L'axe microbiote-intestin-cerveau: acteur de notre santé et de nos maladies

Michel Neunlist

UMR Inserm TENS 'The enteric nervous system in gut and brain diseases'

Institut des Maladies de l'Appareil Digestif , Nantes

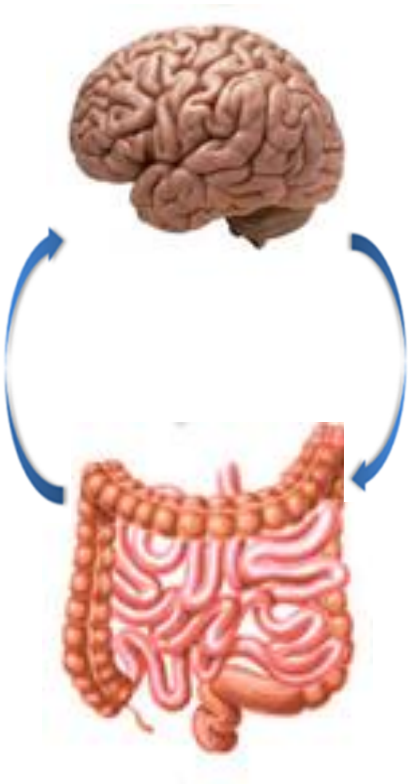
Organisation de la présentation

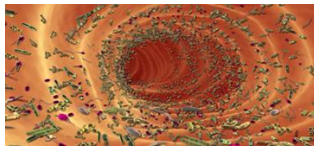
I. L’axe intestin-cerveau

II. Le microbiote intestinal : un nouvel ‘organe’?

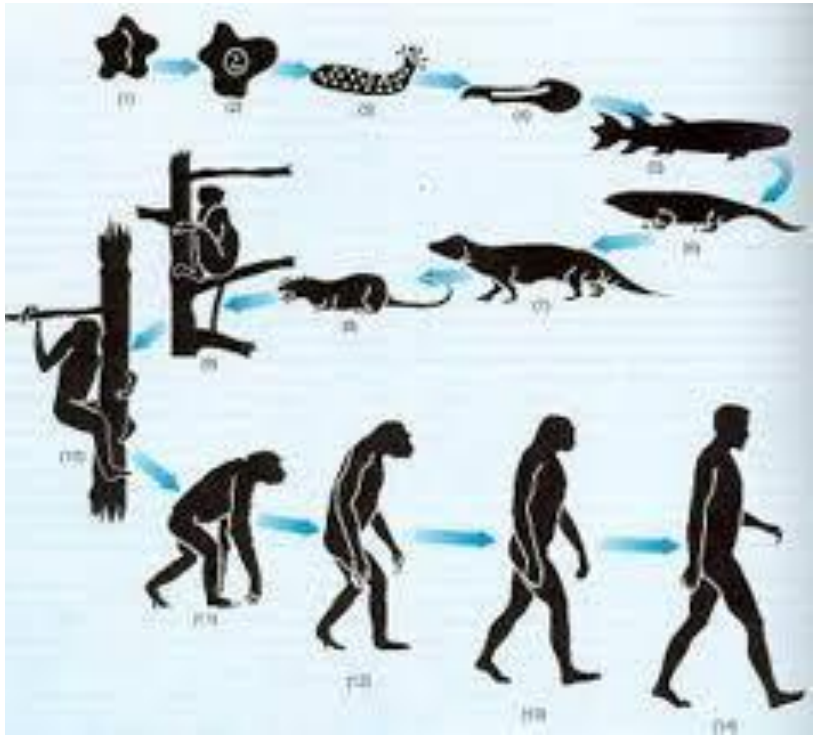
III.Le crosstalk entre le microbiote intestinal et l’intestin (système nerveux entérique)

IV. Le crosstalk entre le microbiote intestinal et le cerveau et son implication dans les pathologies cérébrales



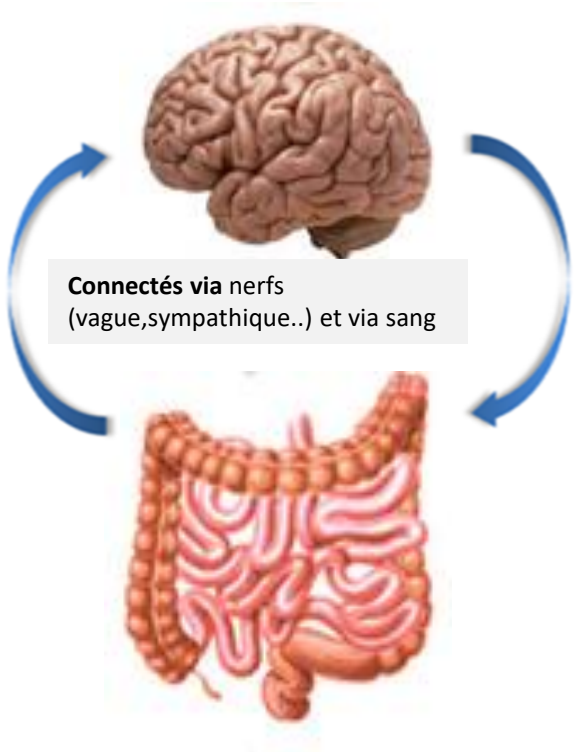


Le cerveau et l'intestin : deux organes clefs de l'évolution et connectés….



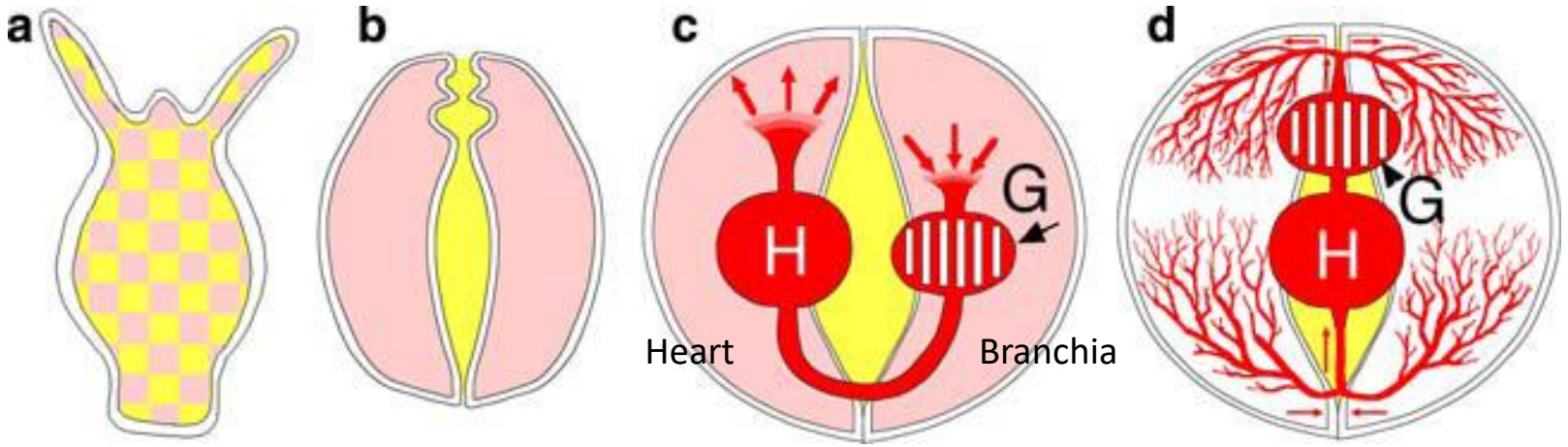
Survie (reproduction) et adaptation à l'environnement

Hypothalamus (prise alimentaire - satiété)
Hippocampe (formation de la mémoire)
Amygdale (agressivité - peur)



Le tube digestif : un organe au coeur de l'évolution

Intestin



Hydra (cnidaire) Nematode Mollusque Fish

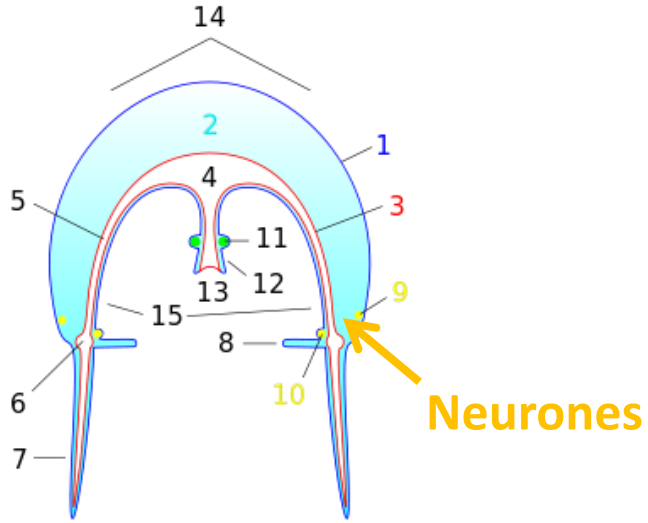
Le tube digestif : premier organe neurologique de l'évolution

LETTER

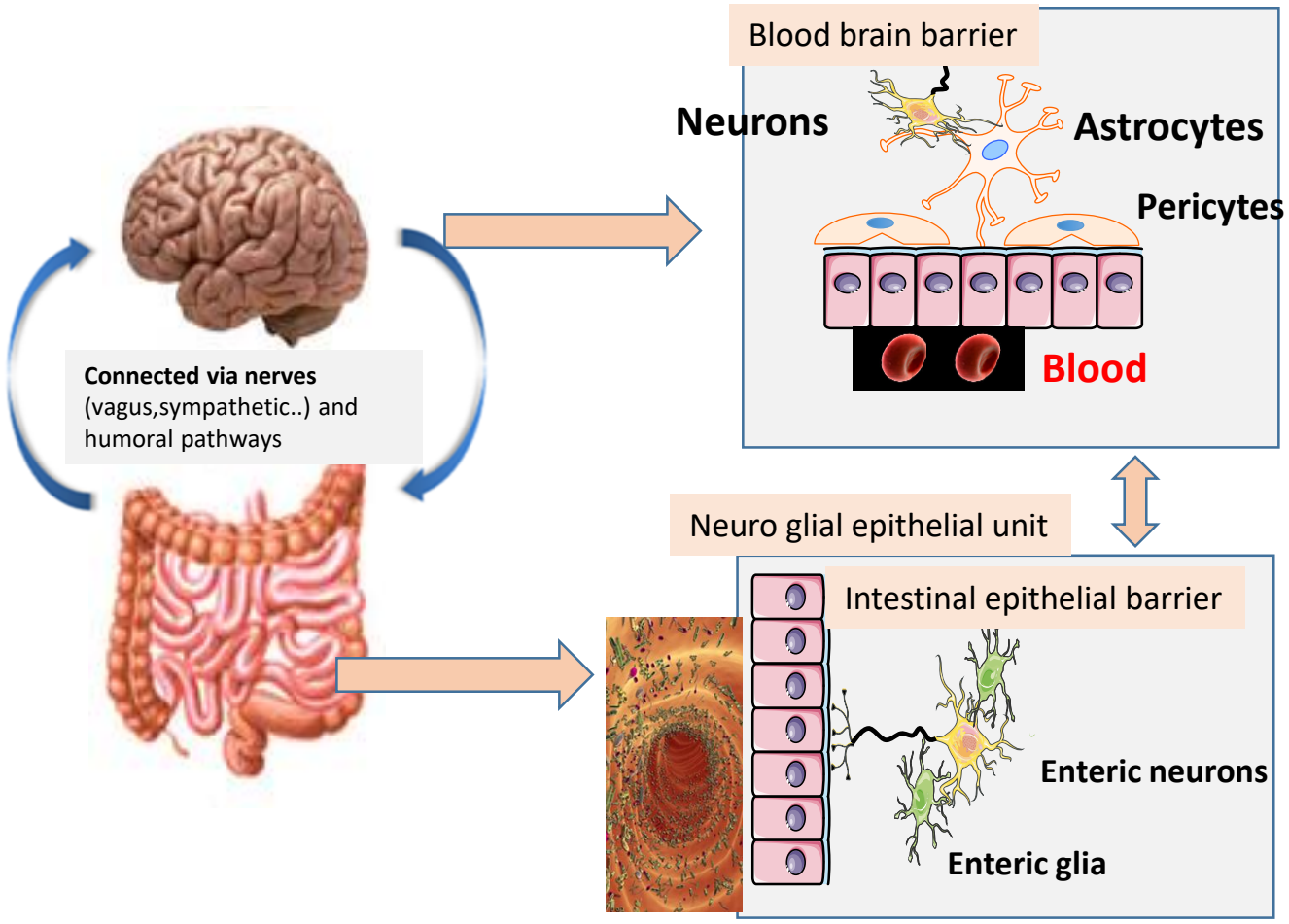
doi:10.1038/nature21072

Meiofaunal deuterostomes from the basal Cambrian of Shaanxi (China)

Jian Han[1], Simon Conway Morris[2], Qiang Ou[3,4], Degan Shu[1] & Hai Huang[5]



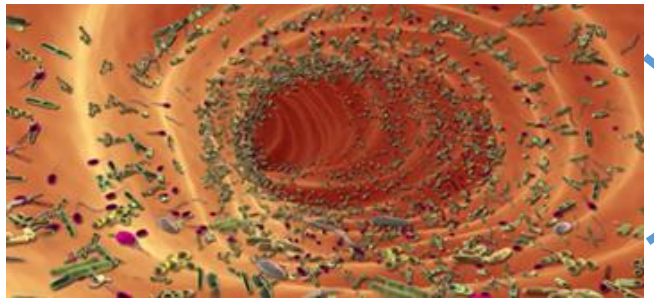
Le tube digestif et le cerveau : deux organes neurologiques

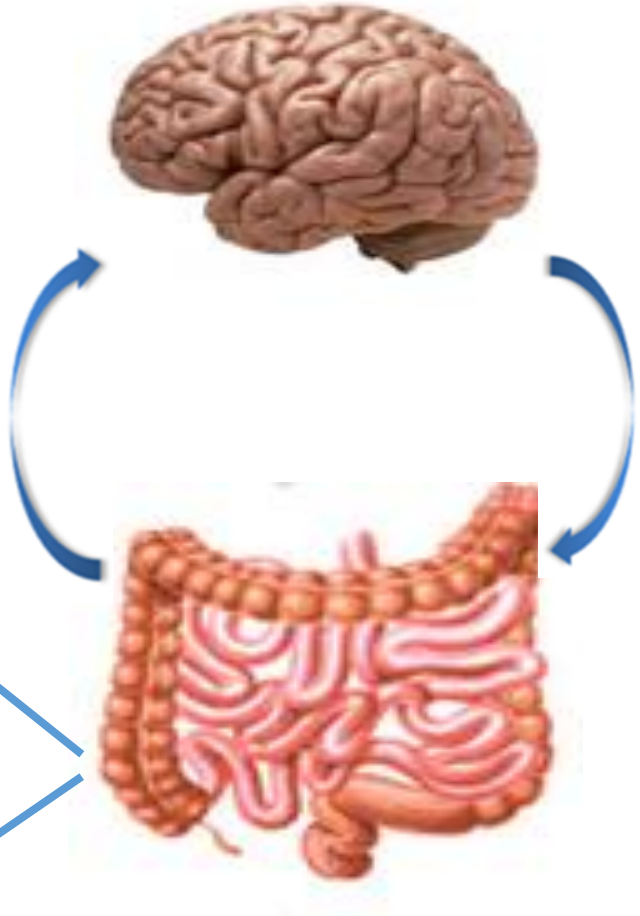


Neunlist et al., *Nat Rev Hep Gast,* 2013

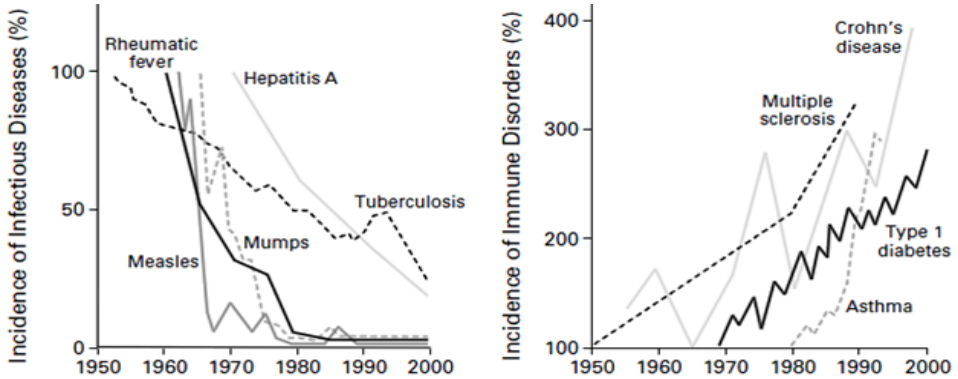
L’environnement (microbiote): régulateur de l’axe intestin-cerveau ?

Environnement (nutrients ; microbiote ; polluants,……)

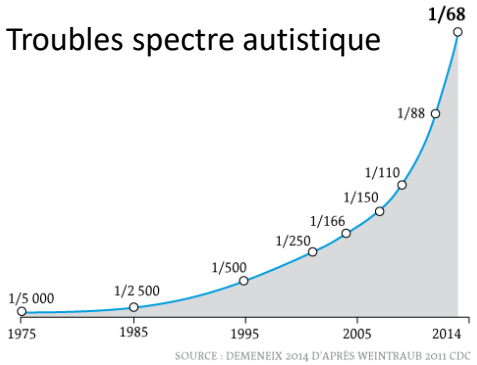




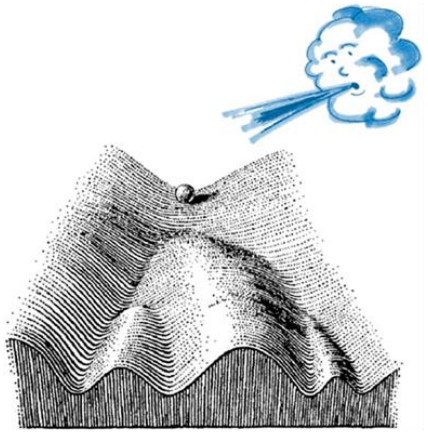
L'intestin (et la barrière intestinale) : au coeur des pathologies chroniques ?



