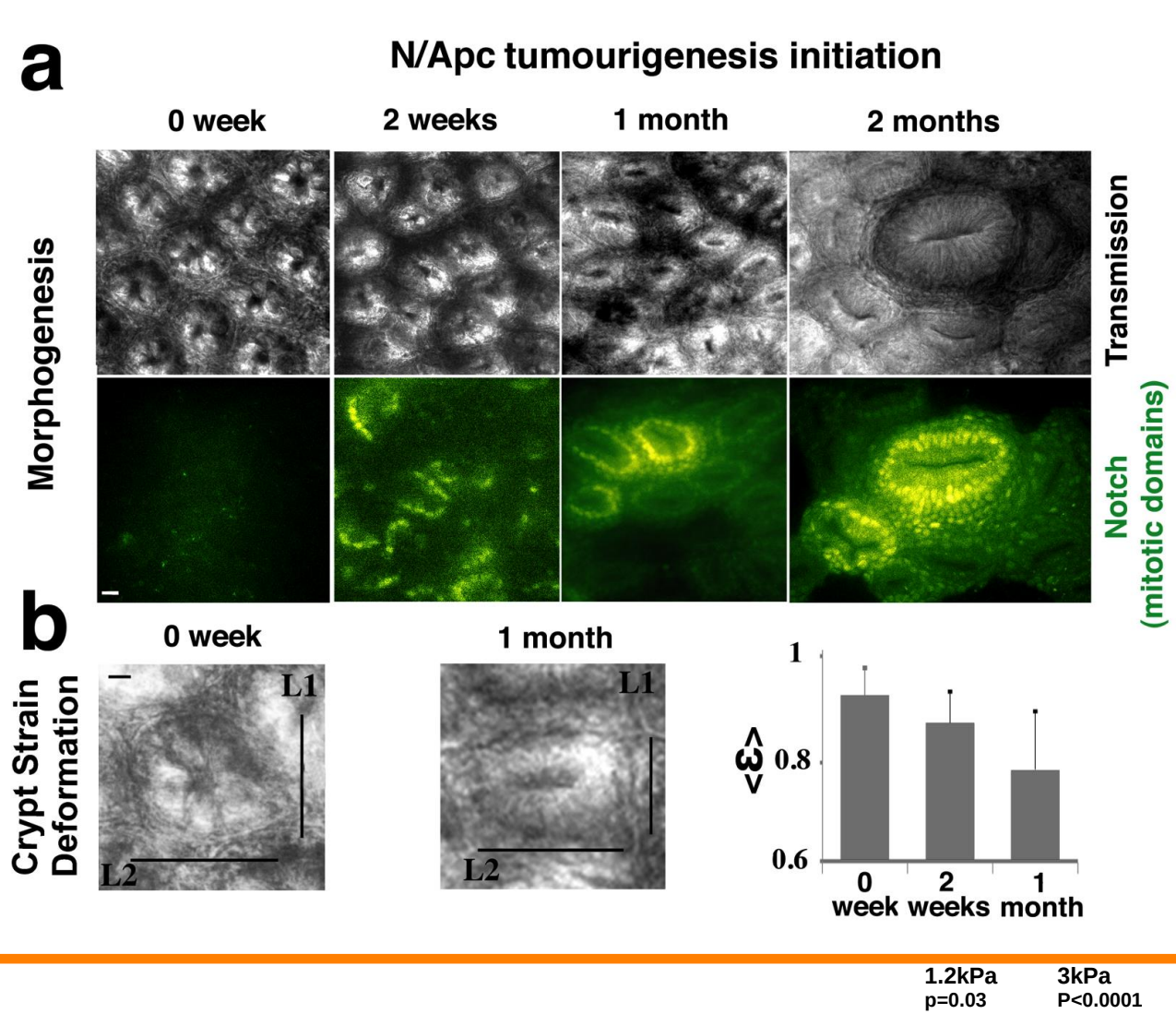
–Anne-Christine Brunet:
–Ingénieur de recherche

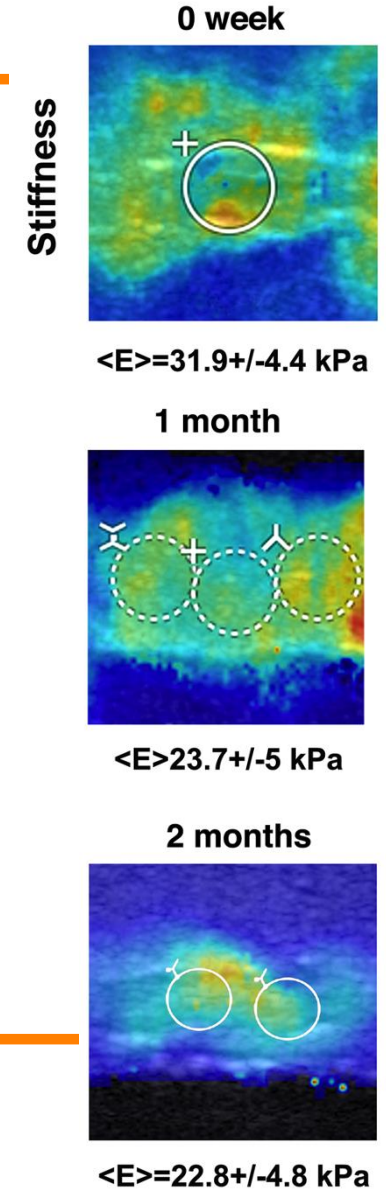
Collaborators:
Nora Dempsey (I. Néel), C. Ménager, Paris 6) , Emmanuel Beaurepaire (Optics, Polytechnique),
Glenn Edwards (Duke U), L. Solnica-Krezel (Zebra)
Silvia Fre, Sylvie Robine (Colon cancer, I. Curie), Jean-Luc Genisson, Michael Tanter (I. Langevin)

Anne Plessis (Droso, IJM, Paris)
Dino Yanicostas (Zebra, UPMC, Paris)

ARC, C'Nano, Fondation Pierre Gilles de Gennes, Inca, Labex CelTisPhysBio

Notch hyper-proliferative domains induce crypt strain deformation without change of stiffness

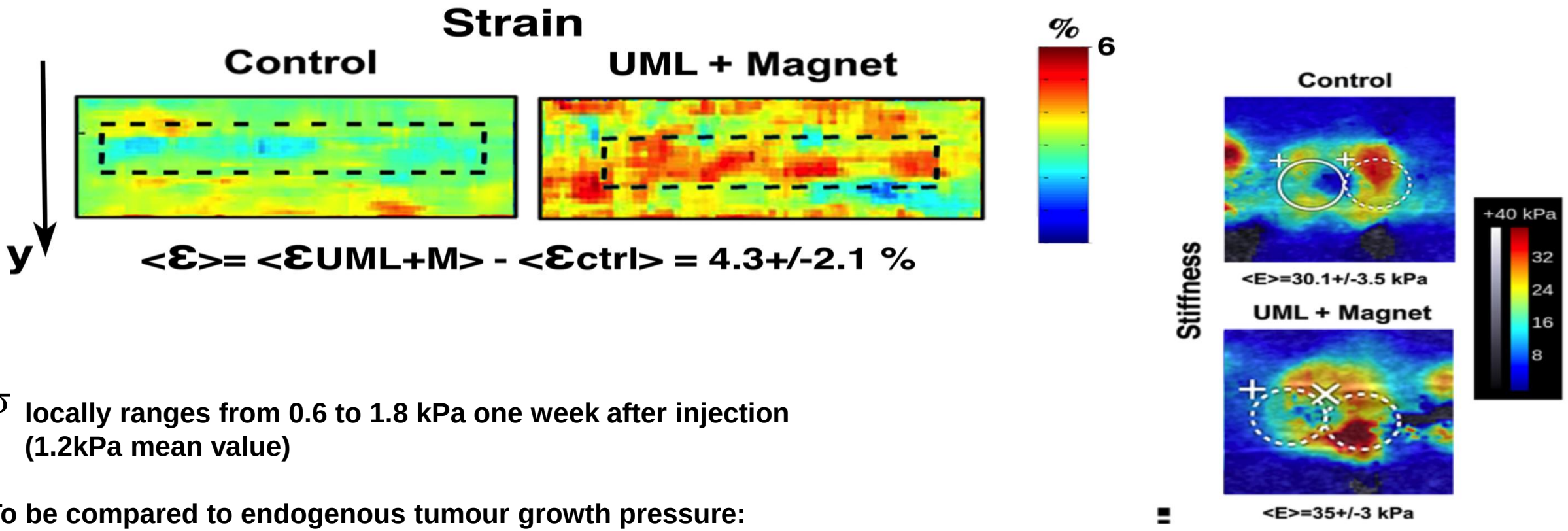




σ locally ranges from 0.4 to 5.6 kPa at one month
(3kPa mean value, 13% mean strain deformation)

institutCurie

Magnetic forces induce a mean mechanical pressure on the order of 1kPa, equivalent to tumour growth pressure



- σ locally ranges from 0.6 to 1.8 kPa one week after injection (1.2kPa mean value)