Bach et al., *N Eng J Med,* 2002



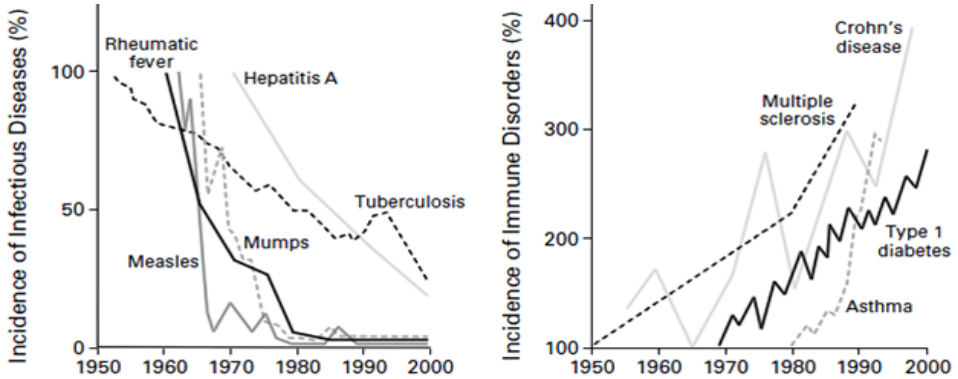
Facteurs environnementaux



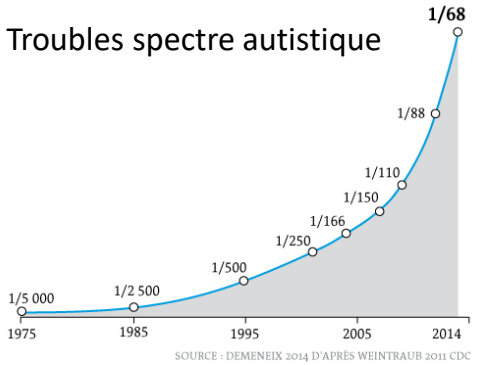
- **Microbiote**
- **Polluants**
- **Stress**
- **Pathogènes…**
- **Nutrition…..**

Gènes

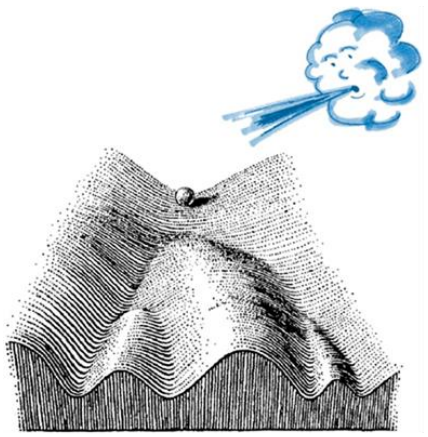
L'intestin (et la barrière intestinale) : au coeur des pathologies chroniques ?



Bach et al., *N Eng J Med*, 2002



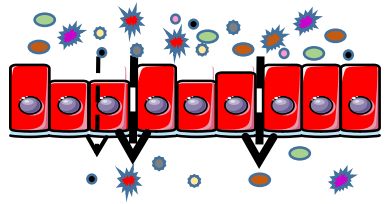
Facteurs environnementaux



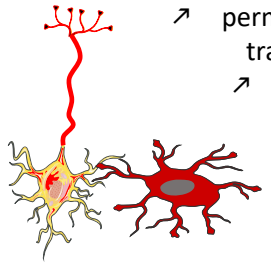
- **Microbiota**
- **Pollutants**
- **Stress**
- **Pathogenes…**
- **Nutrition…..**

Gènes

Maladies chroniques: 'leaky gut'



↗ permeabilité (paracellular / transcellular)– ↘ repair
↗ Alteration transit



Système nerveux entérique?

Organisation de la présentation

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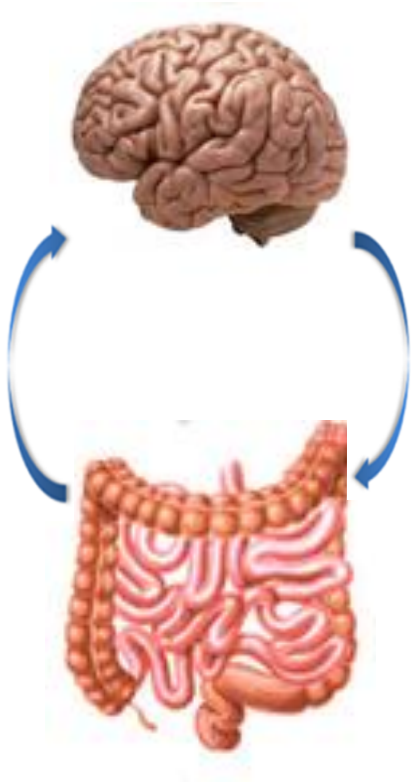

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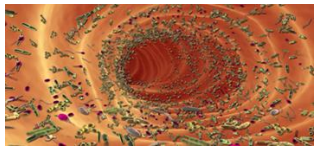
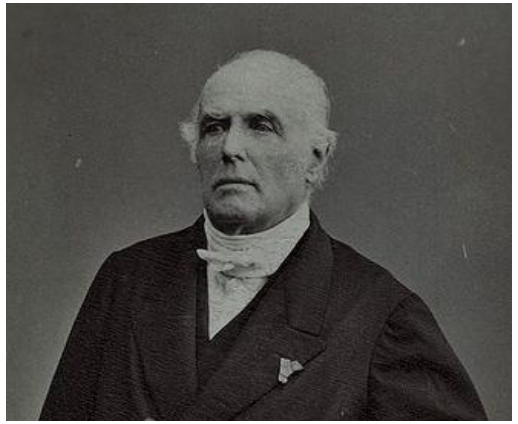
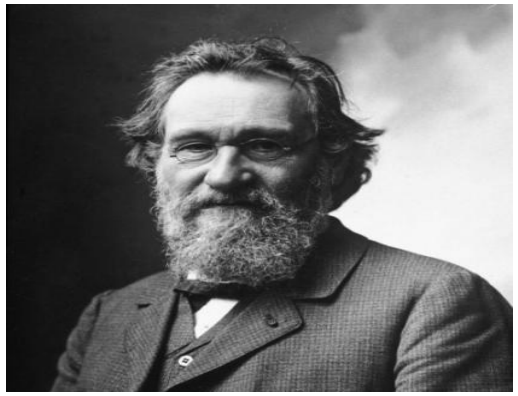


Microbes : acteurs de notre santé et de nos maladies….

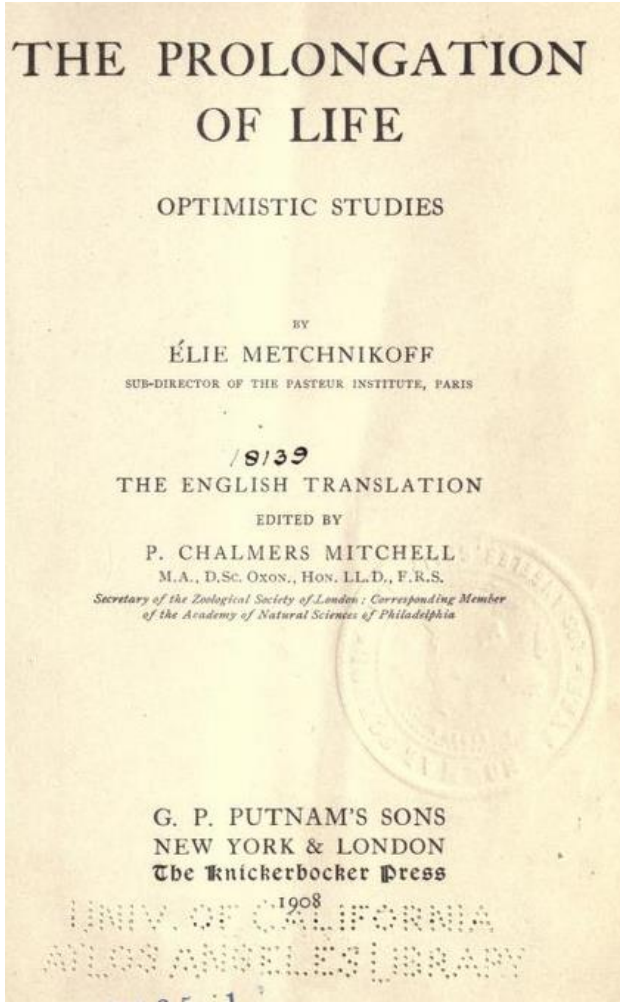


Charles-Emmanuel Sédillot
(1804-1883)

Louis Pasteur
(1825-1885)



Elya Metchnikov
(1845-1916)



THE PROLONGATION OF LIFE

OPTIMISTIC STUDIES

BY

ÉLIE METCHNIKOFF

SUB-DIRECTOR OF THE PASTEUR INSTITUTE, PARIS

/9139

THE ENGLISH TRANSLATION

EDITED BY

P. CHALMERS MITCHELL

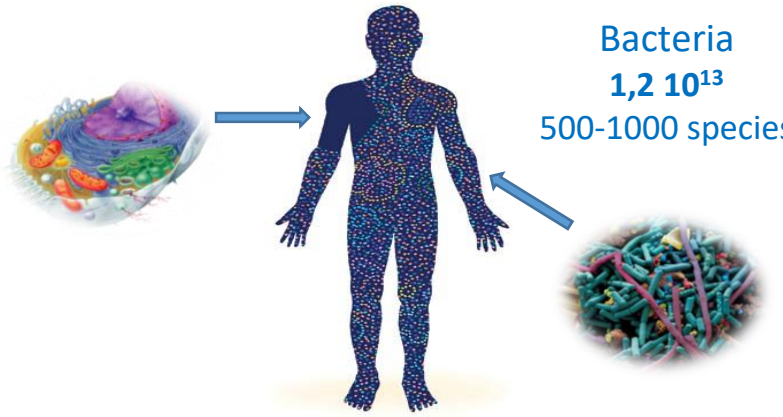
M.A., D.Sc. Oxon., Hon. LL.D., F.R.S.

Secretary of the Zoological Society of London; Corresponding Member of the Academy of Natural Sciences of Philadelphia

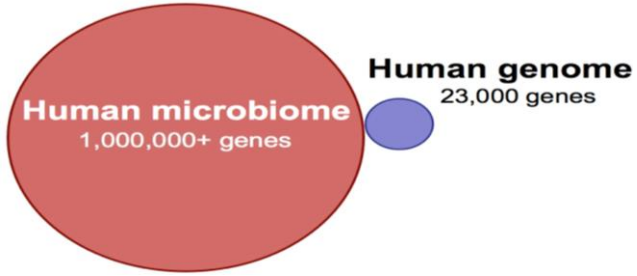
G. P. PUTNAM'S SONS
NEW YORK & LONDON
The Knickerbocker Press
1908

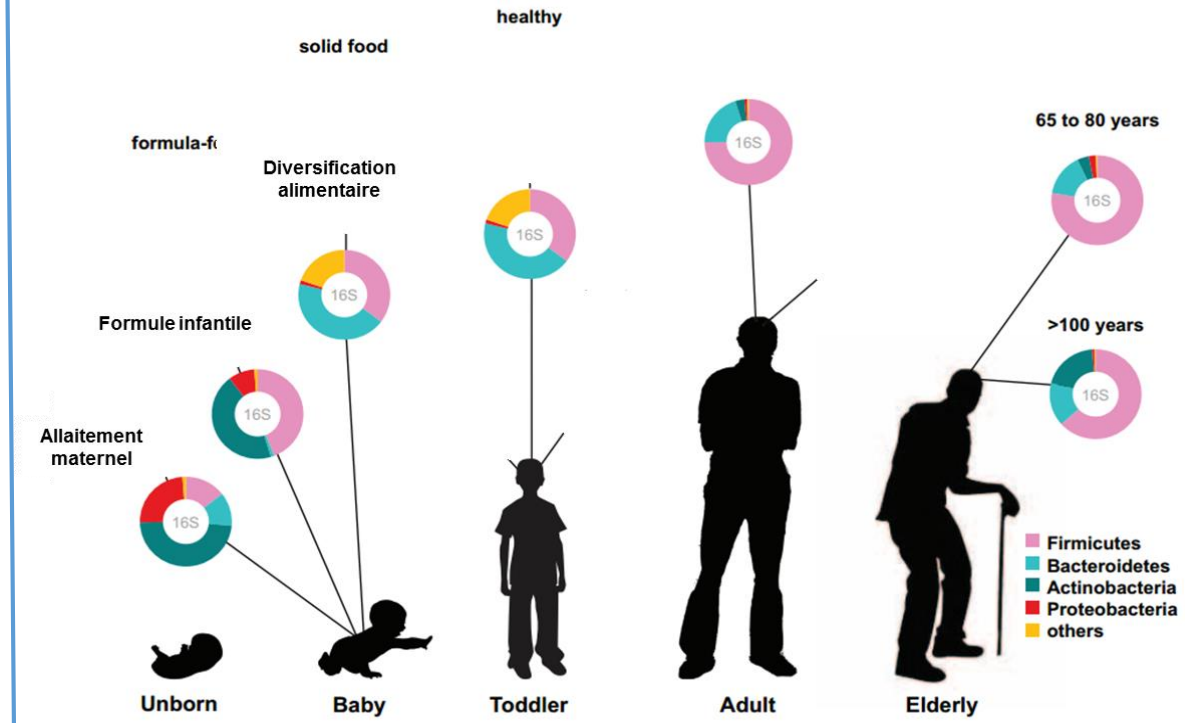
Le microbiote intestinal et son évolution au cours de la vie

Eucaryotes **10^{13}**

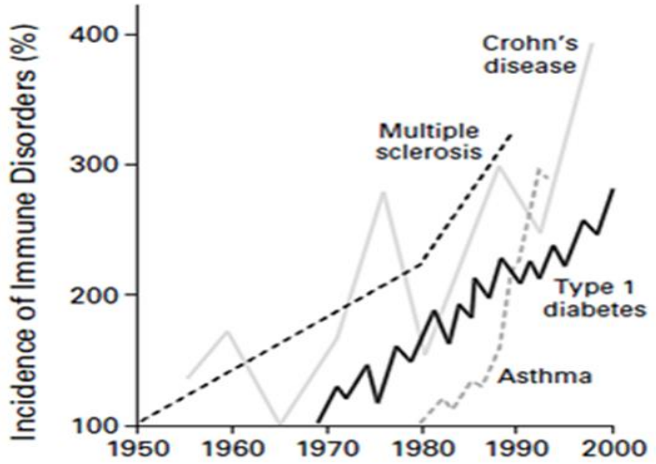


Bacteria
$1{,}2\ 10^{13}$
500-1000 species

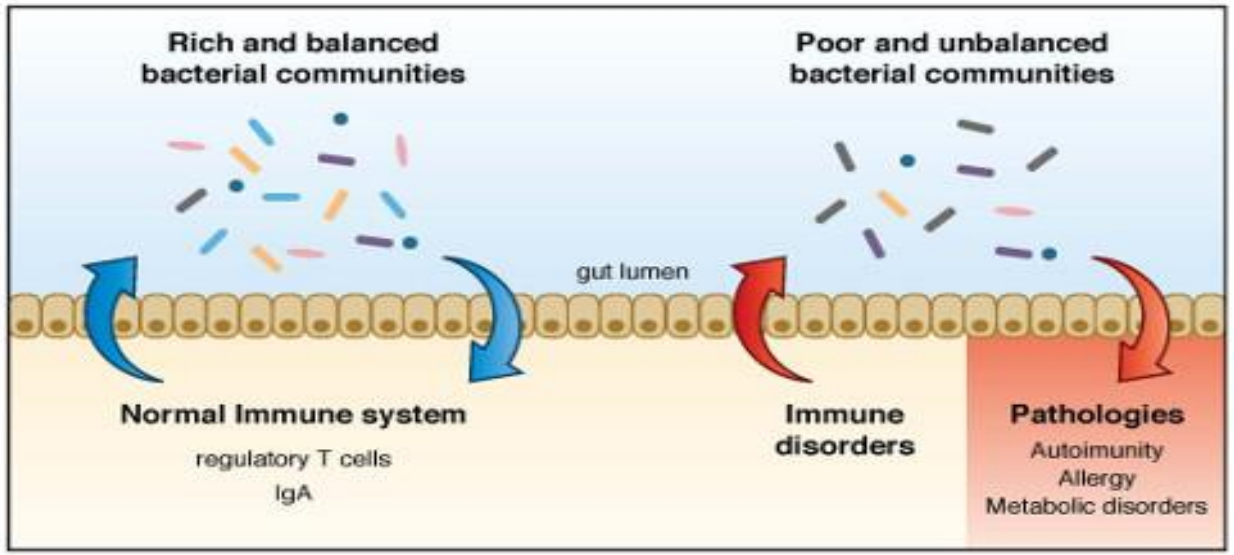




Dysbiose : perte de la diversité / richesse /résilience du microbiote au centre des maladies chroniques ?



Bach et al.,*N Eng J Med*, 2001




Le Monde Biodiversité

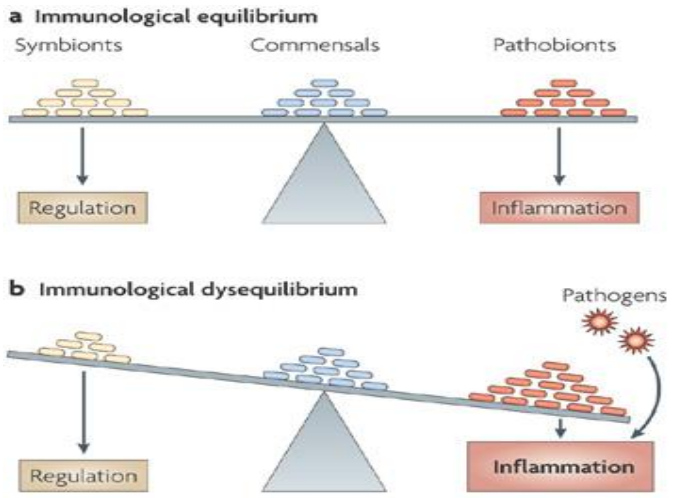
PLANÈTE BIODIVERSITÉ

En trente ans, près de 80 % des insectes auraient disparu en Europe

Ce déclin catastrophique est dû à l'intensification des pratiques agricoles et au recours aux pesticides. Il menace la chaîne alimentaire.

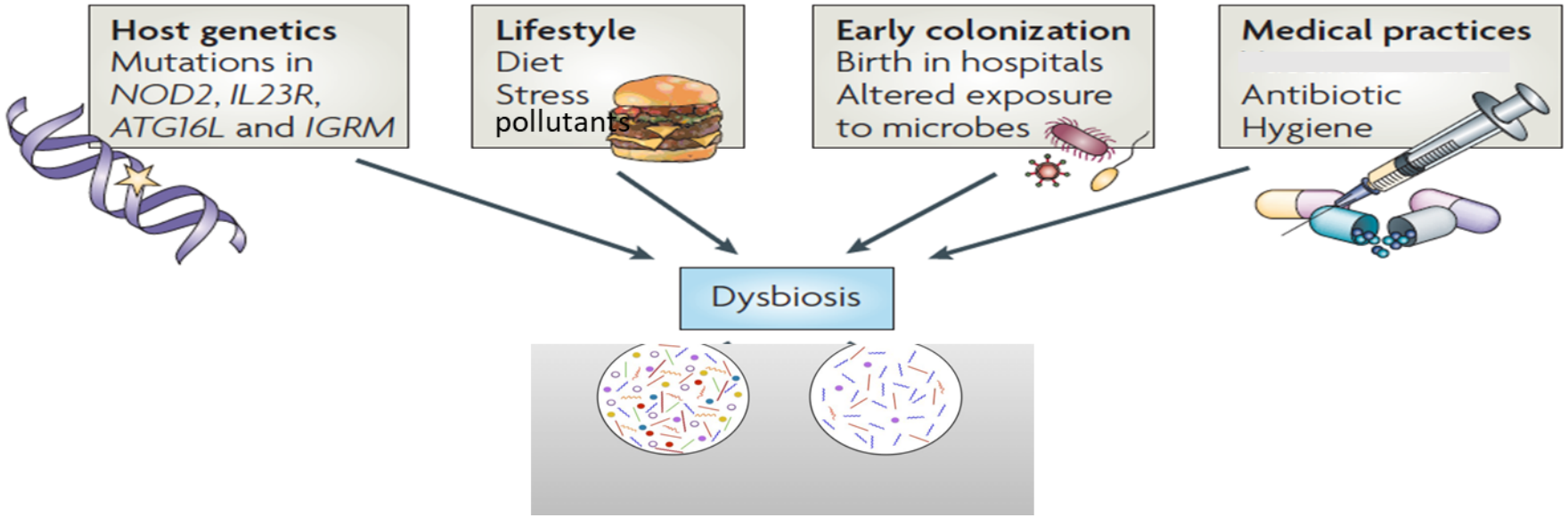
LE MONDE | 18.10.2017 à 20h01 • Mis à jour le 18.10.2017 à 20h21 |

Par Stéphane Foucart



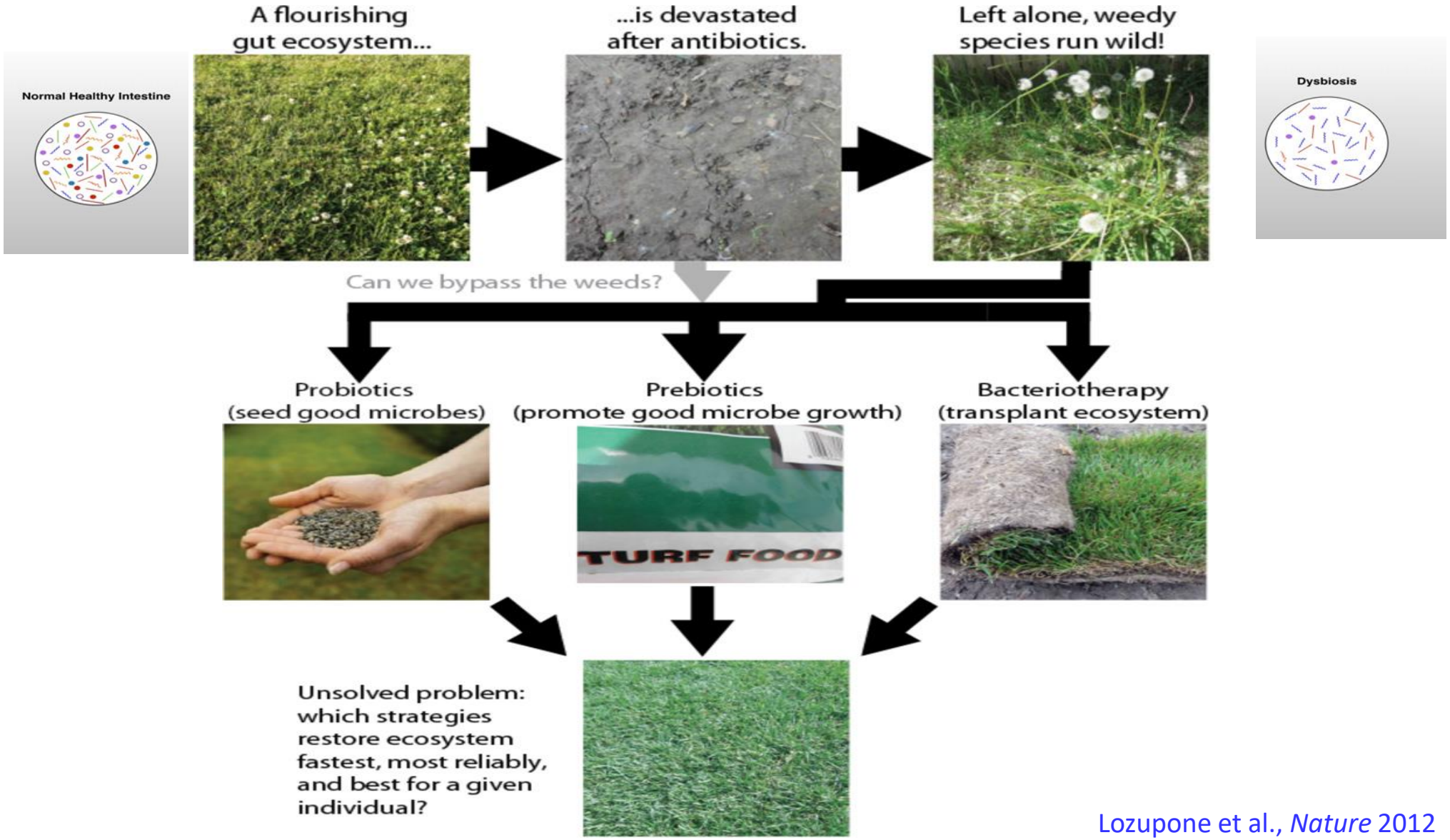
Round and Mazmanian *Nat Rev Immunol* 2009

Quels facteurs sont responsables des modifications du microbiote ?



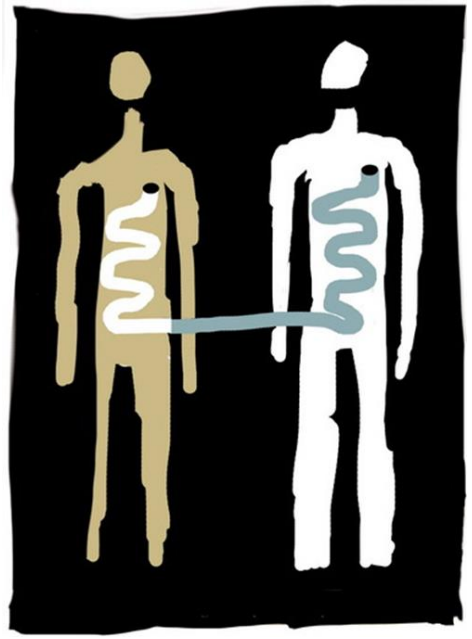
Round and Mazmanian *Nat Rev Immunol* 2009

Le microbiote intestinal : nouvel cible thérapeutique dans prévention/traitement des maladies chroniques ?



Lozupone et al., *Nature* 2012

Vers la greffe du microbiote : premiers succès à confirmer



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 31, 2013 VOL. 368 NO. 5

Duodenal Infusion of Donor Feces for Recurrent *Clostridium difficile*

Els van Nood, M.D., Anne Vrieze, M.D., Max Nieuwdorp, M.D., Ph.D., Susana Fuentes, Ph.D., Erwin G. Zoetendal, Ph.D., Willem M. de Vos, Ph.D., Caroline E. Visser, M.D., Ph.D., Ed J. Kuijper, M.D., Ph.D., Joep F.W.M. Bartelsman, M.D., Jan G.P. Tijssen, Ph.D., Peter Speelman, M.D., Ph.D., Marcel G.W. Dijkgraaf, Ph.D., and Josbert J. Keller, M.D., Ph.D.

Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial

Sudarshan Paramsothy, Michael A Kamm, Nadeem O Kaakoush, Alissa J Walsh, Johan van den Bogaerde, Douglas Samuel, Rupert W L Leong, Susan Connor, Watson Ng, Ramesh Paramsothy, Wei Xuan, Enmoore Lin, Hazel M Mitchell, Thomas J Borody

Lancet 2017; 389: 1218–28

Published Online February 14, 2017 http://dx.doi.org/10.1016/S0140-6736(17)30182-4

Summary

Background The intestinal microbiota is implicated in the pathogenesis of ulcerative colitis. Faecal microbiota transplantation is a novel form of therapeutic microbial manipulation, but its efficacy in ulcerative colitis is uncertain. We aimed to establish the efficacy of intensive-dosing, multidonor, faecal microbiota transplantation in active ulcerative colitis.

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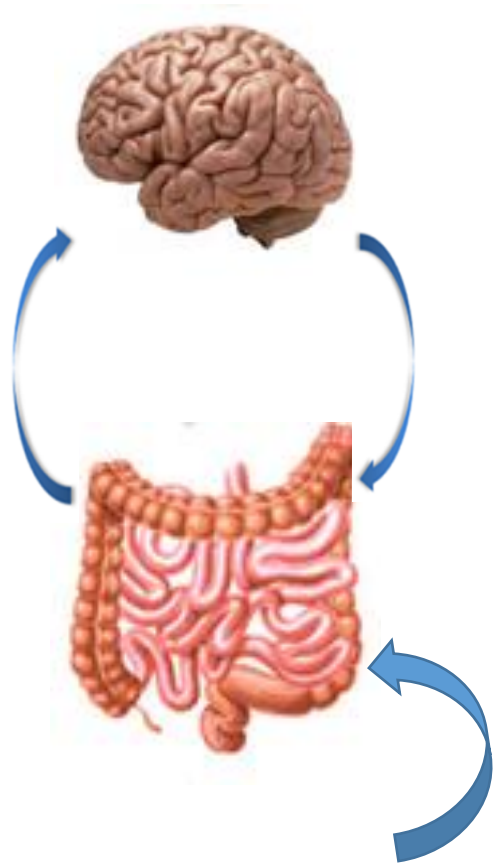

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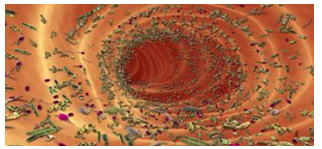


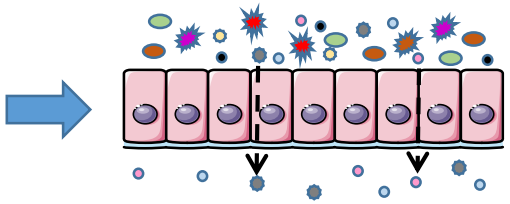
Pourquoi avoir un système nerveux dans l'intestin ?

30 tonnes d'aliments

50 tonnes de liquides

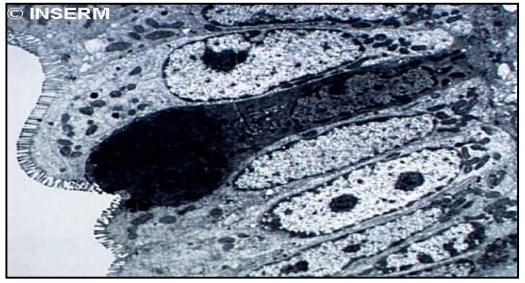
1- Transport

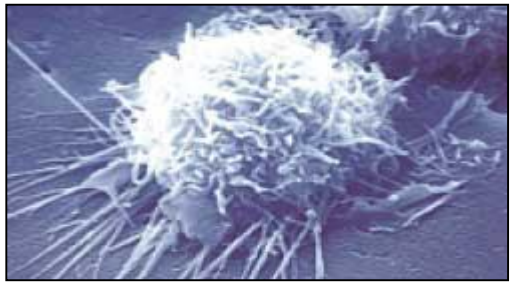
2- Absorption des nutriments / minéraux / électrolytes



Cellules épihéliales intestinales

3- Barrière / fonctions immunes





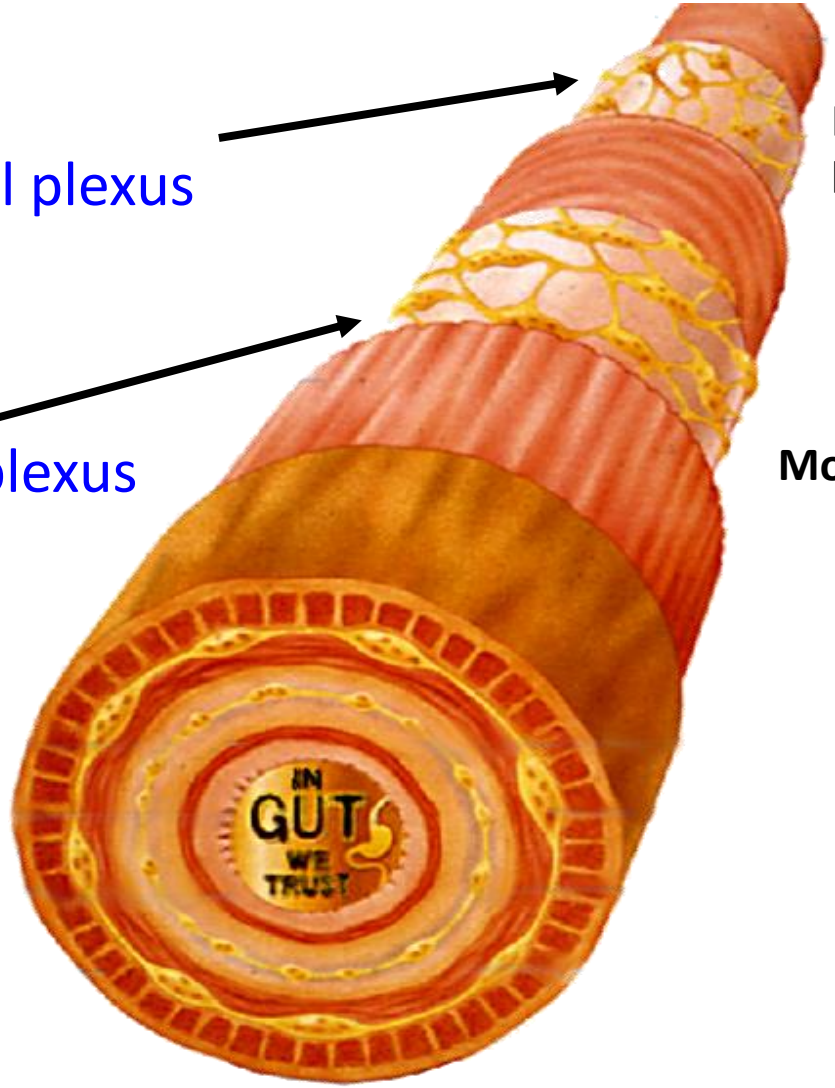
Microbiote

Des fonctions sous le contrôle d'un système nerveux intrinsèque…….