To be compared to endogenous tumour growth pressure: 1.2kPa (2 weeks of Notch activation)

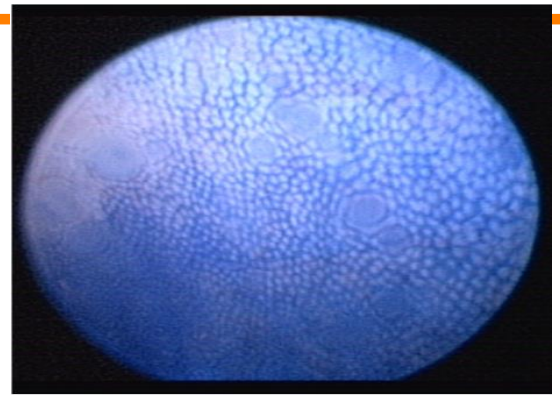
institutCurie

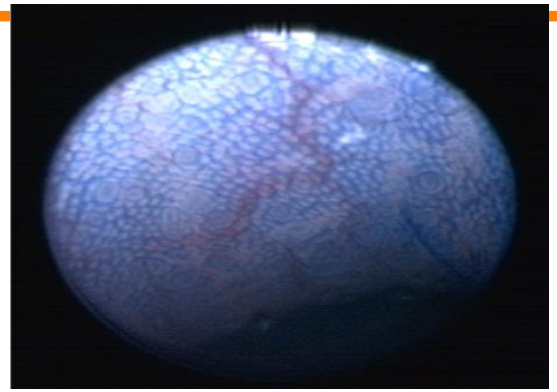
Magnetic forces mimicking tumour growth pressure can induce adenoma-carcinoma, in Apc heterozygous mice colon

control

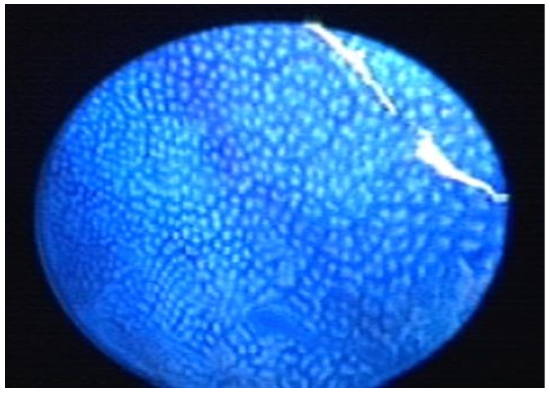
UML

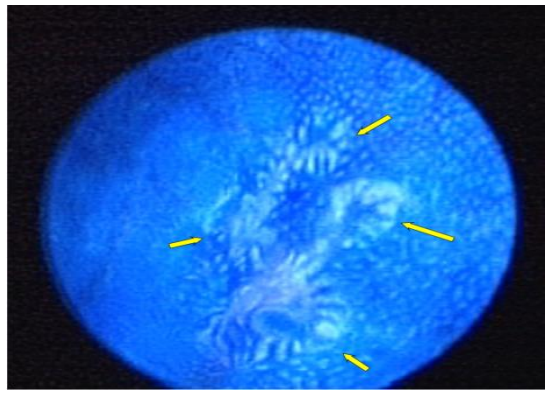
t=0



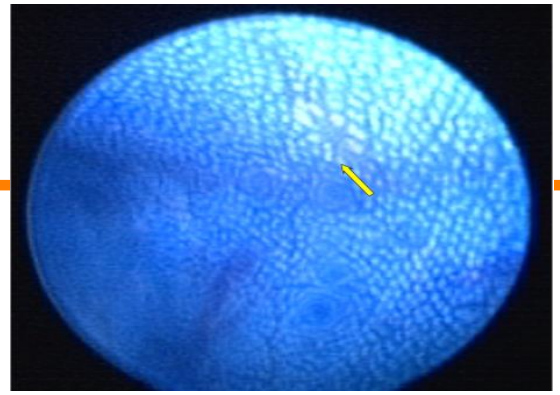


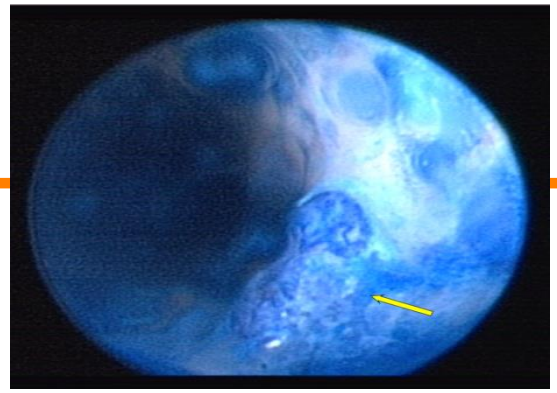
5 days



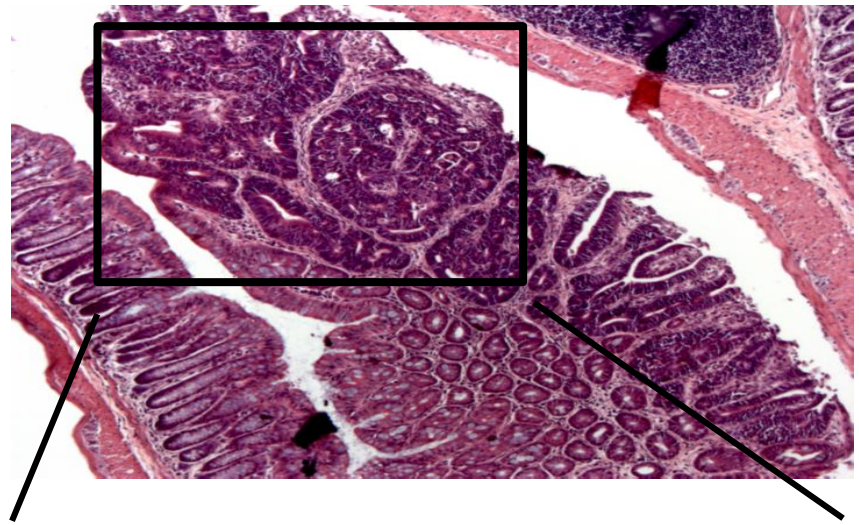


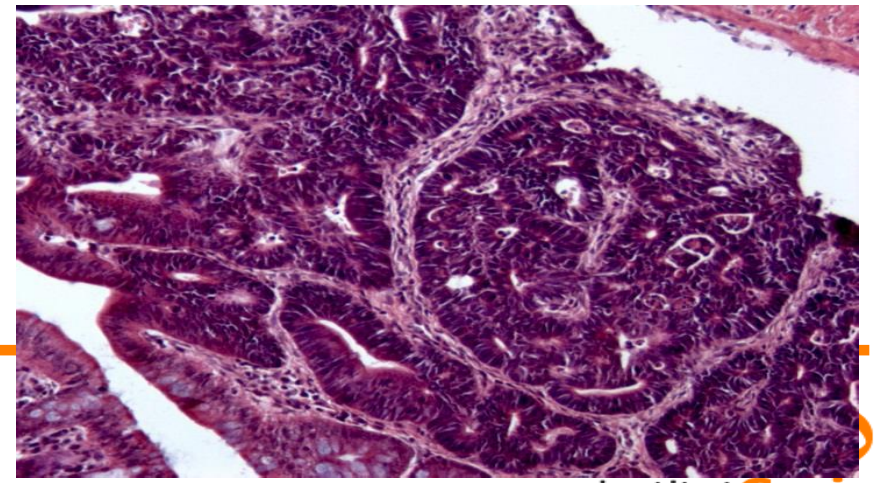
2.5 months





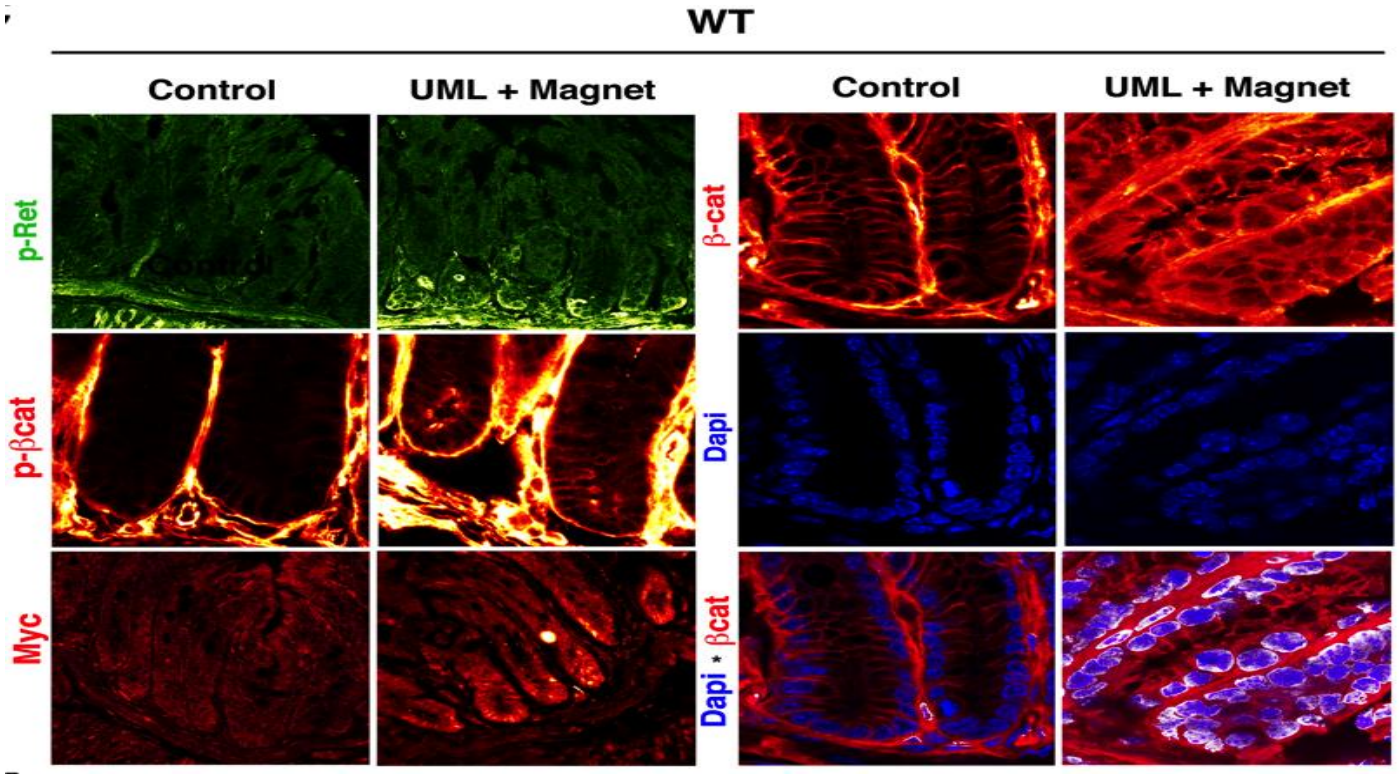
UML - 2.5 months

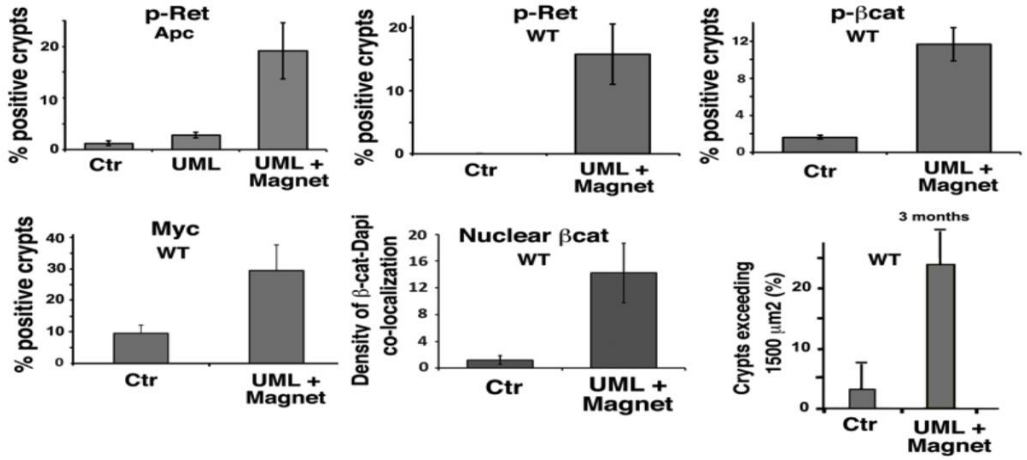




institutCurie

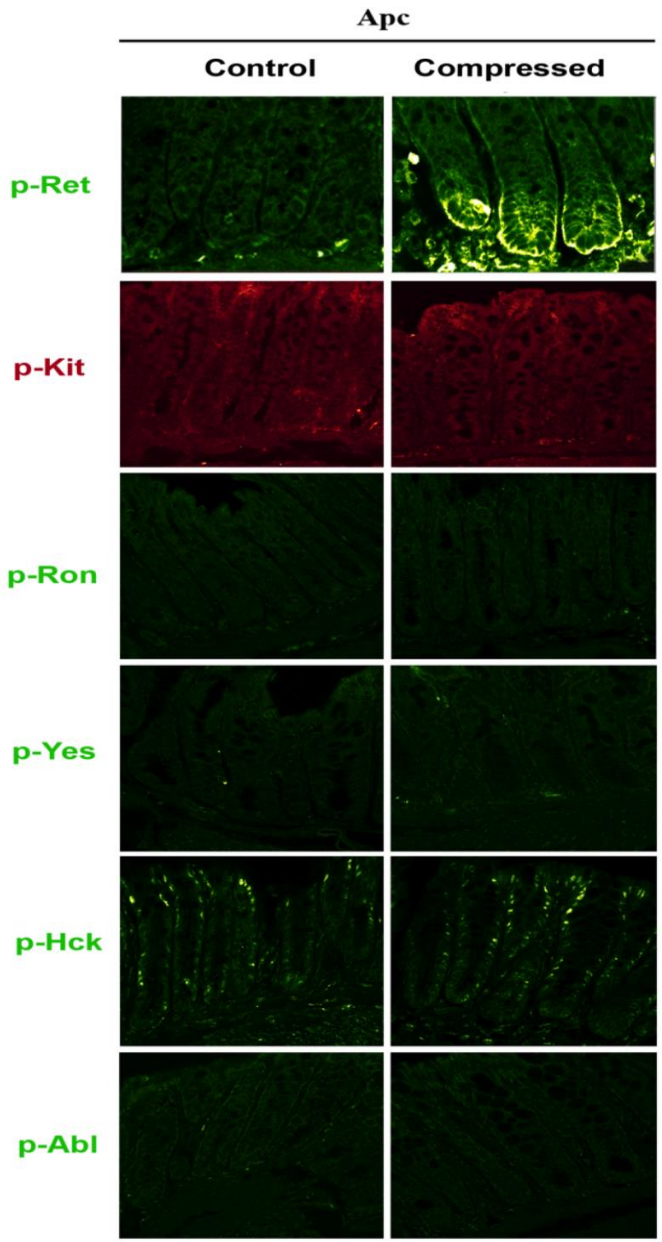
Magnetic forces mimicking tumour growth pressure activates the β-cat tumorogenic pathway, in WT mice colon too

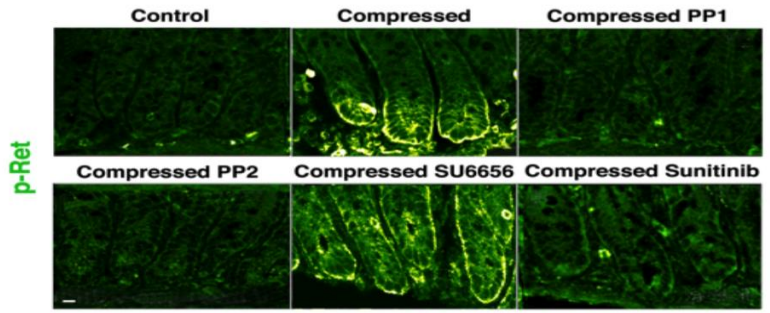




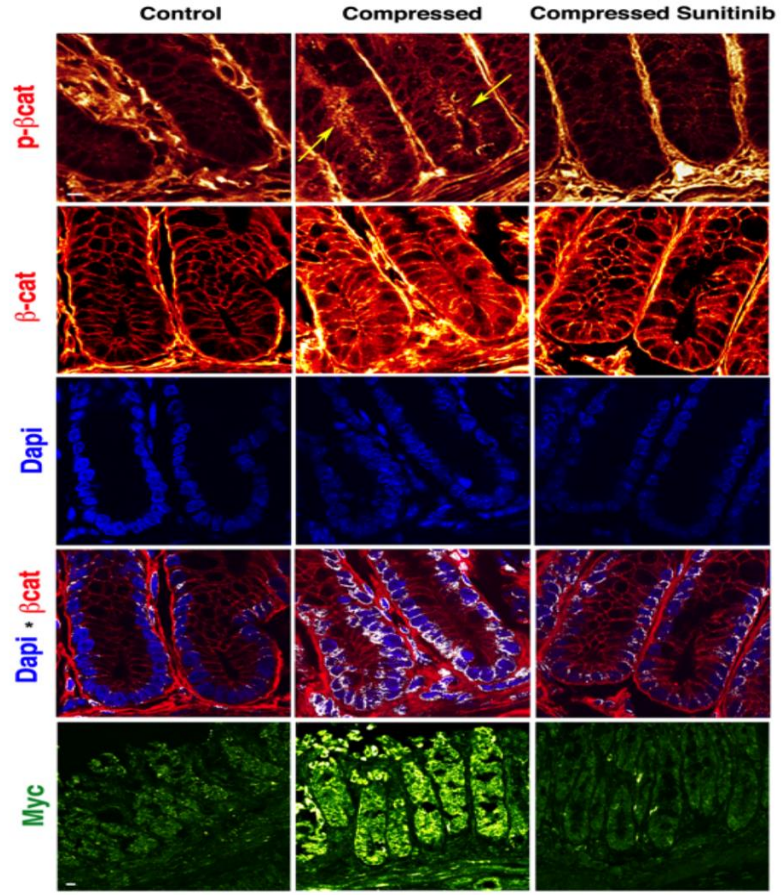
institutCurie

Mechanotransdcutive pathway: Ret phosphorylation is upstream of β-cat tumorogenic pathway mechanical activation