Le système nerveux entérique : organisation

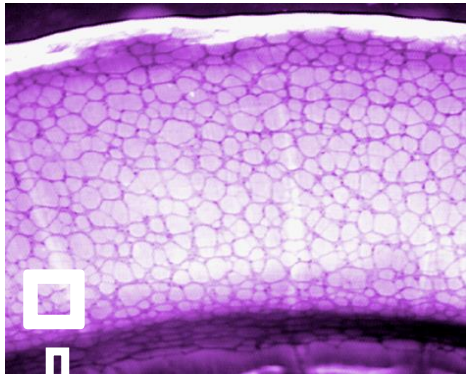
Submucosal plexus

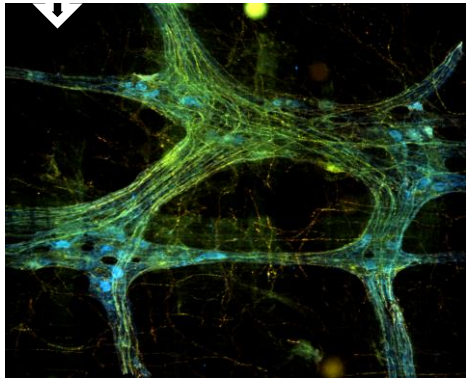
Myenteric plexus

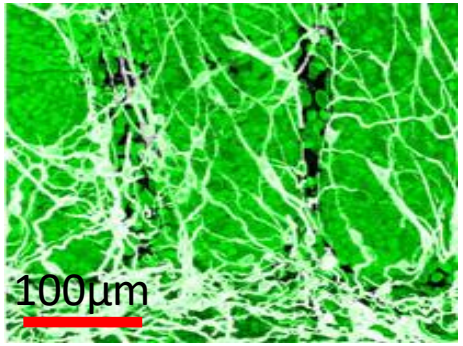


Intestinal epithelial barrier functions

Motility

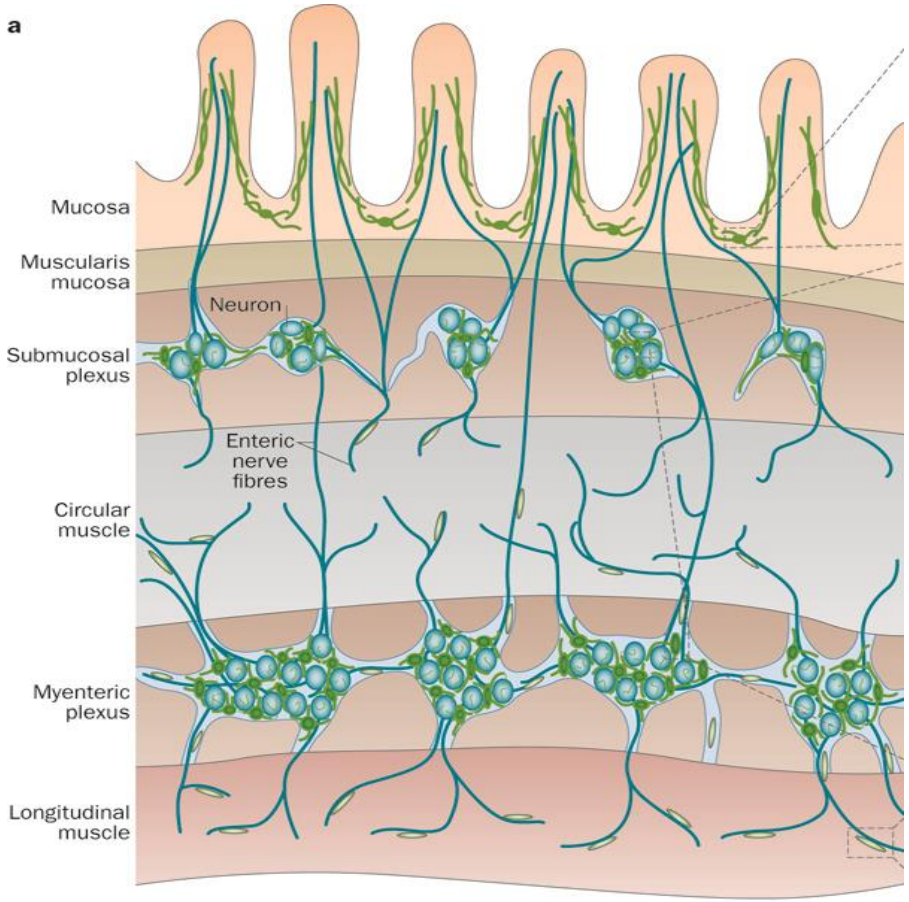




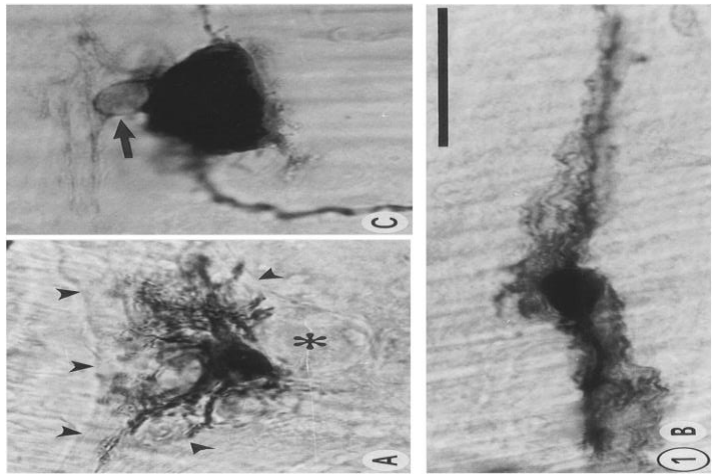


200 milions neurons – 1 billion glial cells

Le SNE: des neurones et des cellules gliales…



Gulbransen and Sharkey, *Nat. Rev. Gastroenterol. Hepatol,* 2012



Hanani and Reichenbach, *Cell Tissue Research*, 1994

Association cortex
= Neurons
↗ astrocytes

Diamond et al., *Exp Neurol*, 1985

↗ through phylogeny ➔ the ratio of astrocytes to neurons ↗

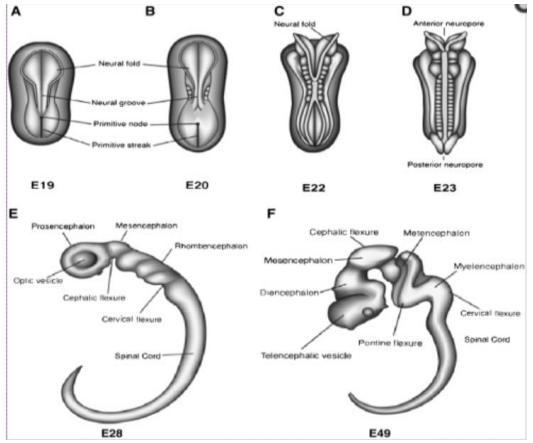
C. elegans 1 : 6
Human 10 : 1

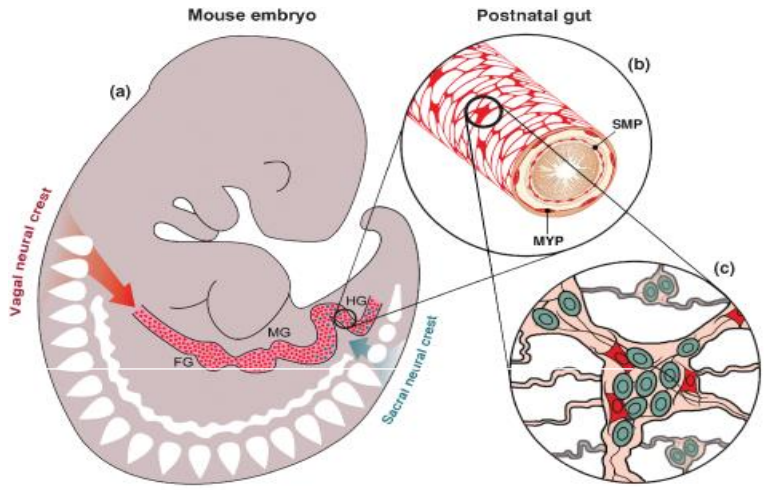
Araque et al., *Ann Rev Phys*, 2001

Développement du SNE et du cerveau

Development of the brain

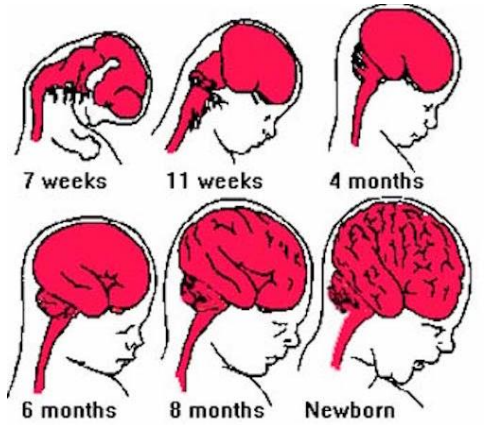
Embryonic period (GW8)

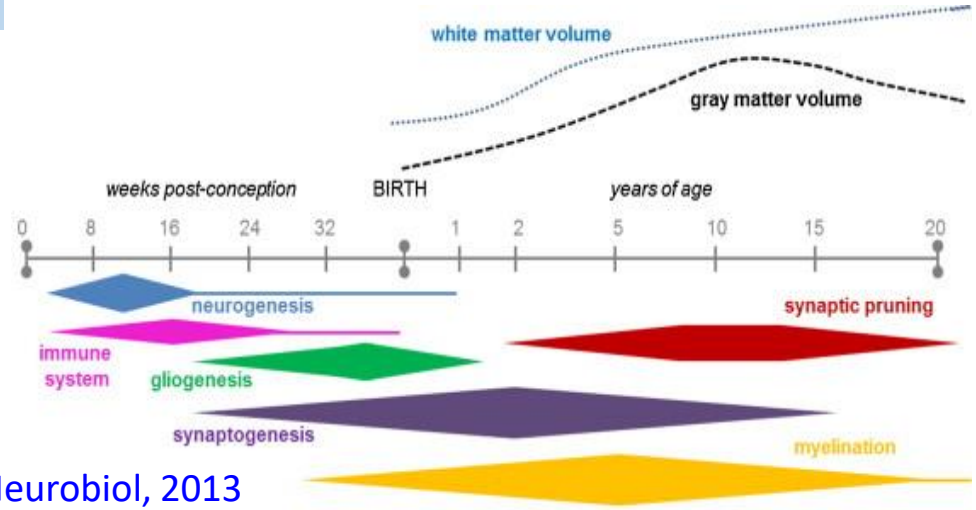




Heanue TA, Pachnis V, *Nat. Rev. Neurosci*. 2007

Fetal period (GW9-birth)

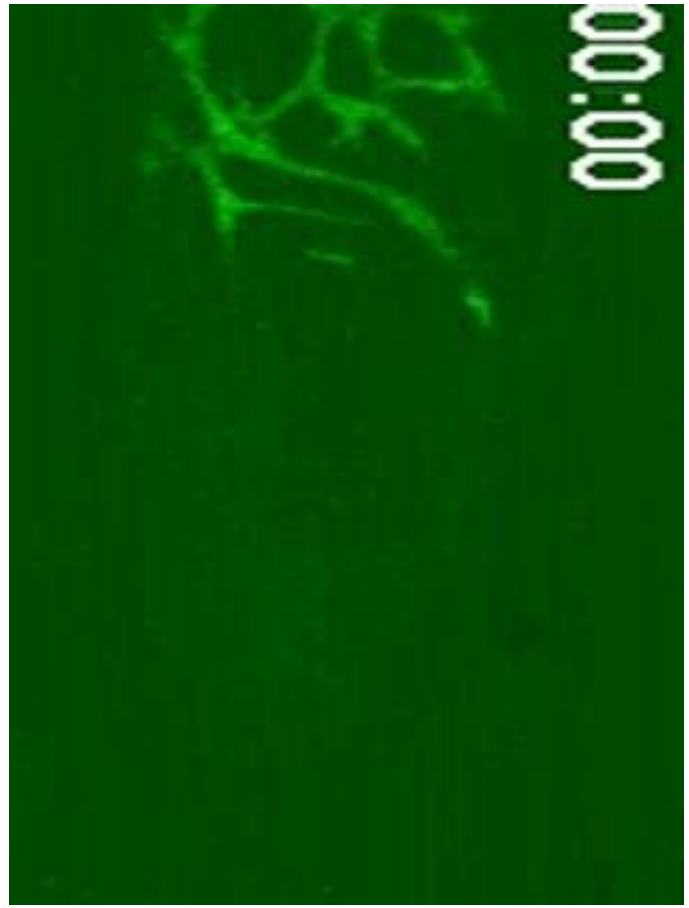




Semple et al., Prog Neurobiol, 2013

Development of the ENS

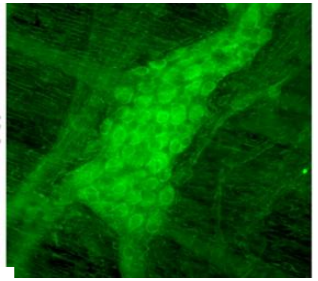
Colonisation of gut by neural crest cells (W4-7 human)

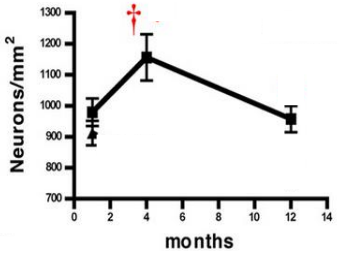


Nyshiyama et al., *Nat Neuroscience*, 2012

La période postnatale: période clef de maturation du SNE

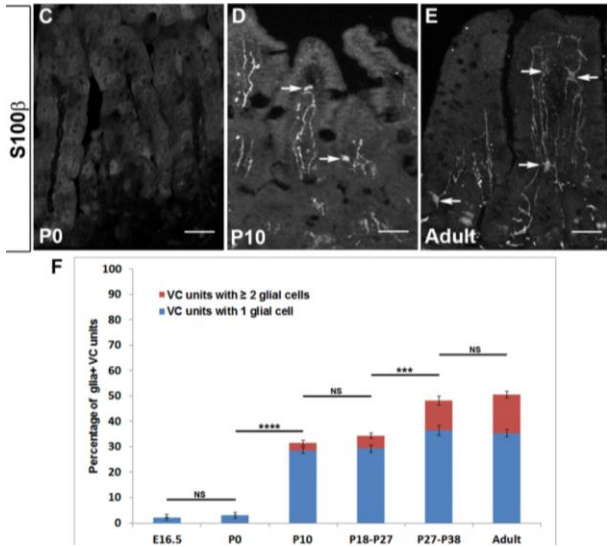
Neurogenesis





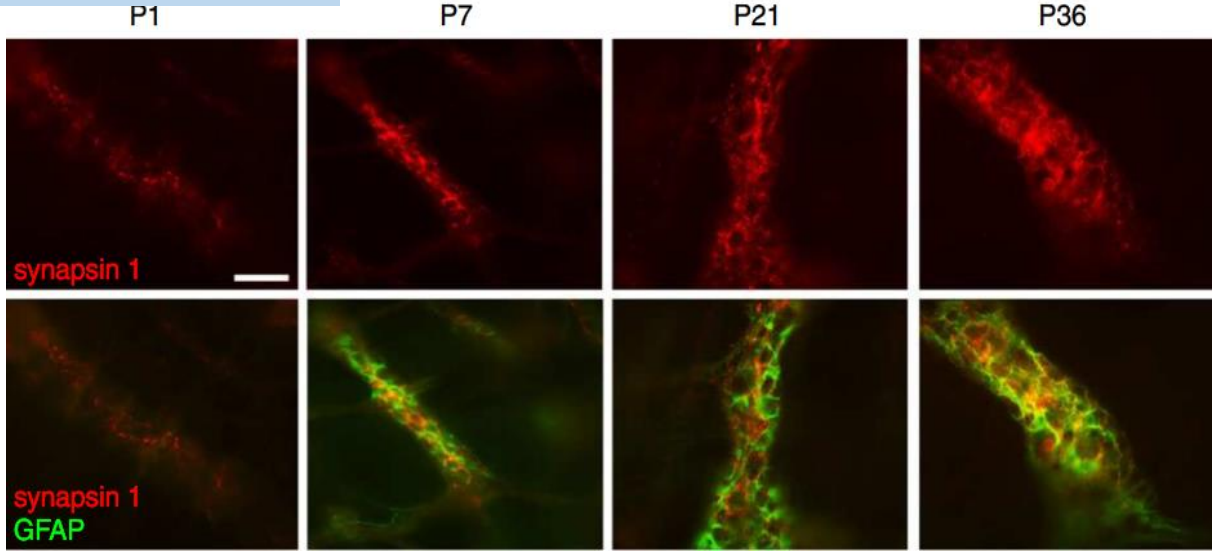
Liu et al., *J Neuroscience*, 2010

Gliogenesis



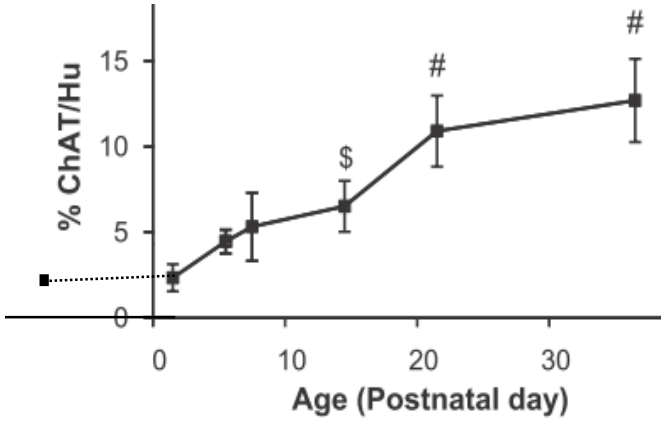
Kabouris et al., *Neuron*, 2015

Synaptogenesis



Le Berre Scoul et al., *J Phys*, 2016

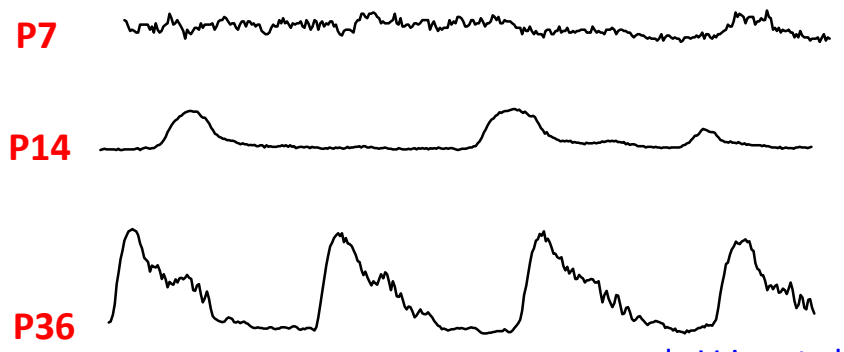
Expression of neuromediators



de Vries et al., *Am J Phys*, 2010
Hao et al., *J Comp Neurol*, 2013

Motility

Colonic contractile activity

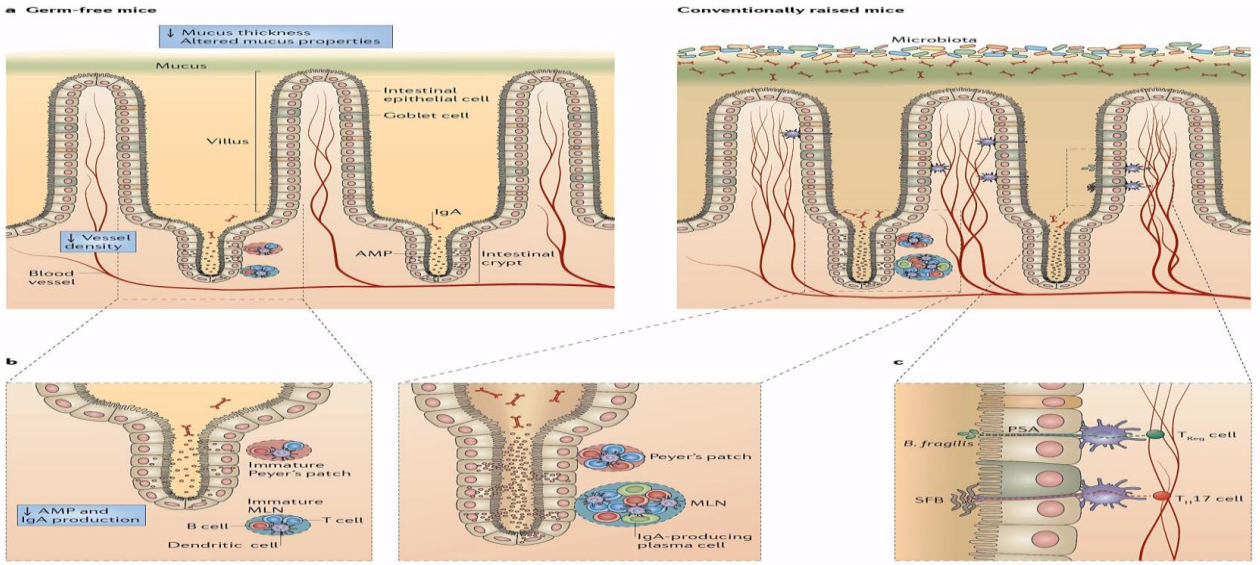


de Vries et al., *Am J Phys*, 2010
Robberts et al., Am J Phys, 2007

Le microbiote : acteur de la maturation post-natale du tube digestif…..

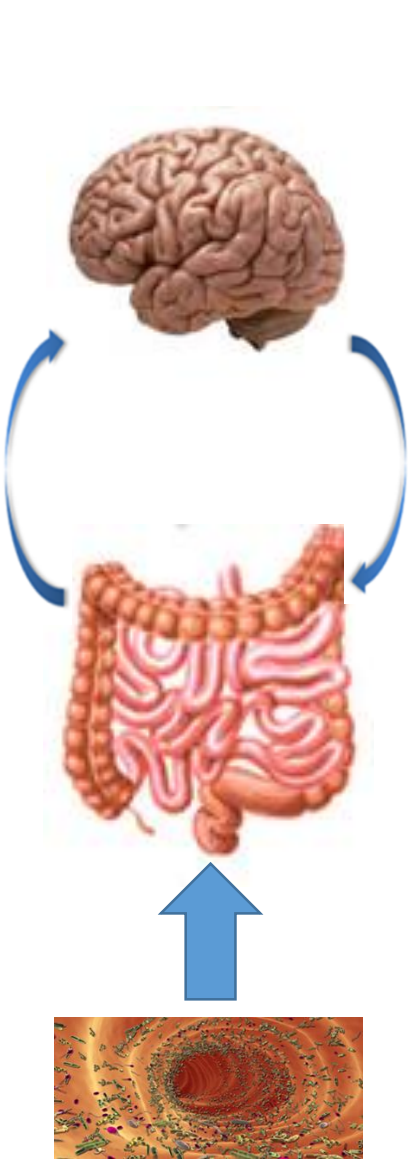
Intestin sans microbiote

Intestin avec microbiote

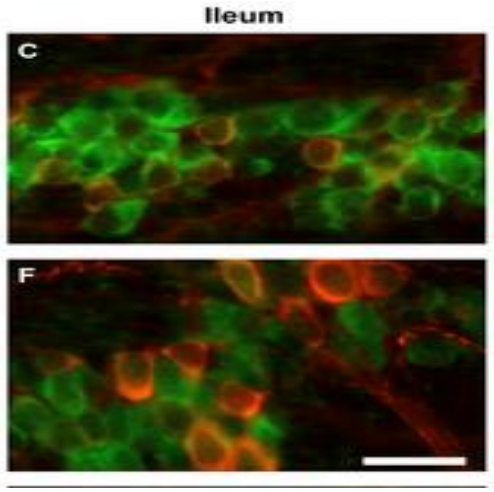


Macpherson and Harris, *Nat rev Immunol*., 2004

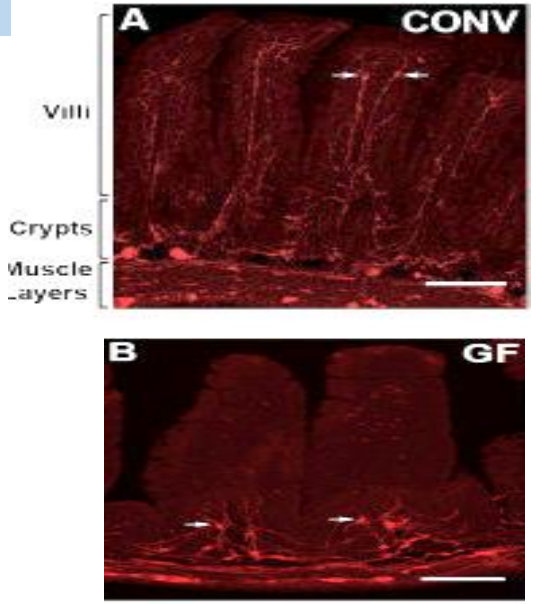
Le microbiote : acteur de la maturation post-natale du SNE…..

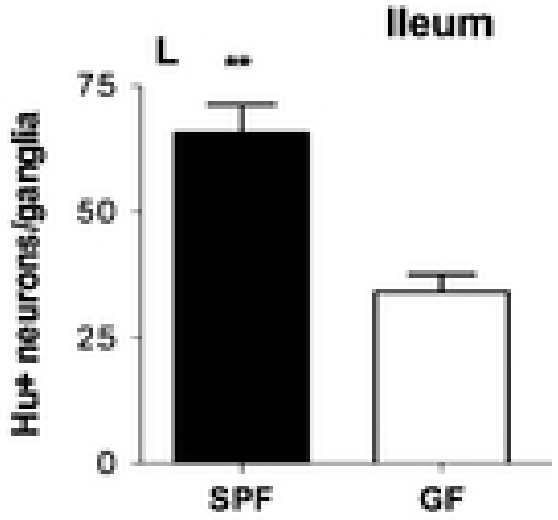


Neurons

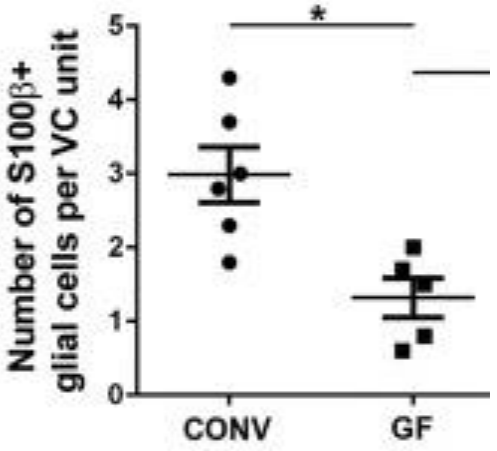


Glia cells



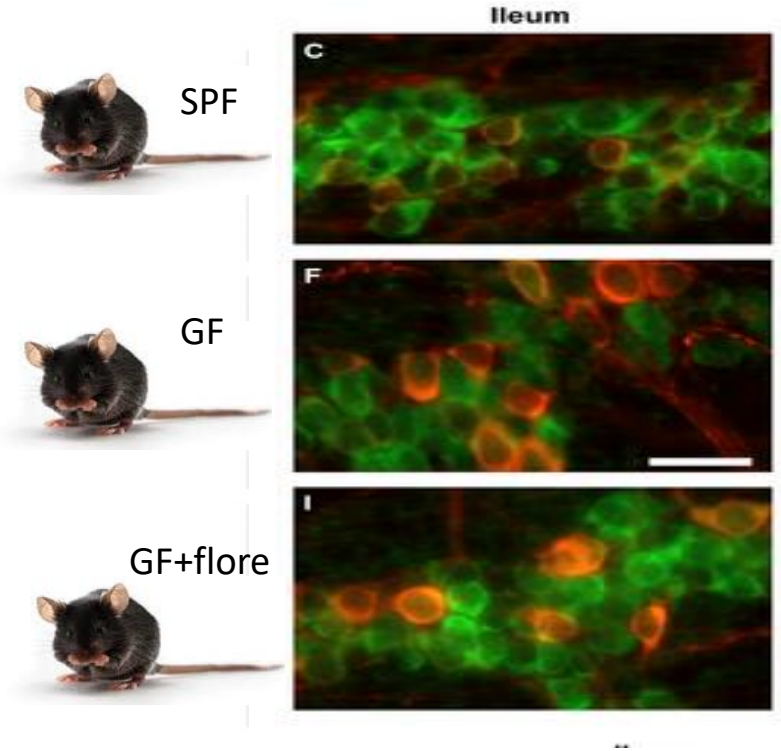


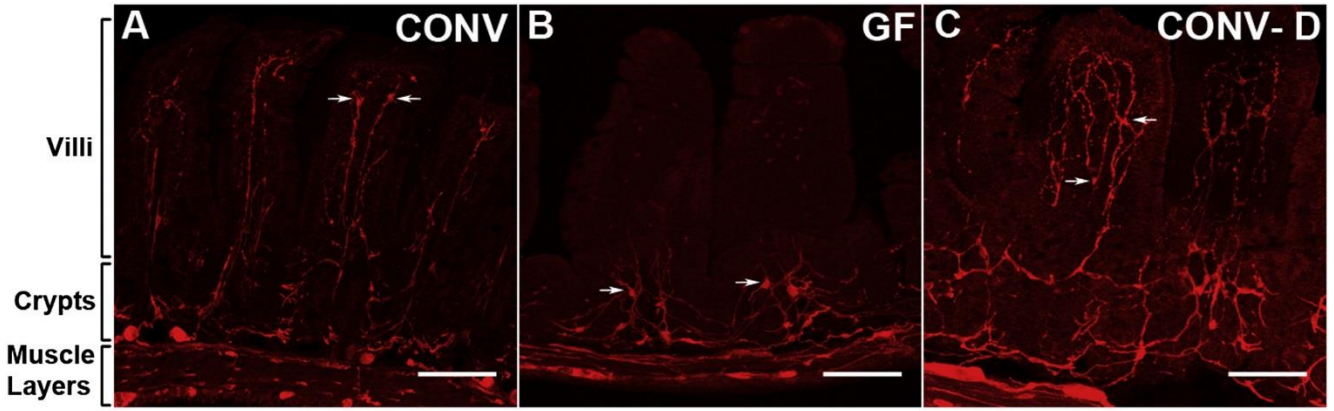
Collins et al., *Neurogastroenterology Mot,* 2013

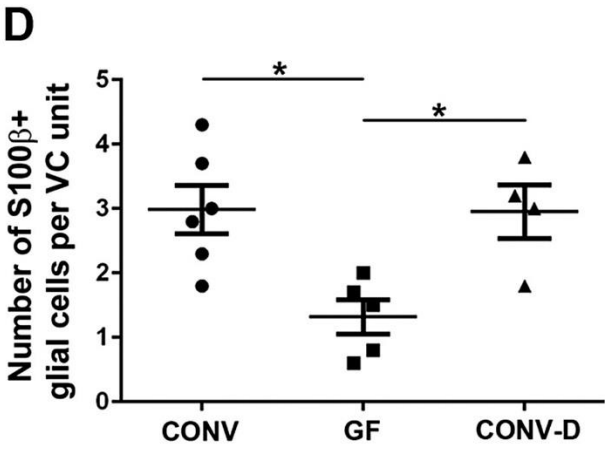


Kabouridis et al., *Neuron,* 2015

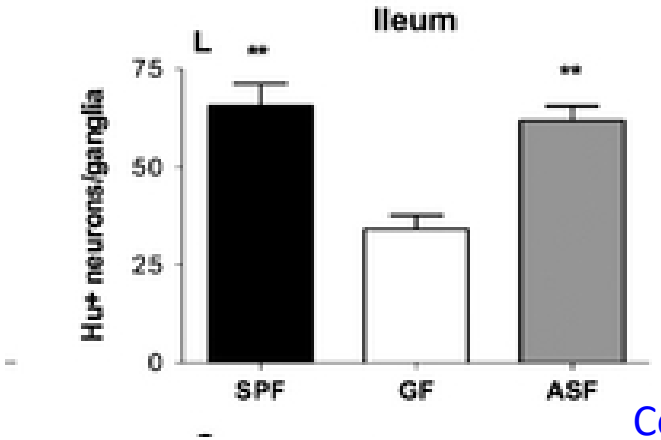
Le microbiote : acteur de la maturation post-natale du SNE…..







Kabouridis et al., *Neuron,* 2015



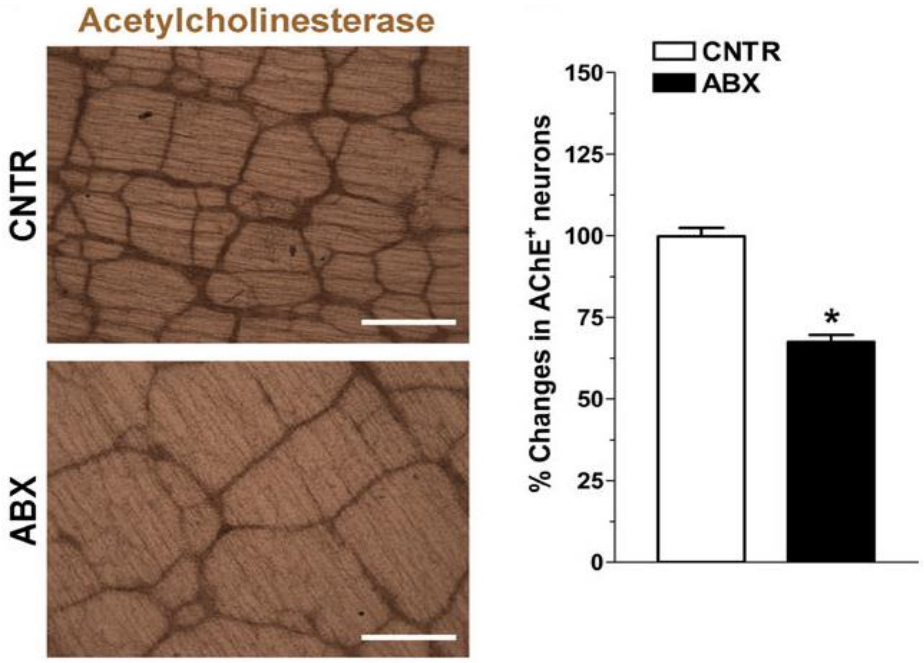
Collins et al., *Neurogastroenterology Mot,* 2013

Le microbiote : acteur de la maturation post-natale du SNE et des fonctions digestives...

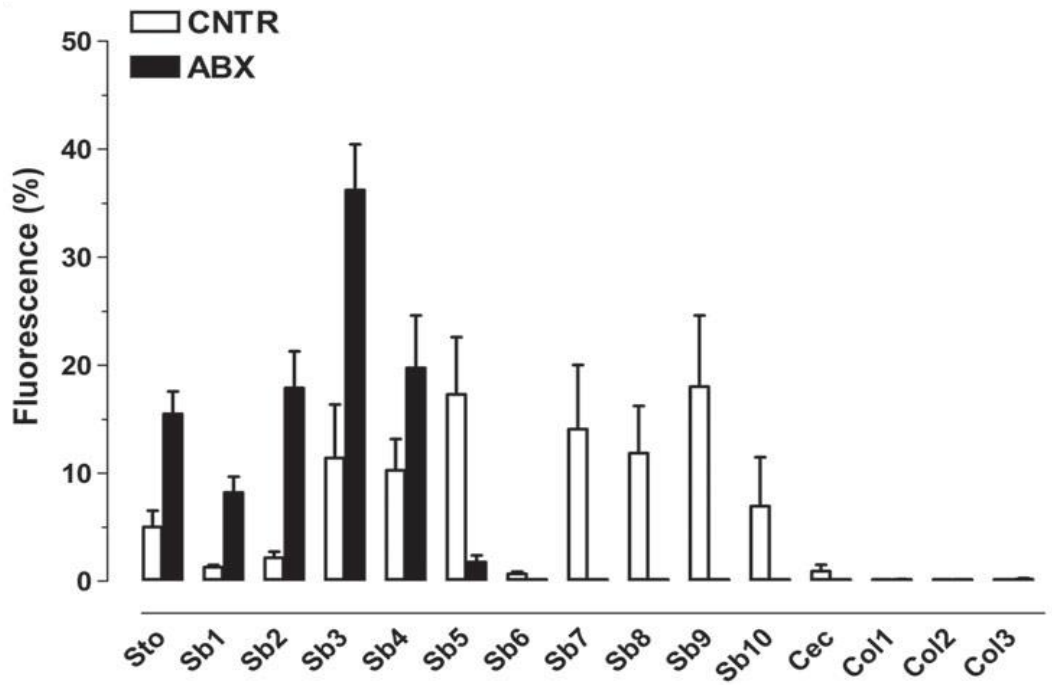
3 weeks old

14 days ± Ab treatment

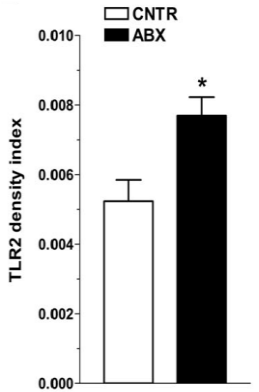
Reduced cholinergic population

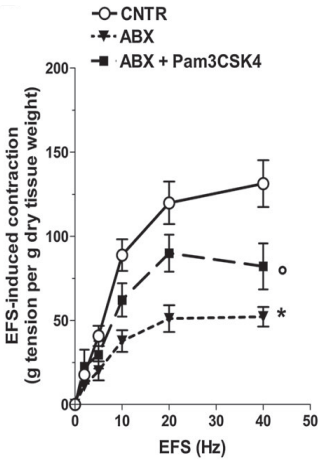


Reduced transit



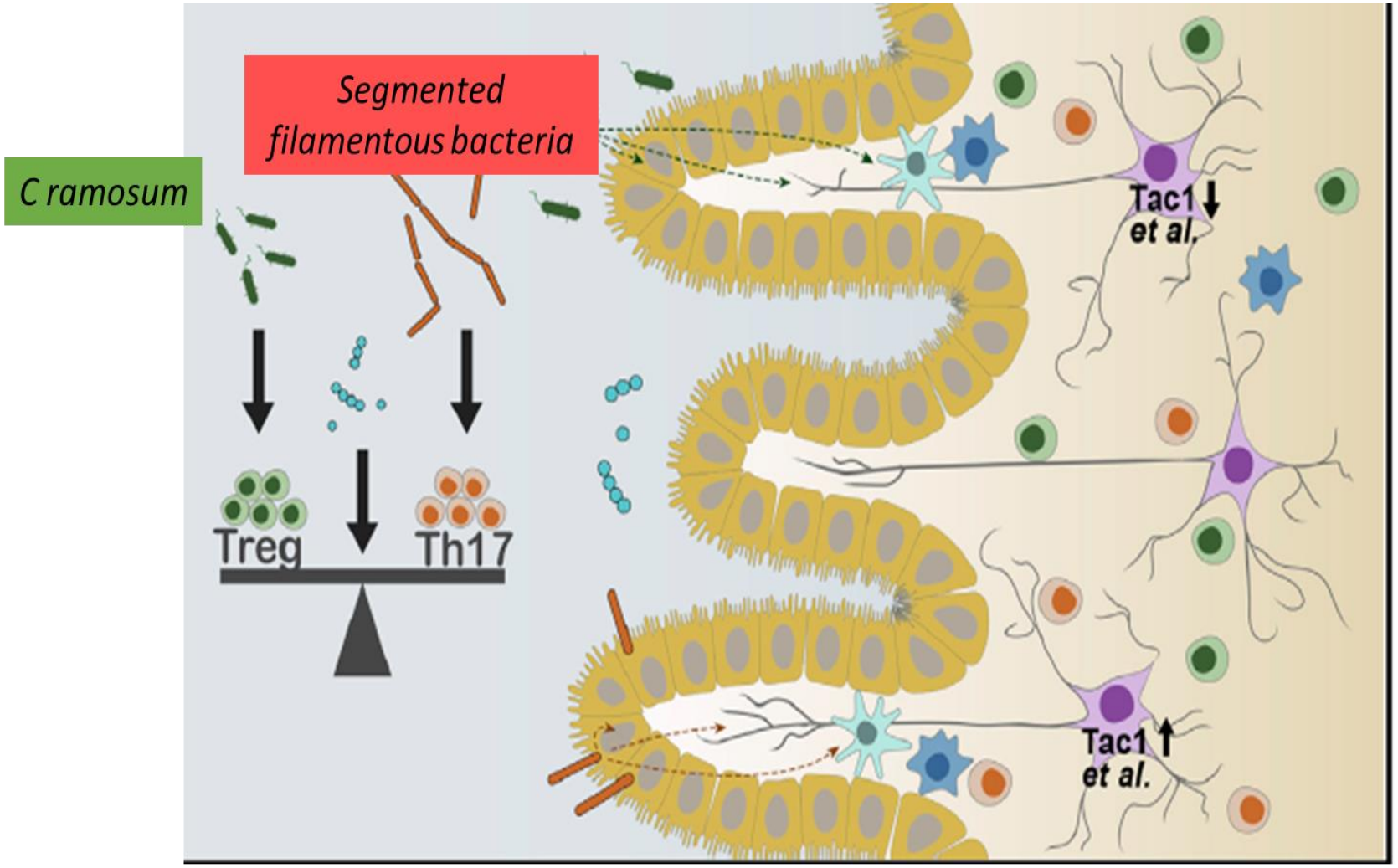
Involvment of TLR2 pathways





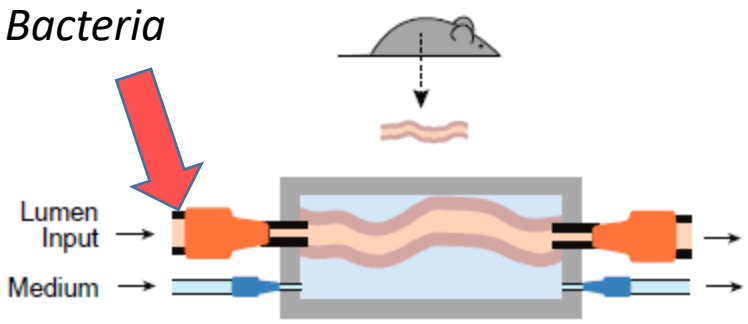
Caputi et al, *British J Pharmacol,* 2017

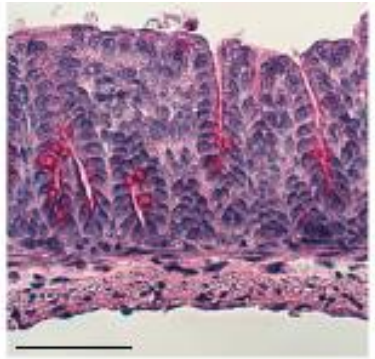
L’axe microbiote-SNE : modulateur de la maturation du système immunitaire digestif?