Y1062p-Ret



Y564 p-βcat

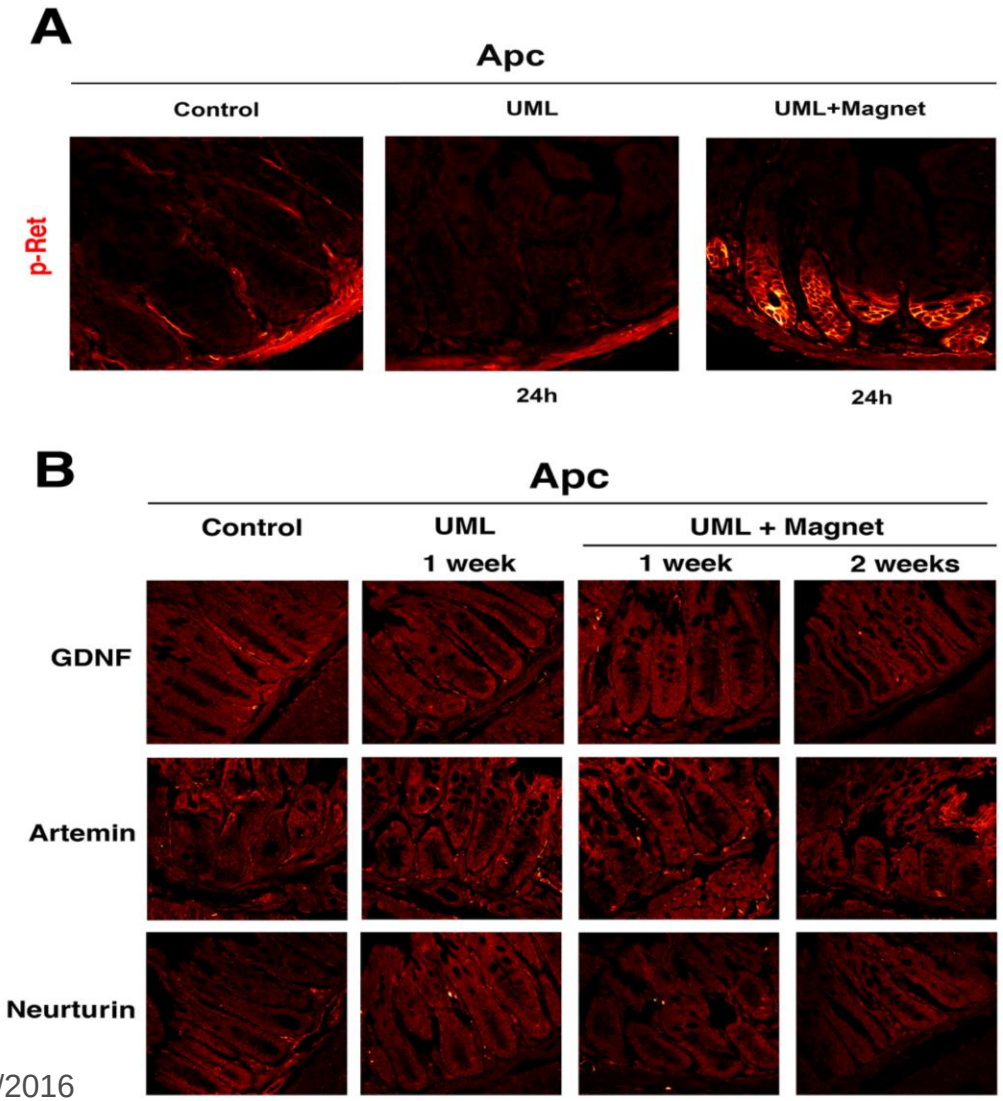
βcat

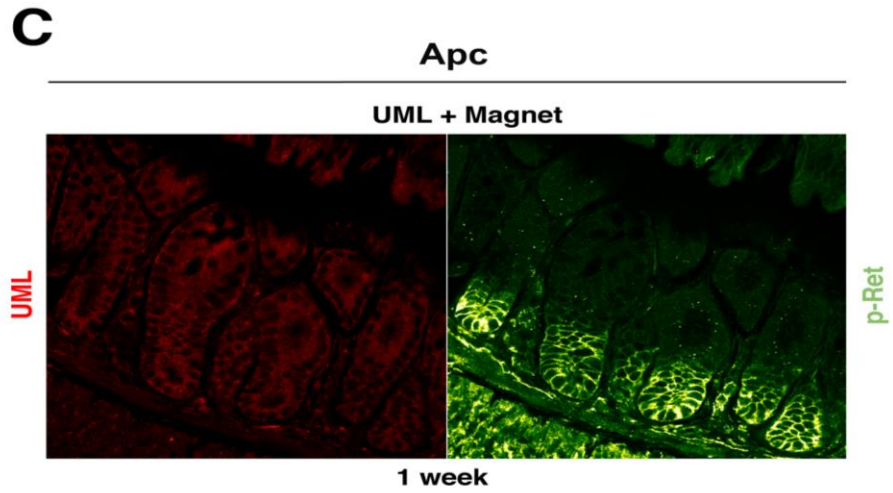
Same results with the 2 other Ret inhibitors Vandetanib and Ponatinib

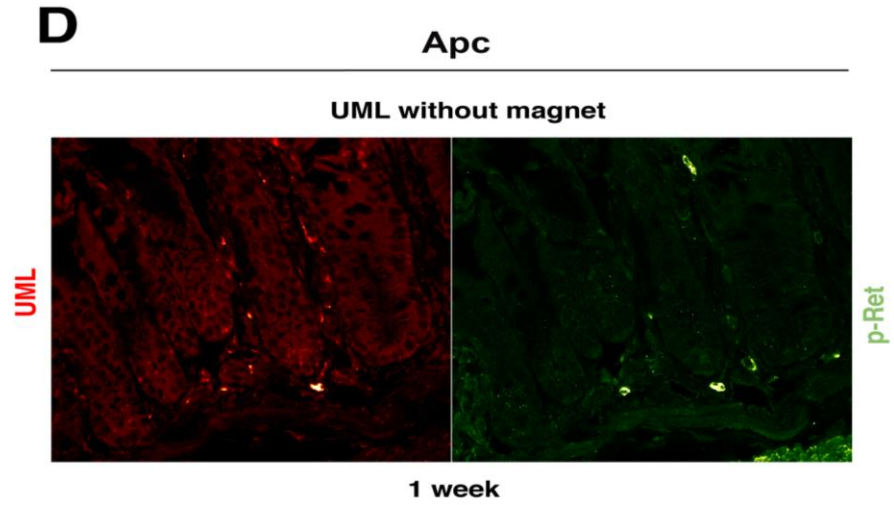
Myc

institutCurie

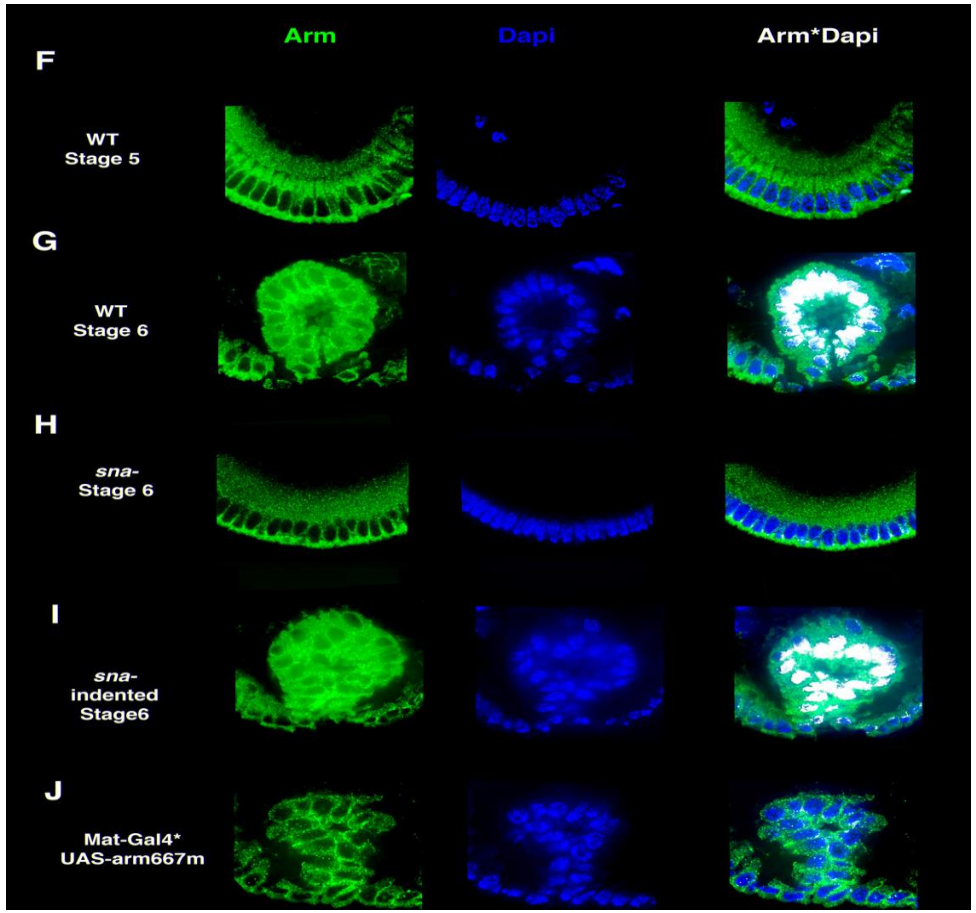
Controls: Ret ligands and UMLs by themself, do not activate Ret