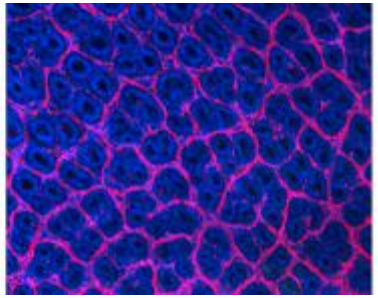
Yissachar et al., *Cell,* 2017

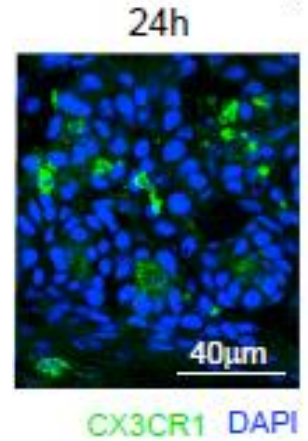
L’axe microbiote-SNE : modulateur de la maturation du système immunitaire digestif?

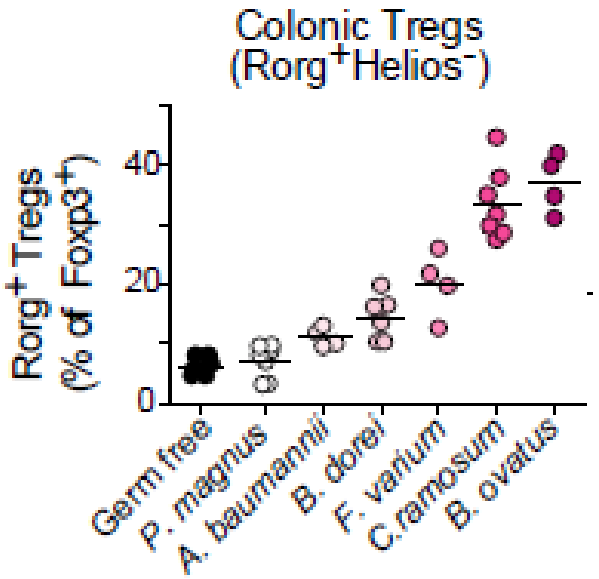


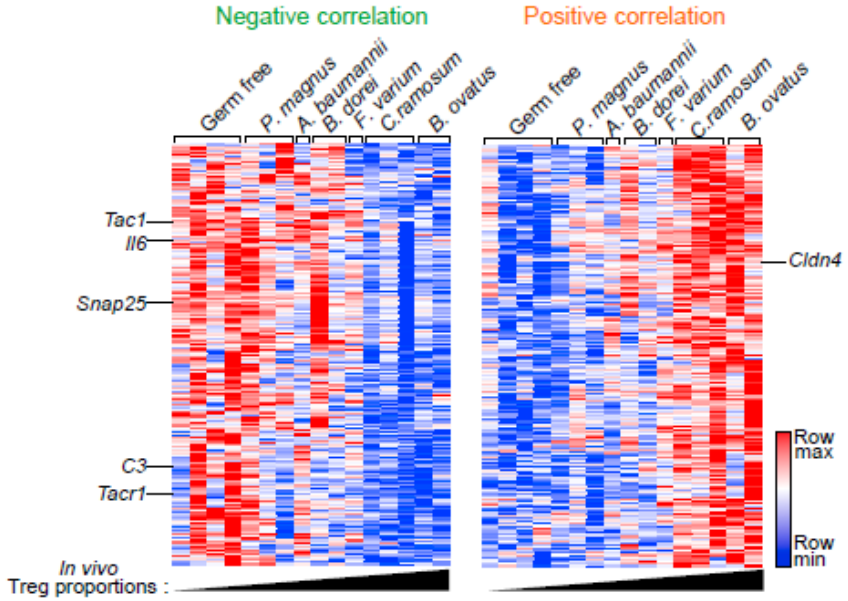


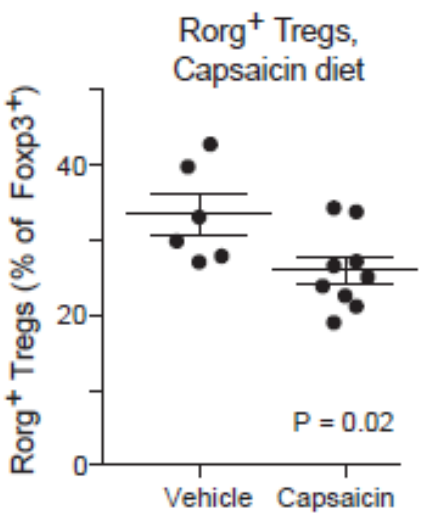
Submucosal plexus

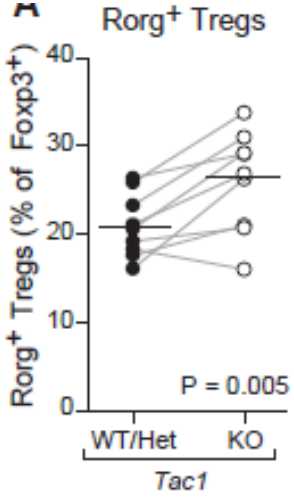






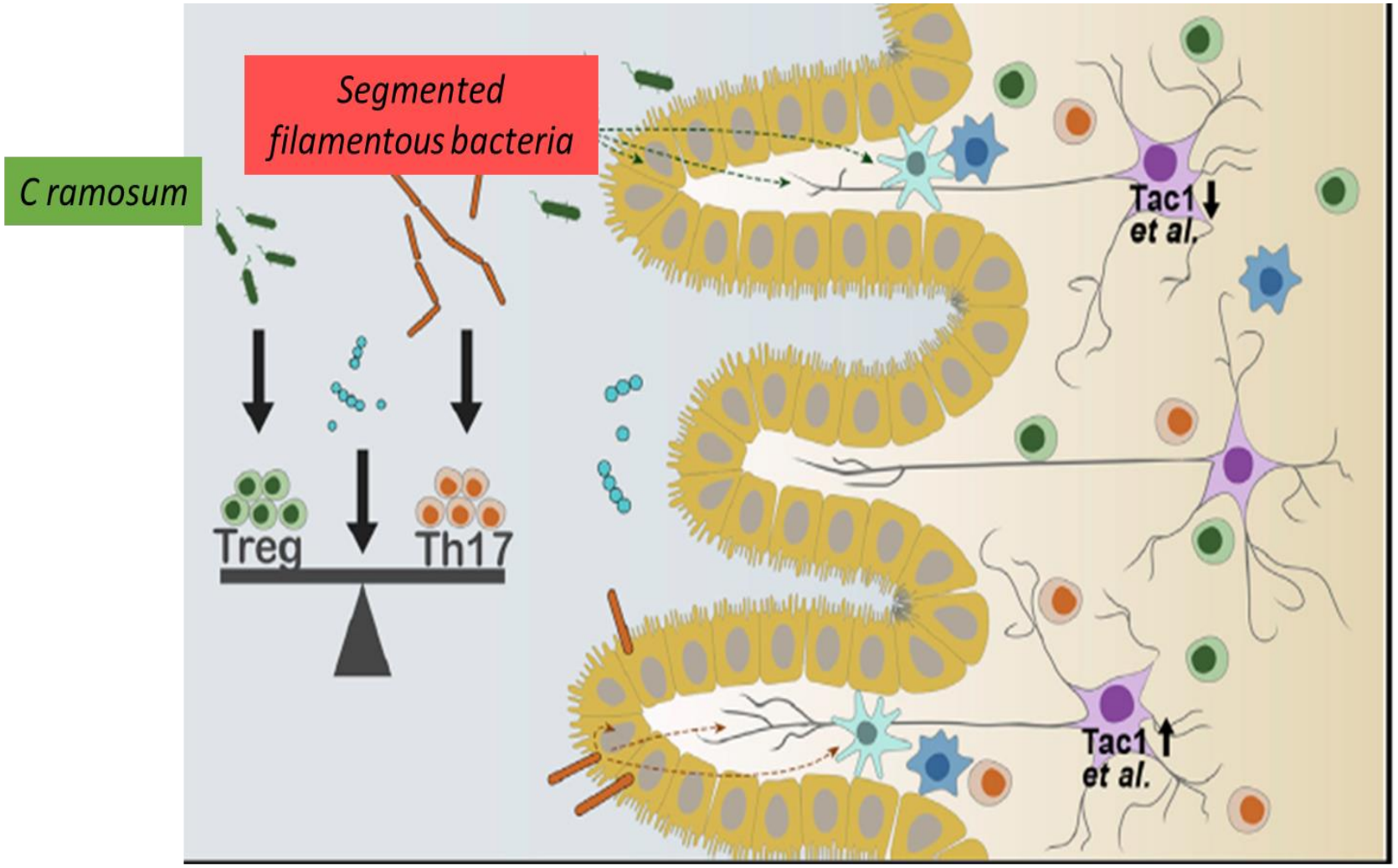






Yiassachar et al., *Cell, 2017*

L’axe microbiote-SNE : modulateur de la maturation du système immunitaire digestif?



Yissachar et al., *Cell,* 2017

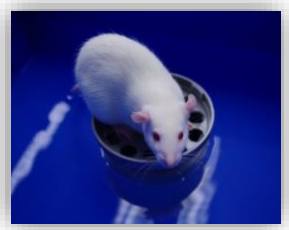
L fermemtum renforce la réponse précoce du tube digestif à l'activation de l'axe HPA

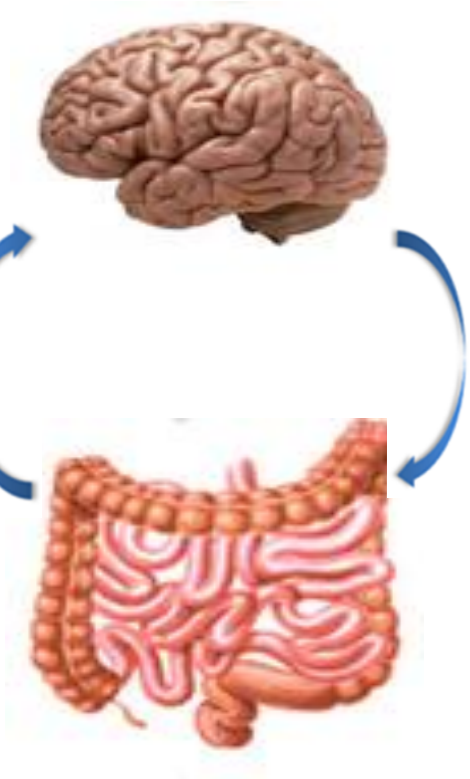
L fermentum

P1 P21 P36

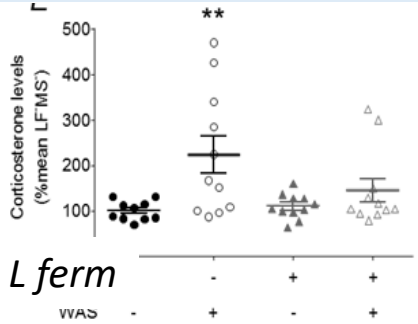
Weaning

± stress

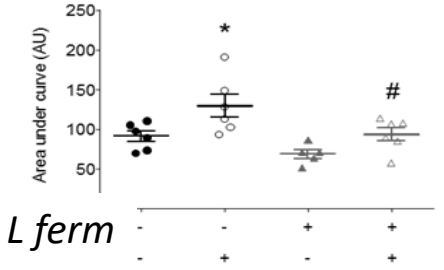




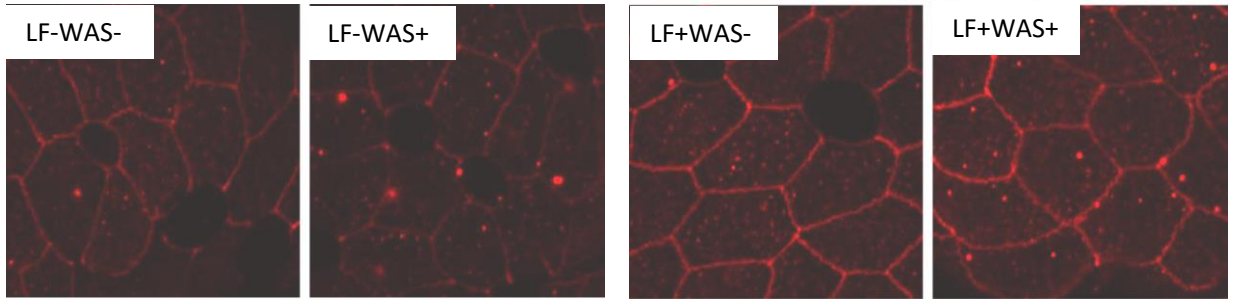
L fermentum reduces stress induced HPA activation



L fermentum prevents stress induced barrier dysfunction

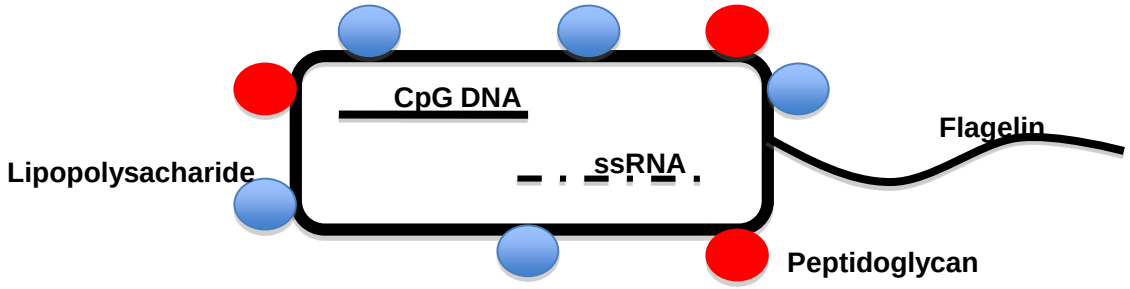


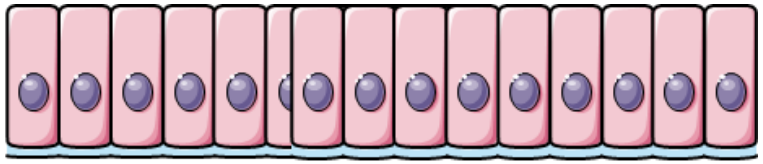
L fermentum increases ZO-1 expression in intestinal epithelial cells



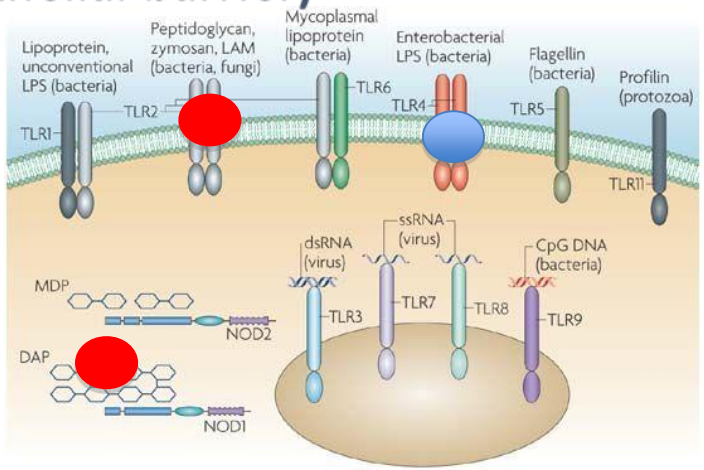
Vanhaecke et al.,*Neurogastro Mot, 2017*

Comment le microbiote régule le phénotype et fonctions du SNE?

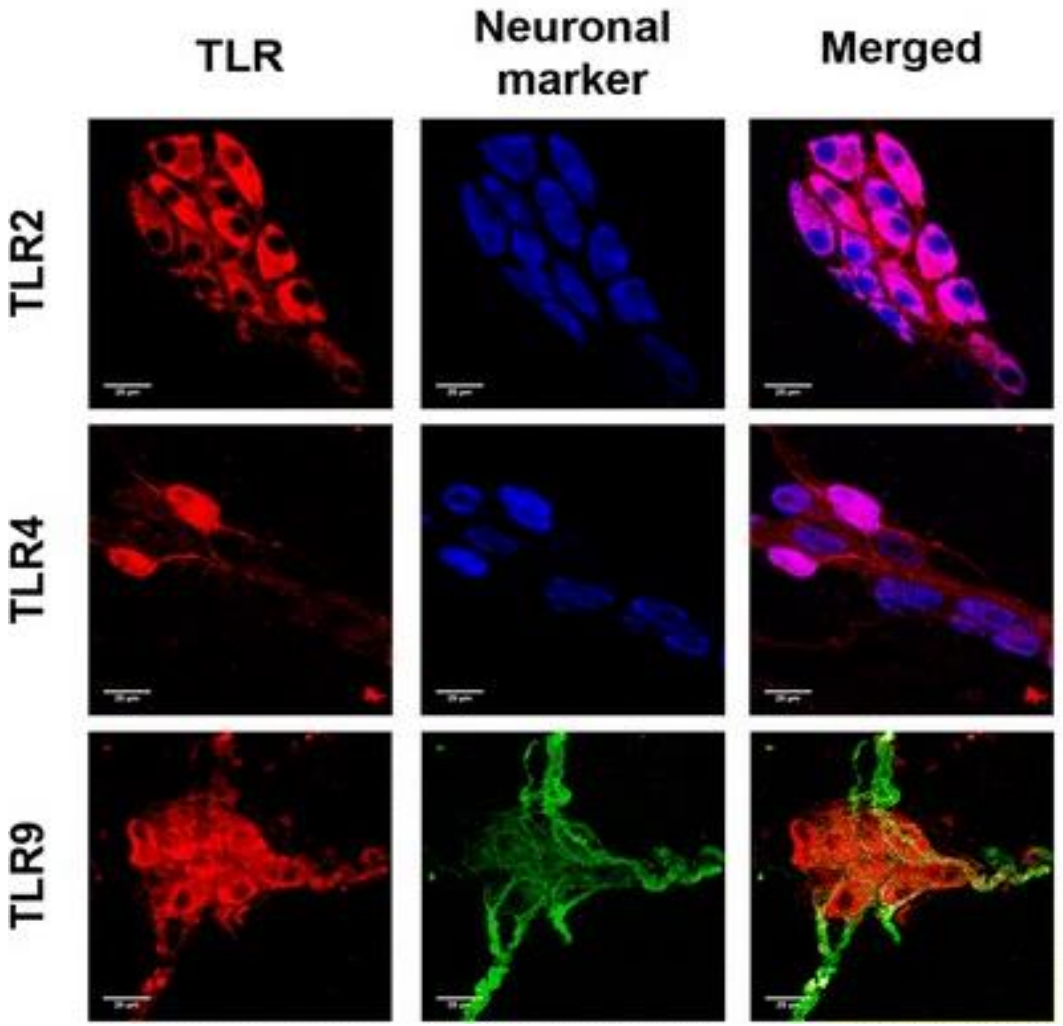




(Epithelial barrier)



Enteric neurons ?