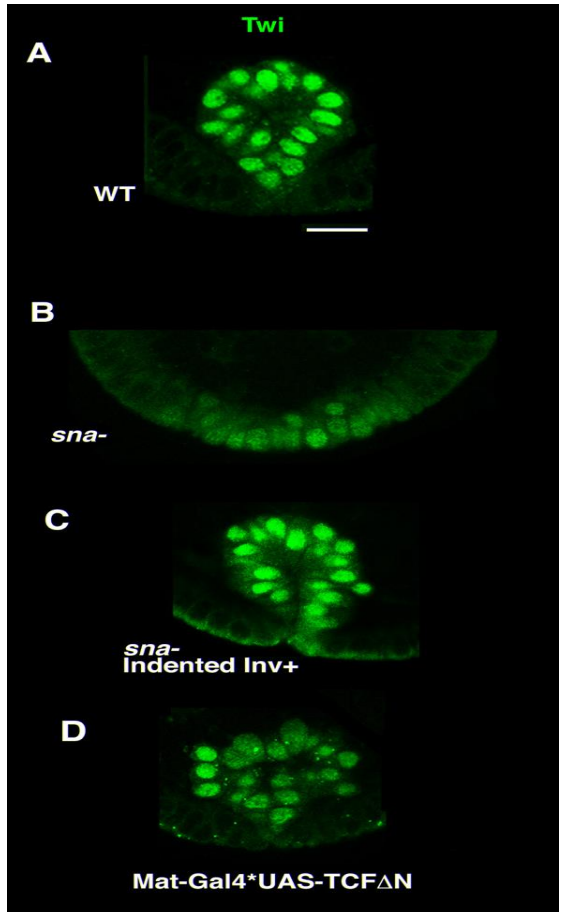


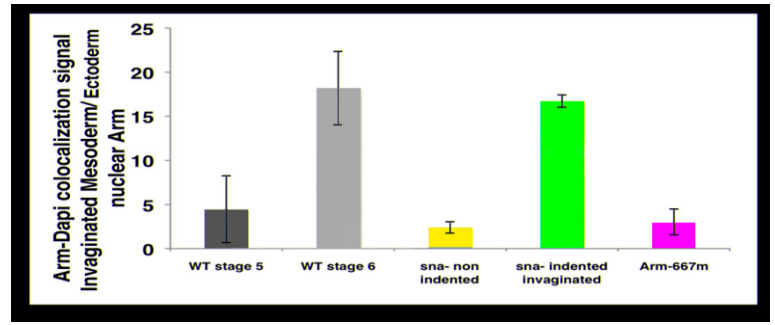


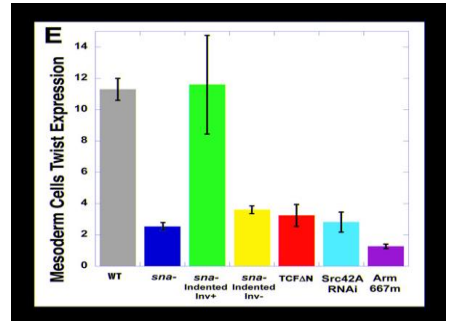


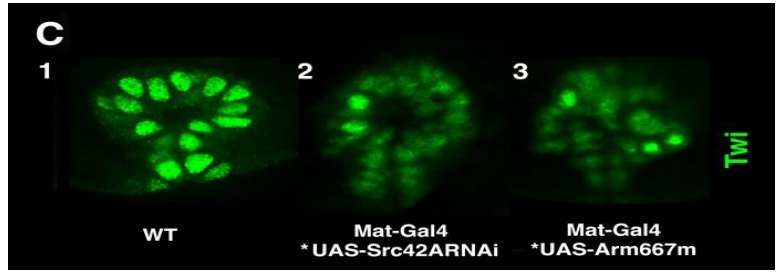
β-catenin cytoplasmic and nuclear translocation are mechanically induced by Y667 β-catenin mechanical phosphorylation and lead to Twist expression maintenance in the mesoderm







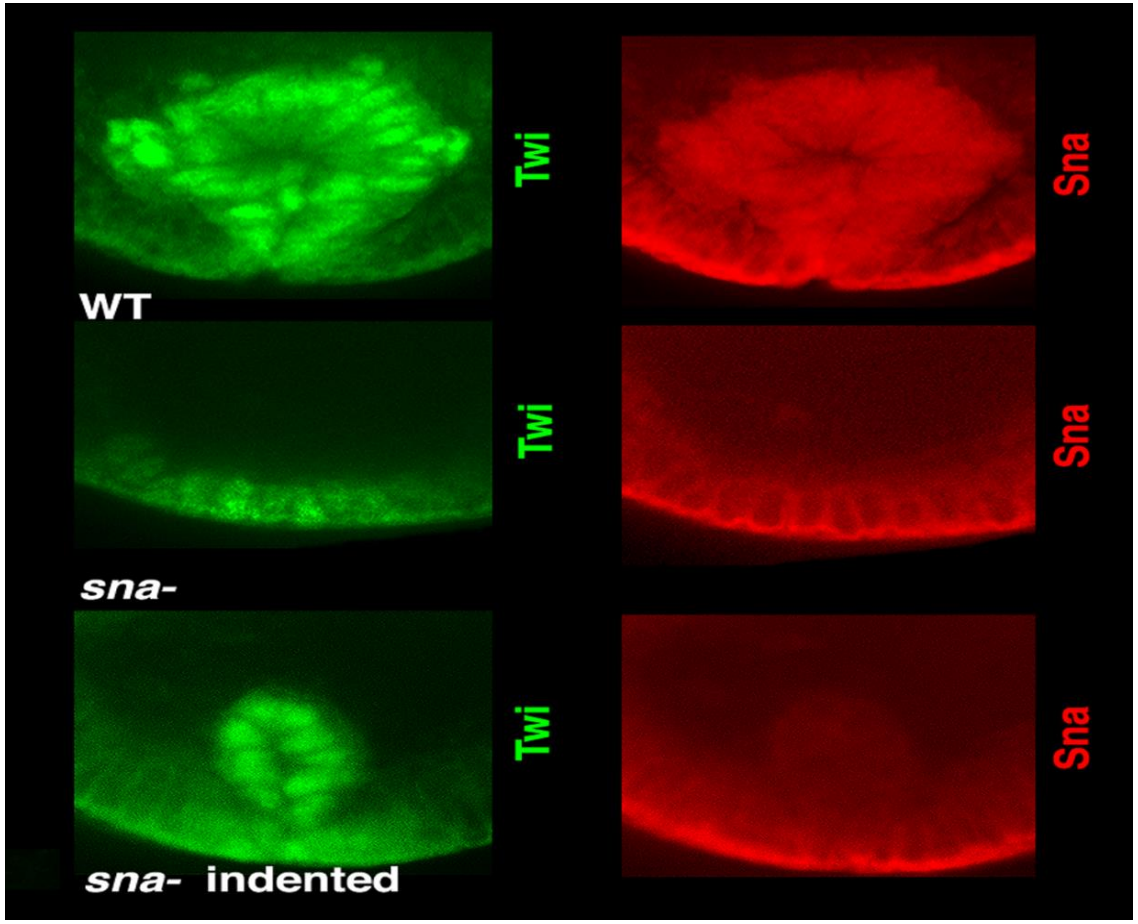


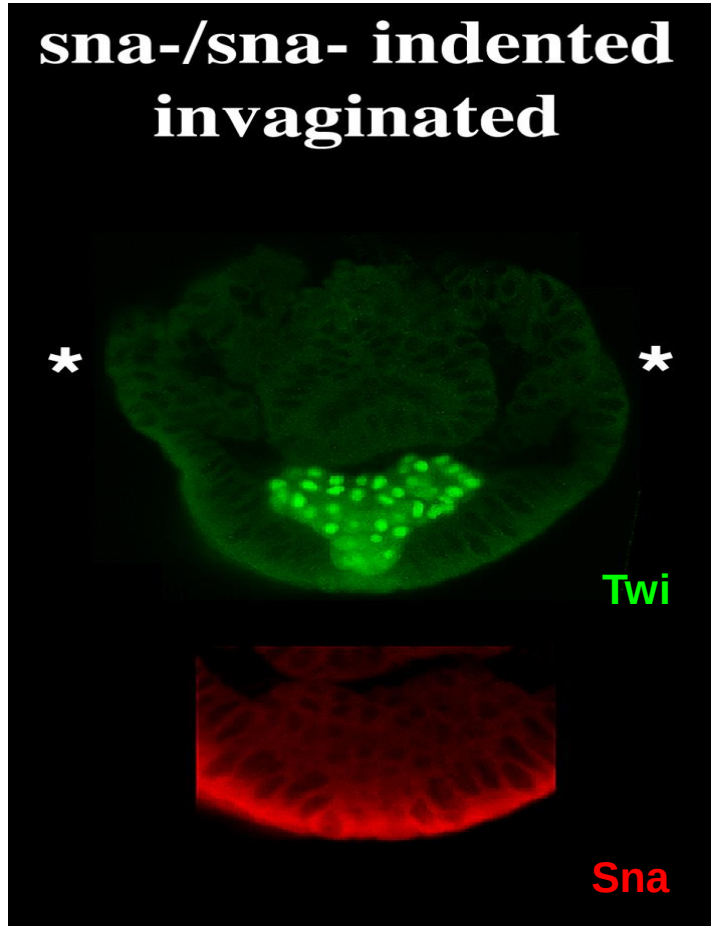


Note: 1%FA Fix procedure for Arm nuclei detection (poor junctional resolution)

institutCurie

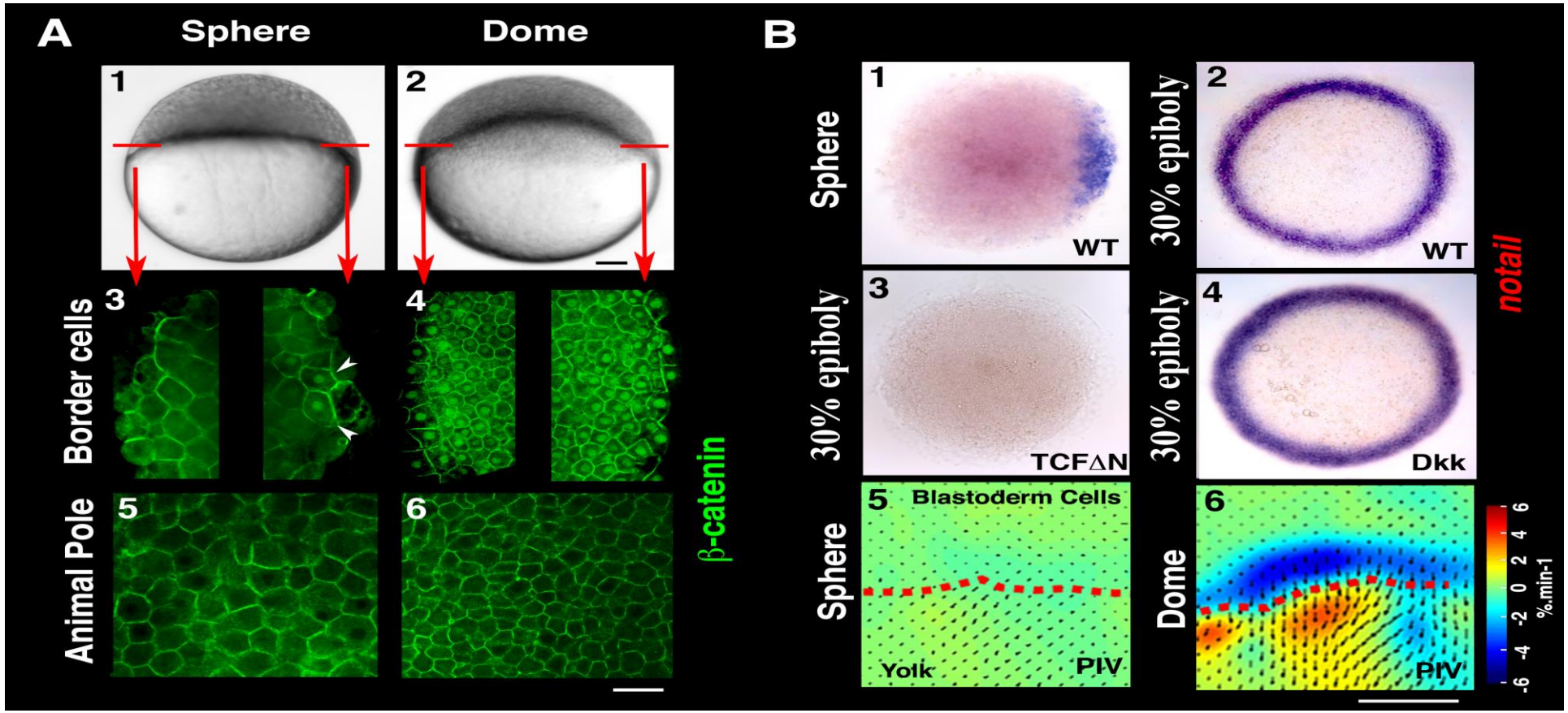
Twi Sna double labelling: indented sna- invaginating and expressing strongly Twist





institutCurie

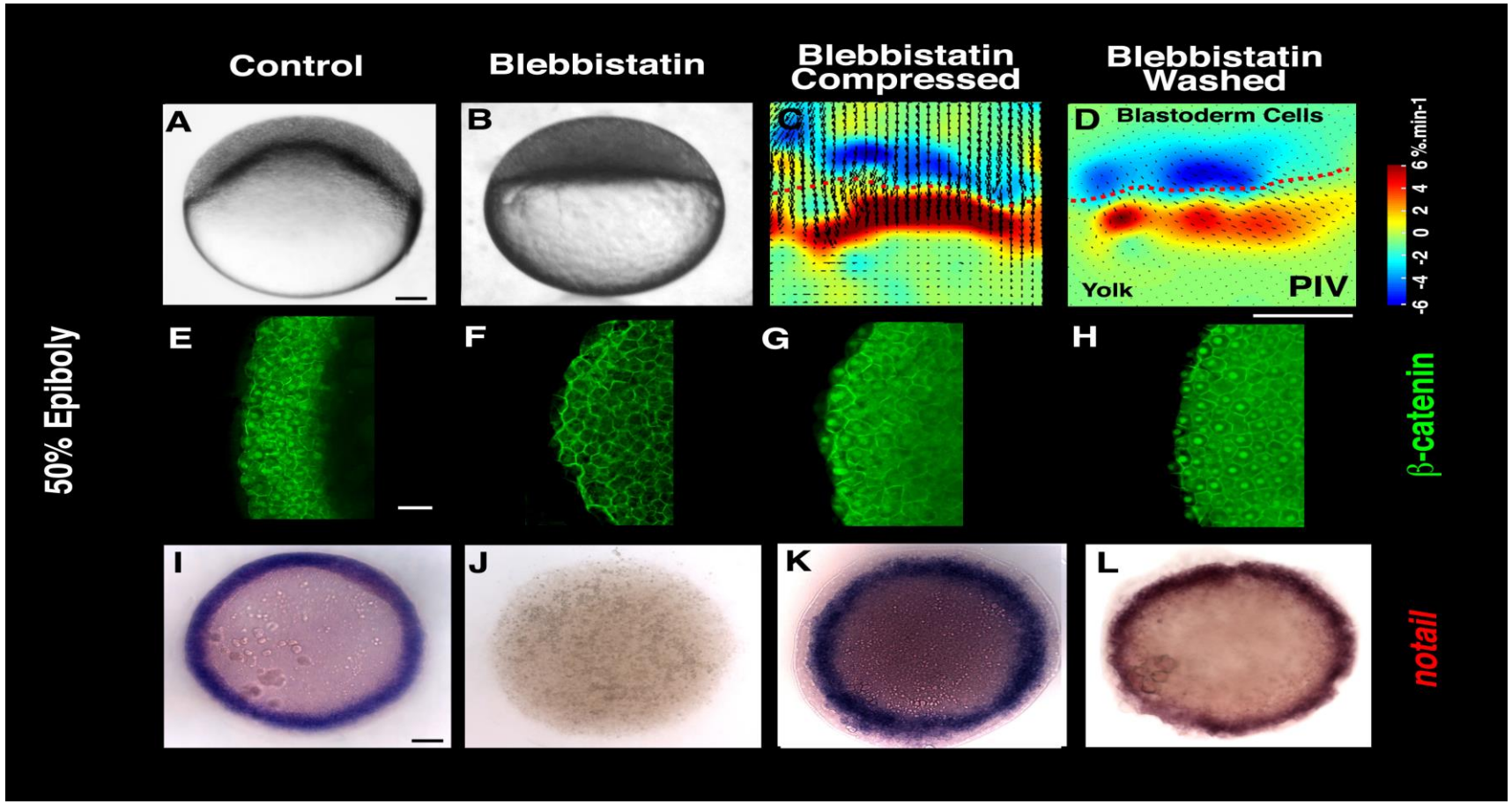
Zebrafish: the mesoderm patterning gene *notail* is expressed at the onset of epiboly in specifically deformed margin cells in a β-catenin dependent but Wnt independent process