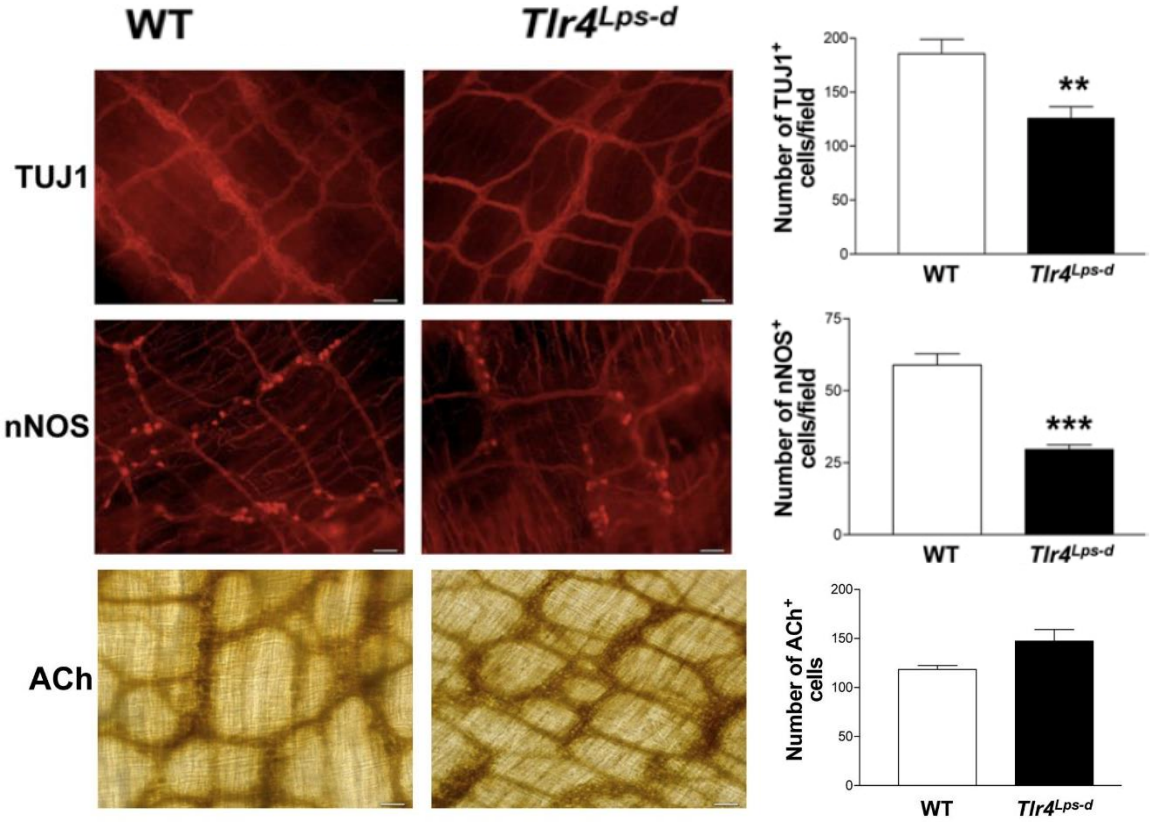


Burguenos et al., J *Neuroinflamm,* 2016

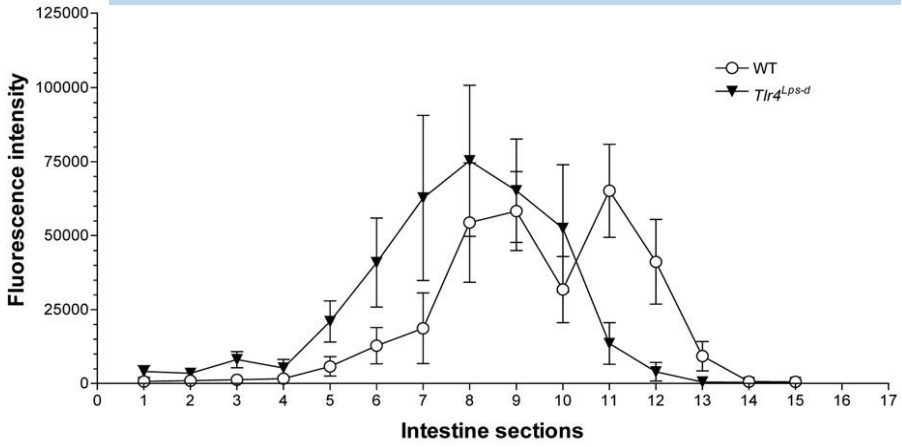
Les effets du microbiote sur le SNE sont en partie régulés par les TLR4

Tlr4$_{lps-d}$ mice

TLR4 regulates specific subpopulation in the ENS

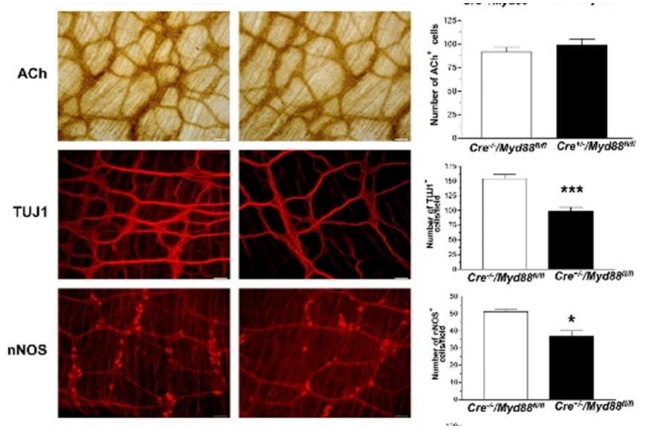


Reduced transit in TLR4 deficient mice



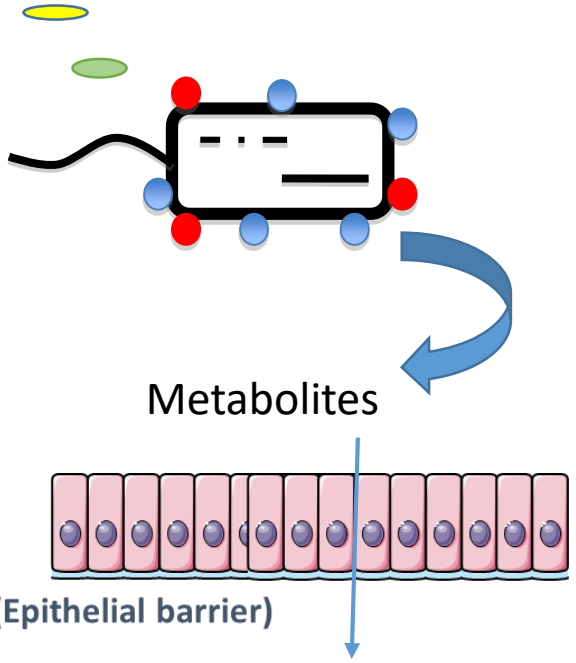
Neuronal specific deletion of MyD88 reproduces the phenotype of TLR4 deficient mice

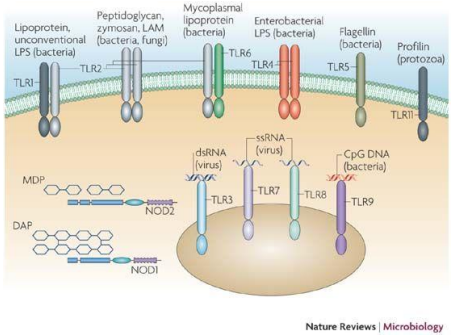
Wnt1Cre$^{+/-}$*/Myd88*$^{fl/fl}$ mice



Anitha et al, *Gastroenterol* ,2012

Les AGCC (butyrate) accélère la maturation du SNE et des fonctions digestives



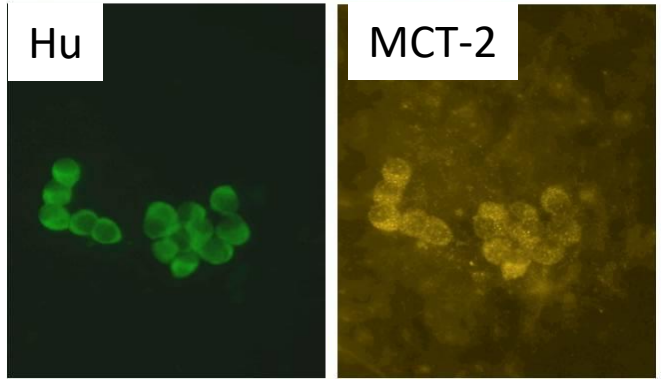


Post natal evolution of [SCFA]

	d 18	d 40
	CTL	CTL
Stool emission between d9–d15	+	n.d.†
Ceco-colonic luminal content‡ (g)	0.08 (0.07)	3.77 (0.77)
D-Lactate‡ (μmol g^{-1})	<3.7	n.d.
L-Lactate‡ (μmol g^{-1})	4.3 (1.1)	n.d.
Acetate‡ (μmol g^{-1})	57 (24)	70 (3)
Propionate‡ (μmol g^{-1})	2 (1)	13 (3)
Butyrate‡ (μmol g^{-1})	3 (1)	33 (8)
Other SCFA‡ (μmol g^{-1})	1 (2)	1 (1)

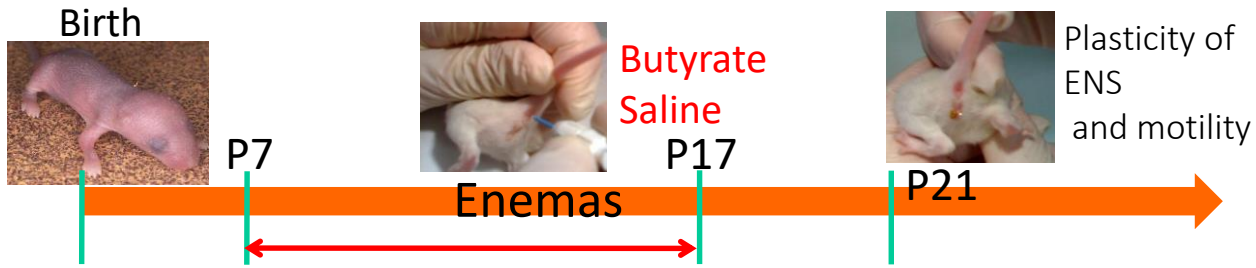
Barrat et al., *Ped Res*, 2008

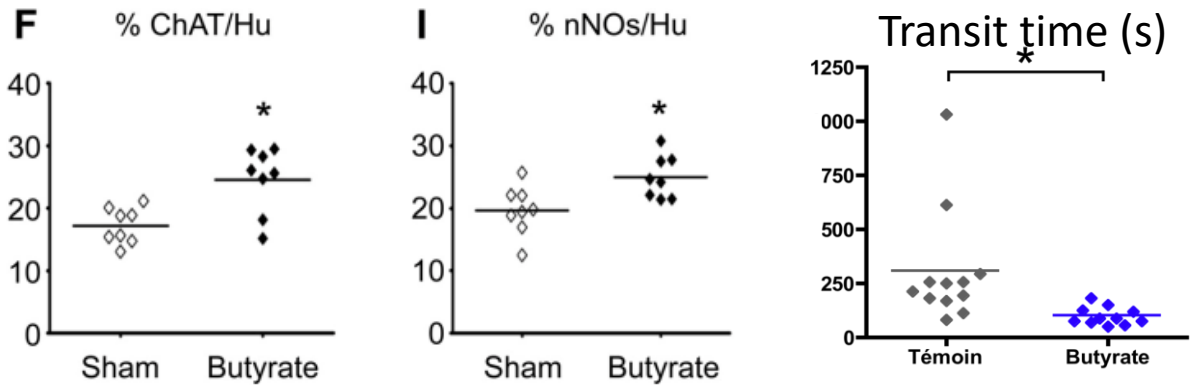
MCT-2 expression in ENS



Soret et al., *Gastroenterology*, 2010

Butyrate enhances ENS maturation and gut functions





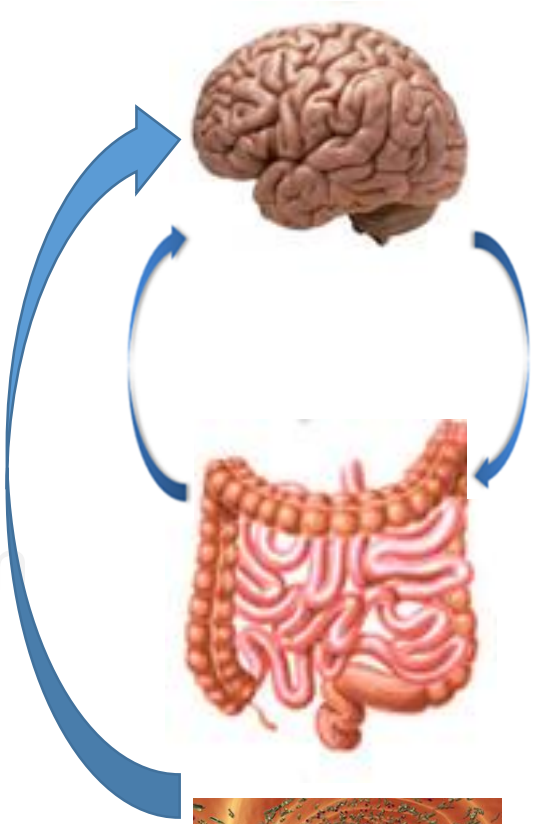
Suply et al, *Am J Physiol* 2012

Organisation de la présentation

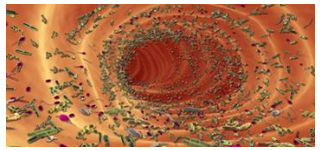
I. L’axe intestin-cerveau

II. Le microbiote intestinal : un nouvel ‘organe’?

III.Le crosstalk entre le microbiote intestinal et l’intestin (système nerveux entérique)



IV. Le crosstalk entre le microbiote intestinal et le cerveau et son implication dans les pathologies cérébrales



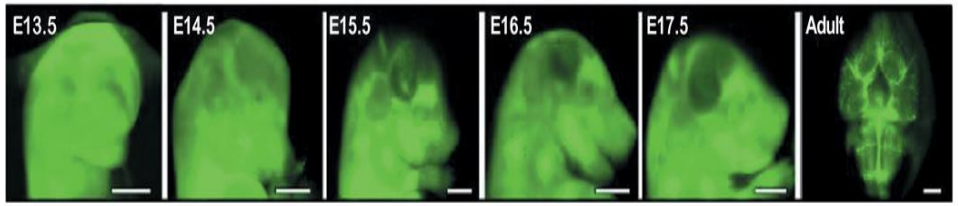
Le microbiote maternel favorise la fermeture de la barrière hémato-encéphalique

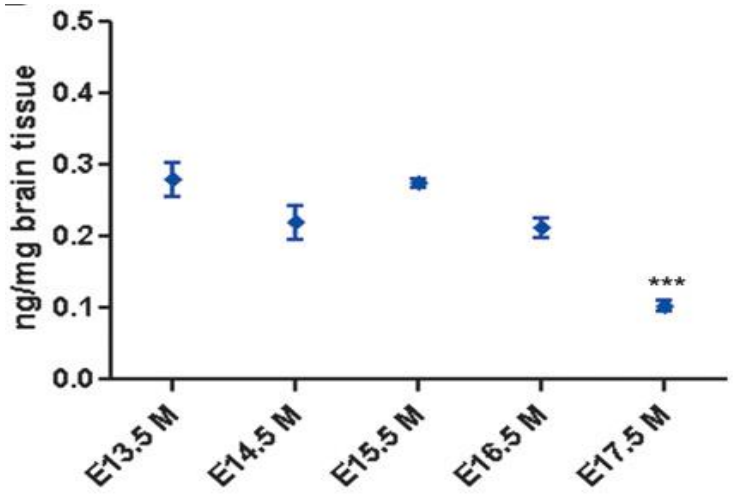
Injection of IgG-IR

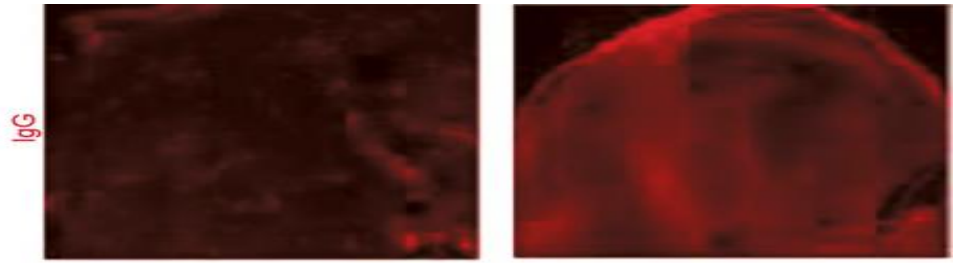
Pregnant rat SPF

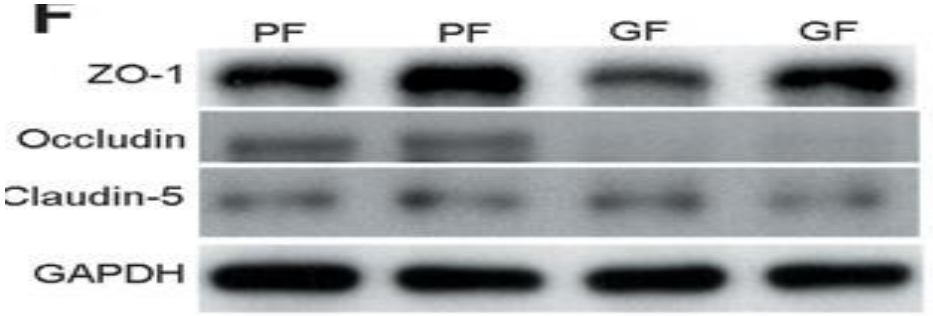
Pregnant rat GF

Developemental establishment of BBB function









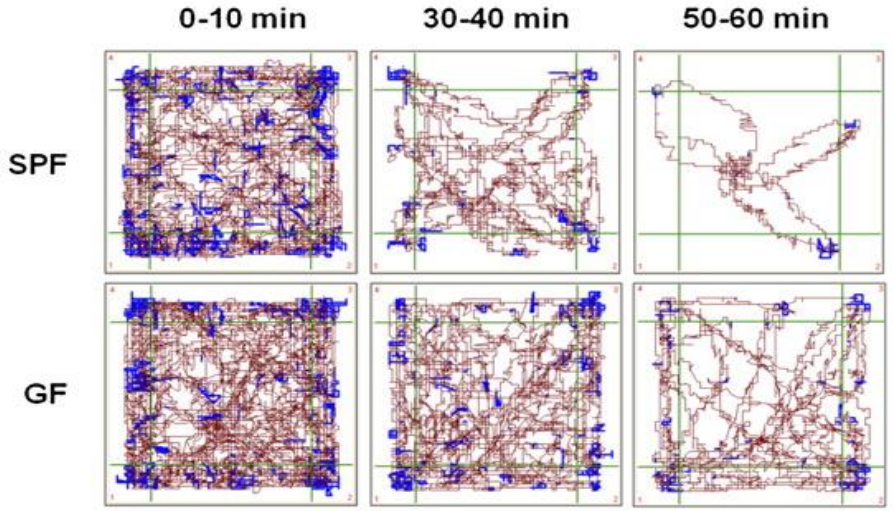
Braniste et al., *Sci Transl Med* 2014

Le microbiote maternel favorise la fermeture de la barrière hémato-encéphalique..role du butyrate?