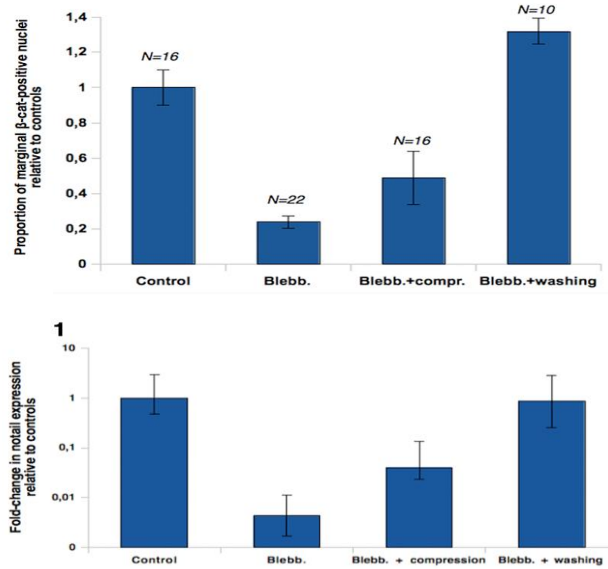


Dkk: inhibitor of Wnts through Lrp6

institutCurie

The β-catenin dependent expression of *notail* in margin cells is induced by the morphogenetic movement of epiboly onset





Uniaxial deformation:
35μm during 20min

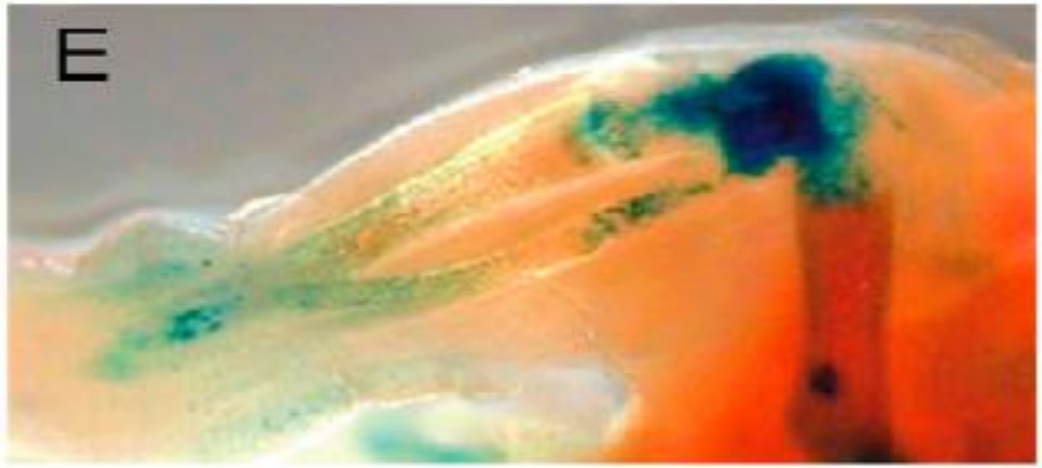
institutCurie

β-catenin/Armadillo is also involved as a Mechano-Transcriptional Pathway in Bone Development

JOURNAL OF BONE AND MINERAL RESEARCH
Volume 20, Number 7, 2005
Published online on February 14, 2005; doi: 10.1359/JBMR.050210

TOPGAL Mice Show That the Canonical Wnt Signaling Pathway Is Active During Bone Development and Growth and Is Activated by Mechanical Loading In Vitro

Julie R Hens,[1] Kimberly M Wilson,[2] Pamela Dann,[1] Xuesong Chen,[1] Mark C Horowitz,[2] and John J Wysolmerski[1]



Hens et al, Journal of Bone and Mineral Research, 2005

Muscle Contraction Is Necessary to Maintain Joint Progenitor Cell Fate

Joy Kahn,[1,6] Yulia Shwartz,[1,6] Einat Blitz,[1] Sharon Krief,[1] Amnon Sharir,[1,2] Dario. A. Breitel,[1] Revital Rattenbach,[3] Frederic Relaix,[3] Pascal Maire,[4] Ryan B. Rountree,[5] David M. Kingsley,[5] and Elazar Zelzer[1,*]
[1]Department of Molecular Genetics, Weizmann Institute of Science, Rehovot 76100, Israel
[2]The Laboratory of Musculoskeletal Biomechanics and Applied Anatomy, Koret School of Veterinary Medicine, Hebrew University of Jerusalem, Rehovot 76100, Israel
[3]UMR-S 787, Myology Group, INSERM-UPMC-Paris VI, Faculté de Médecine Pitié-Salpétrière, Paris 75634, France
[4]Département de Génétique et Développement, Institut Cochin, INSERM U567, CNRS UMR8104 Université Paris Descartes, Paris 75014, France
[5]Department of Developmental Biology and HHMI, Stanford University School of Medicine, Stanford, CA 94305, USA
[6]These authors contributed equally to this work
*Correspondence: eli.zelzer@weizmann.ac.il
DOI 10.1016/j.devcel.2009.04.013

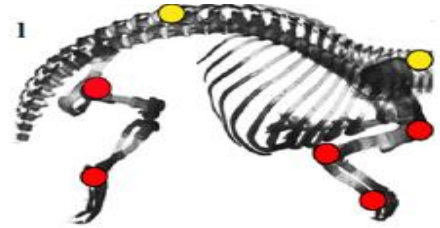


Figure 1. Joint Loss in the Absence of Muscle Contraction

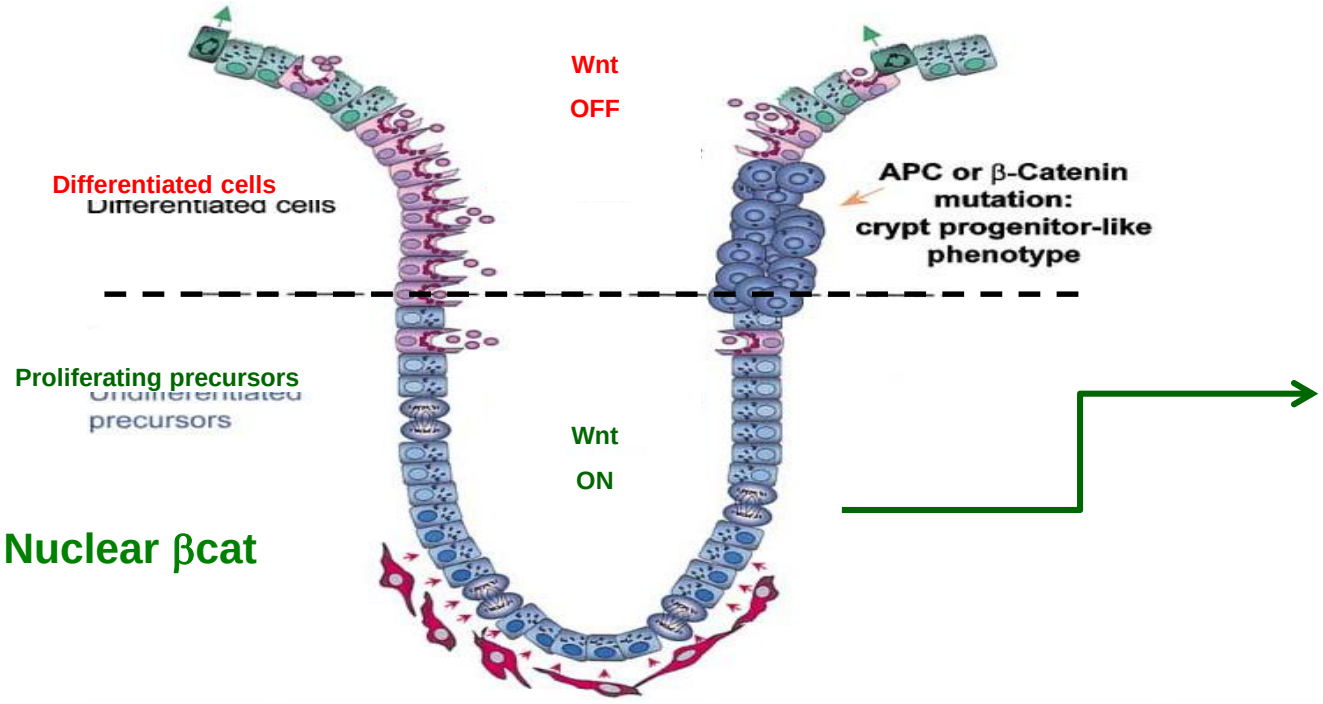
Bone Development: Khan J et al, Dev Cell 2009

Inhibition of Adipogenesis
Sen, B, et al Endicronology, 2008

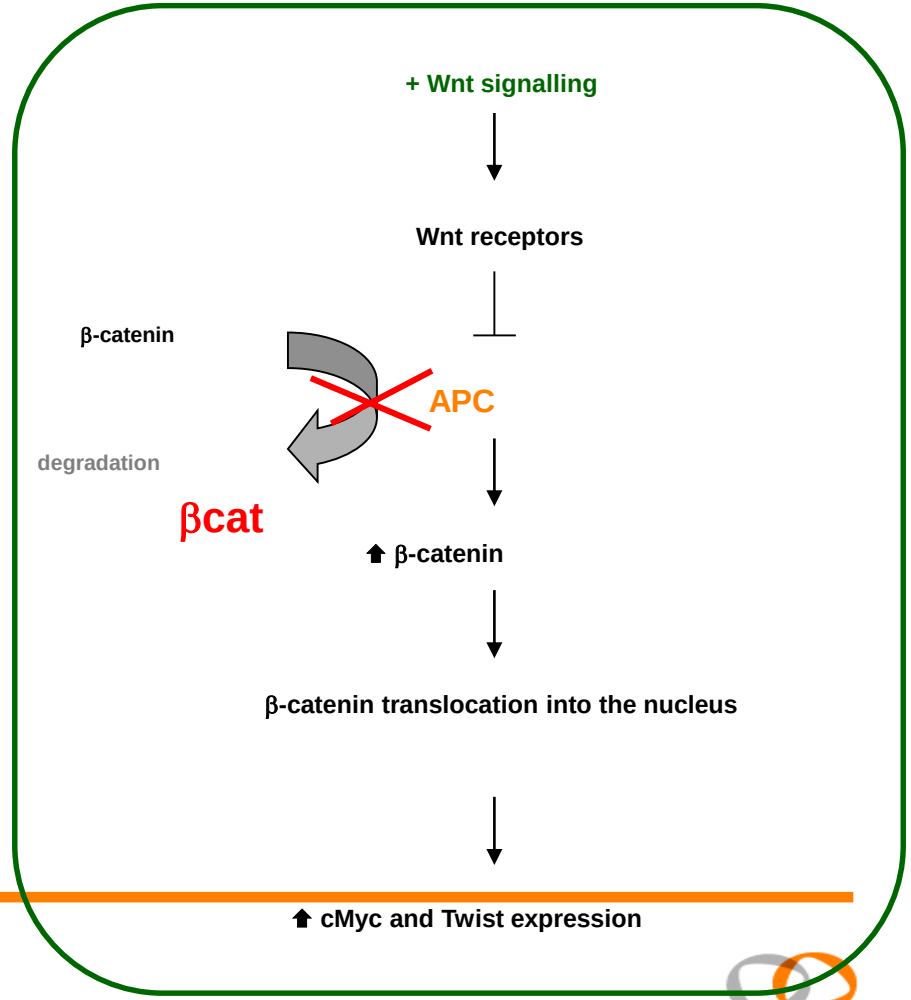
institutCurie

Introduction : mice colon carcinogenesis

Model for the role of β-Catenin in the early stages of intestinal tumorigenesis



Adapted from Van de Wetering *et al*. 2002 Cell

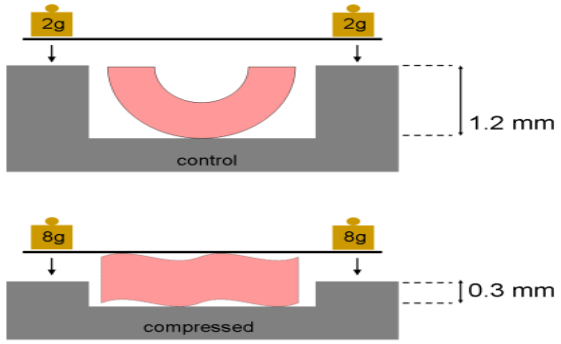


Fre *et al*. 2009; Peignon *et al*. 2011

institutCurie

Ex vivo mechanical compression of the distal colon, 0.8 kPa

APC$^{1638N/+}$

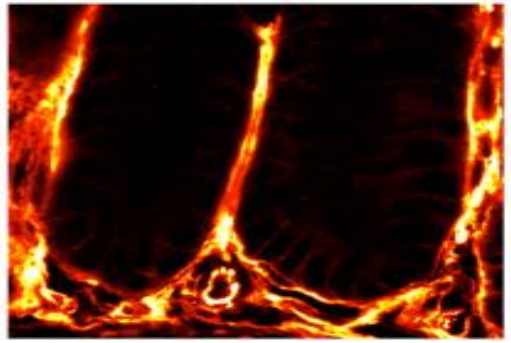


Whitehead *et al.* HFSPJ 2008

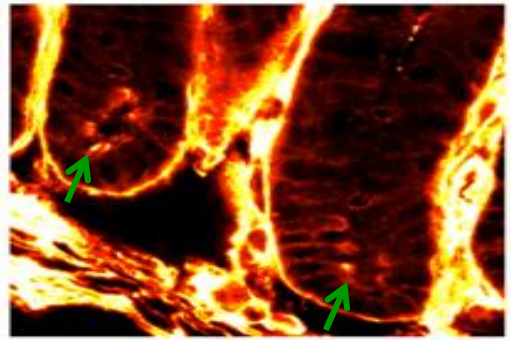
2

pY654 β-catenin

control



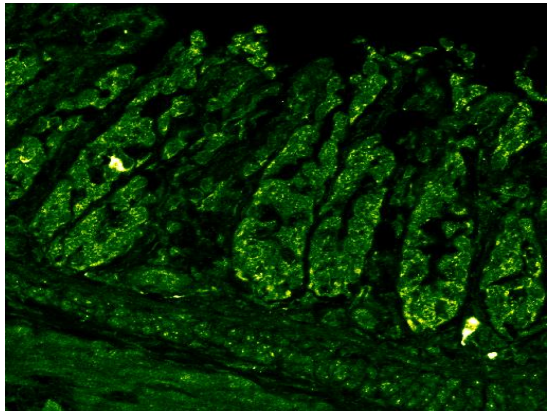
compressed



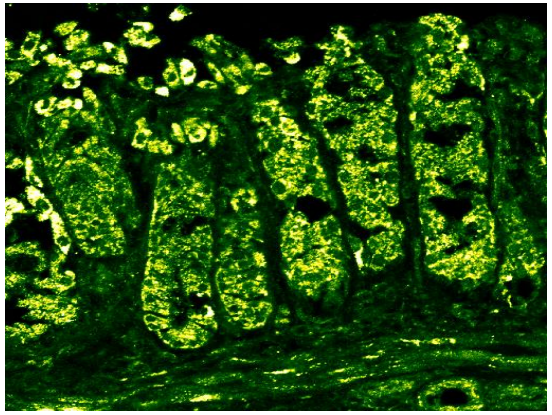
1

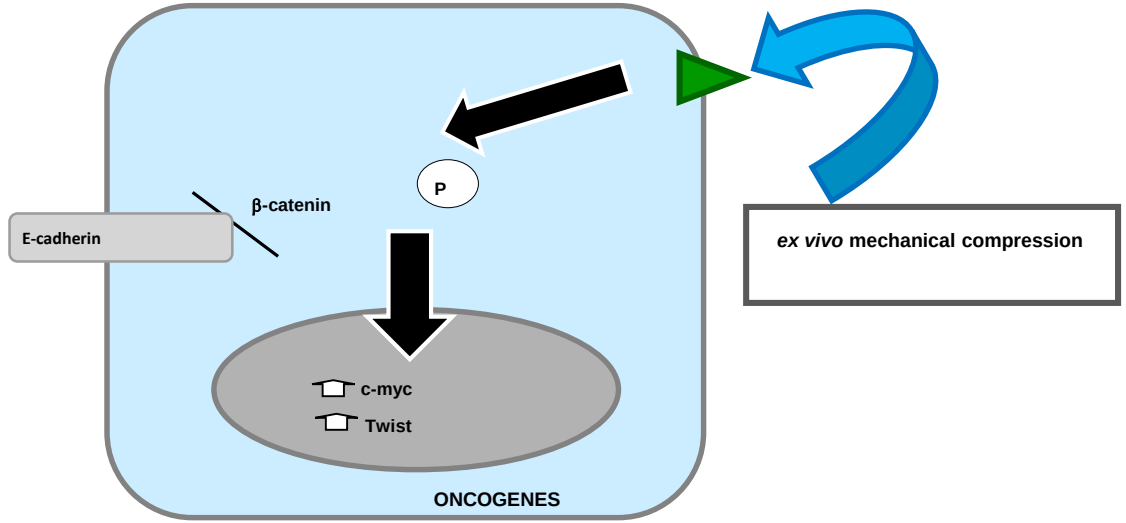
cMyc

control



compressed





Whitehead et al, HFSPJ, 2008 (β-cat pathway activated by external pressure)

Samuel et al, Cancer Cell 2011 (β-cat pathway activated by stiffness increase)

institutCurie