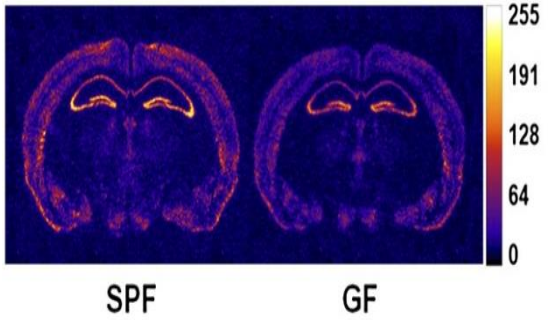
Braniste et al., *Sci Transl Med* 2014

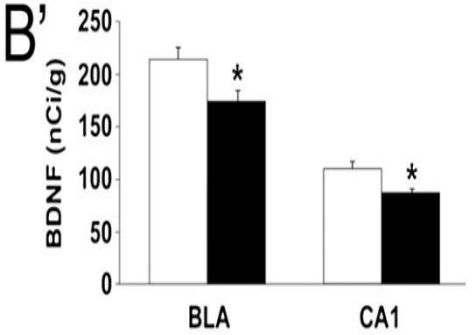
Le microbiote module le comportement exploratoire et l'anxiété

GF mice have increased exploratory behavior

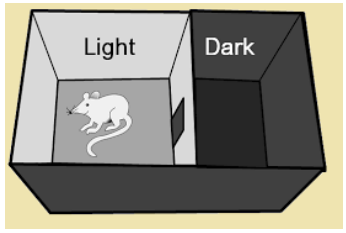


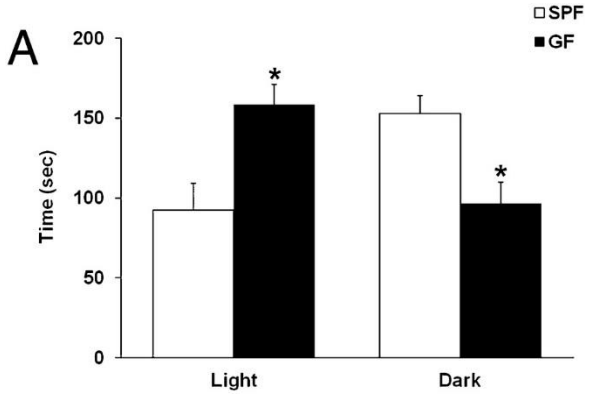
BDNF mRNA expression is reduced in amygdala and dorsal hippocampus in GF mice





GF mice display reduced anxiety-like behavior

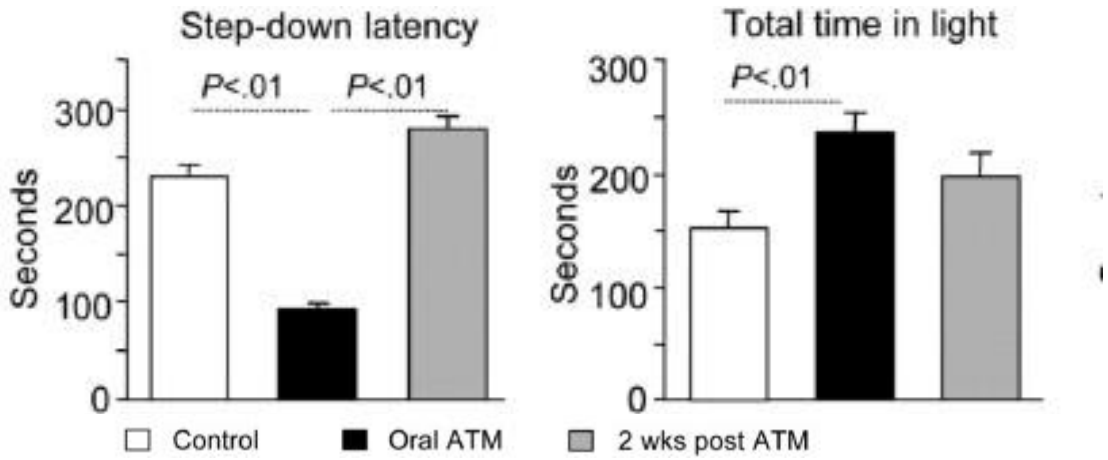




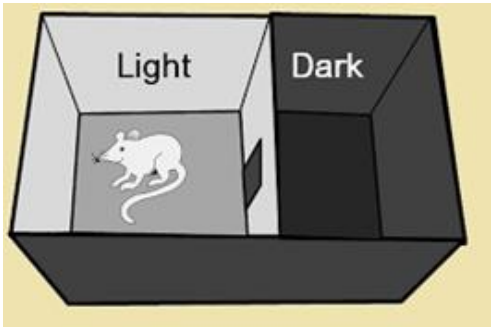
Diaz Heijtz et al. *PNAS* 2011

Le microbiote module le comportement exploratoire et l'anxiété

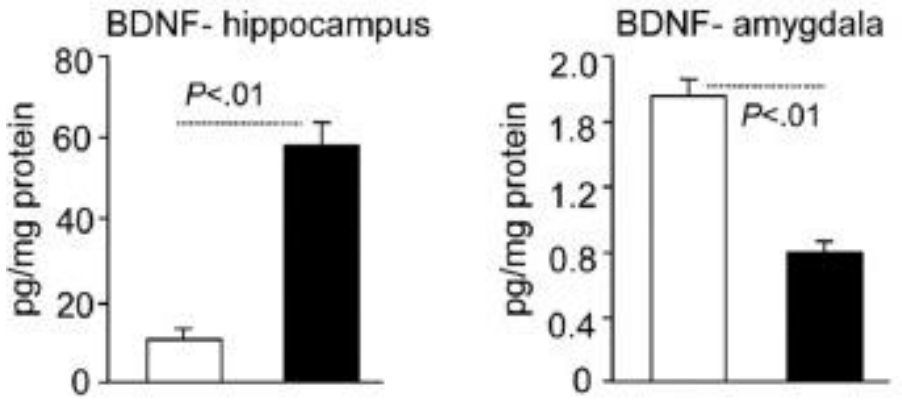
14j +/- antibiotiques



Increase exploration and reduces anxiety

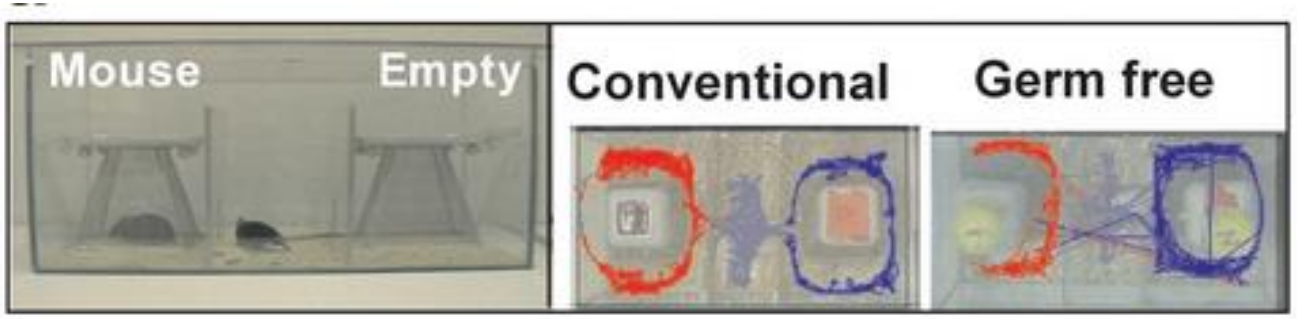


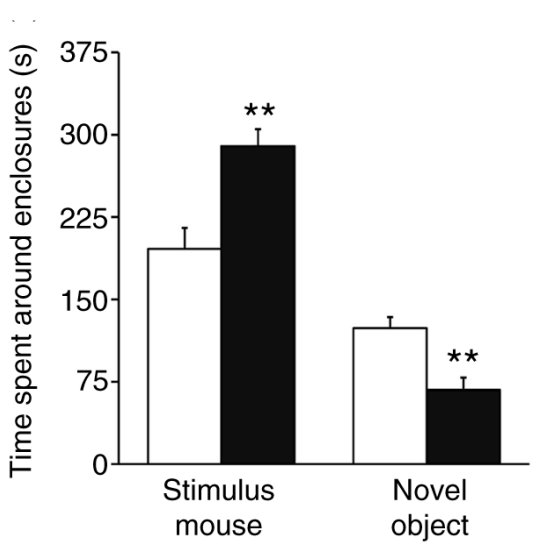
Anxiété

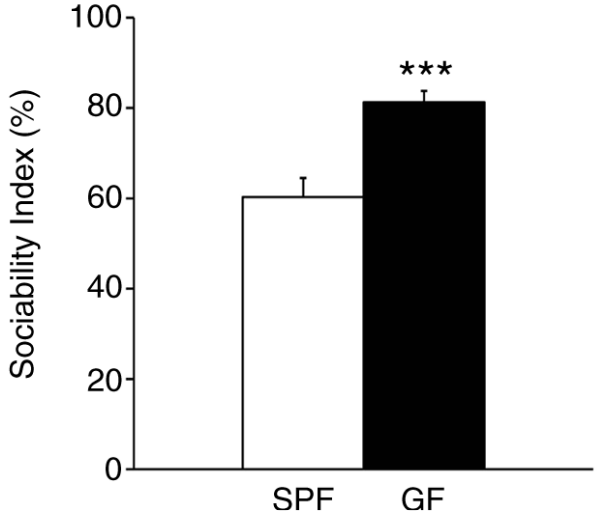


Bercik et al., *Gastroenterology*, 2011

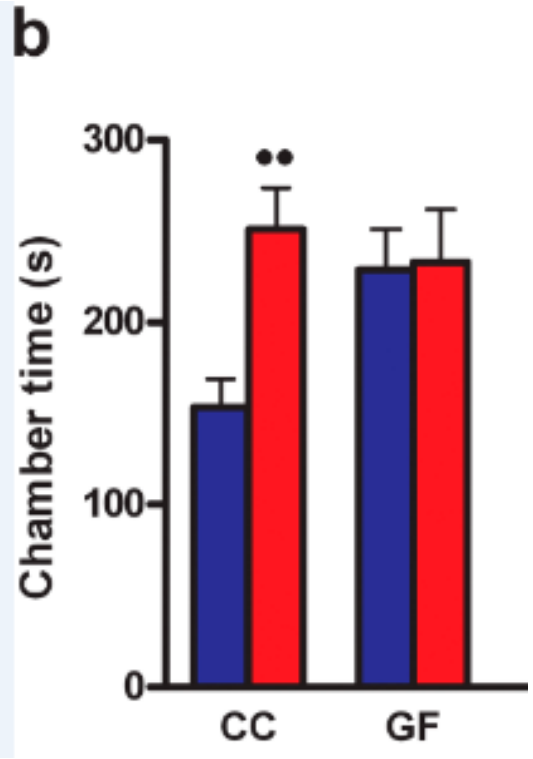
Le microbiote module les interactions sociales… différentiellement en fonction du fond génétique







Arensten et al., *Microb Ecol Health Dis.*, 2015



Desbonnet et al., *Mol Psych,* 2014

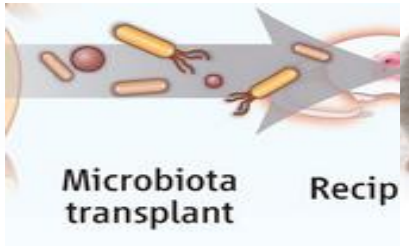
‘Transplantation’ fécale du comportement

BALB/c

Shy and anxious

NIH Swiss

Agressive



Germ free

Shy and anxious

Germ free

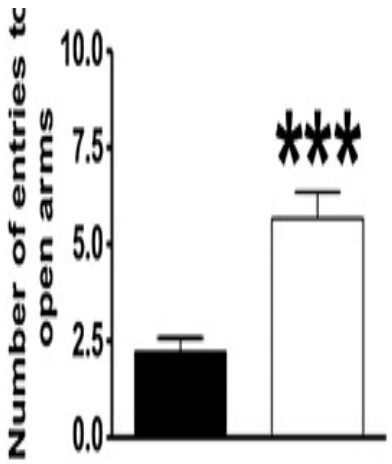
Agressive

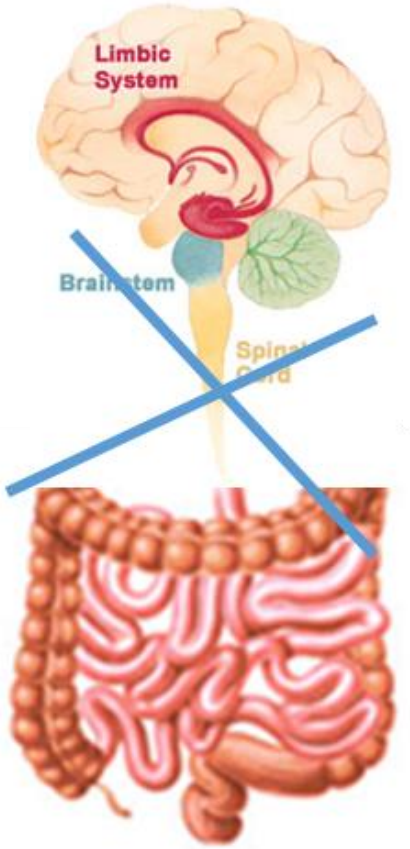
Bercik et al *Gastroenterology* 2016

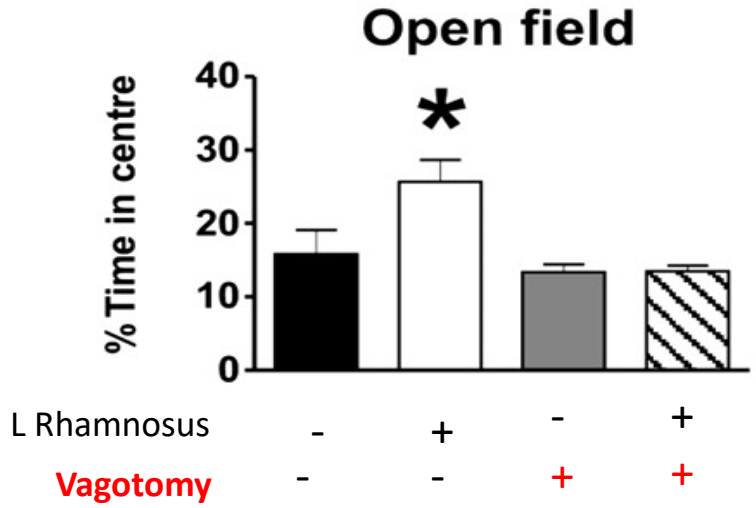
Voies/mécanismes d'action des interactions microbiote intestin-cerveau : bactérie reduit l'anxiété via le nerf vague

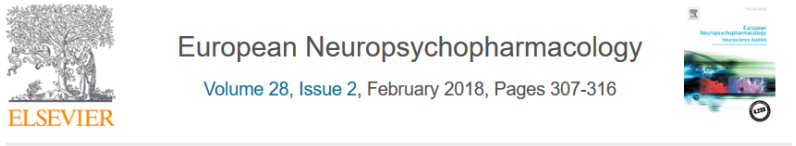
2 weeks +/- L rhamnosus strain

Open field









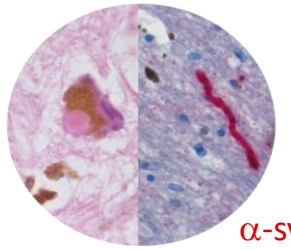
Bravo et al., *PNAS*, 2011

O'Leary et al., 2018

Des maladies du cerveau sont-elles aussi des maladies de l'intestin et du SNE ?

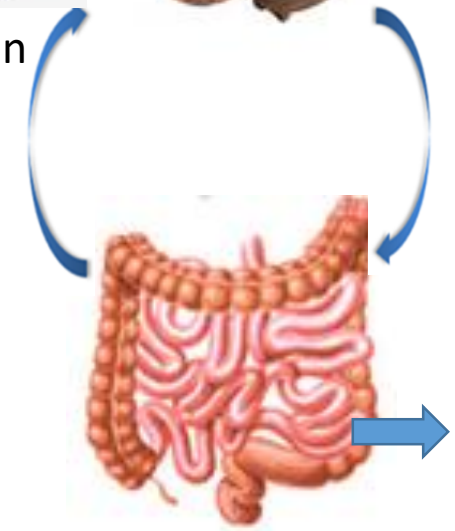
Parkinson

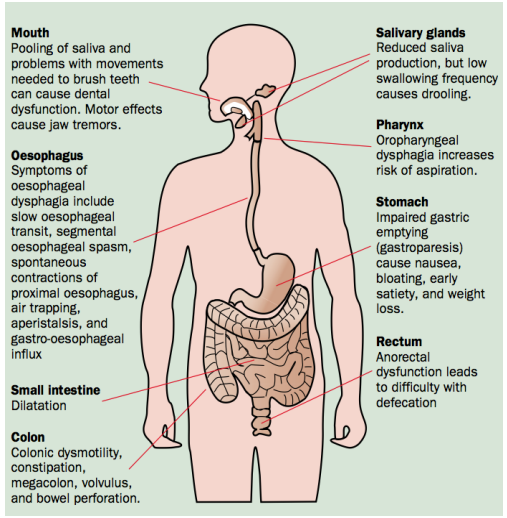
Substance Noire



α-synucléine

Symptomes moteurs
(rigidité; tremblement; instabilité)



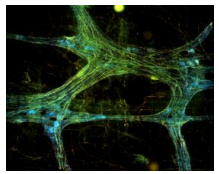


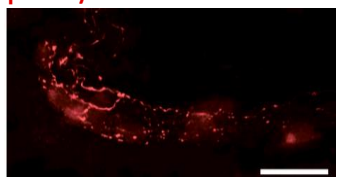
pα-synucléine

Risque de Parkinson si <1selle/jour

Nbre selles	1/j	2/j	>2/j
Risque relatif	2.7	4.1	4.5

Abbott et al., Neurology 2001

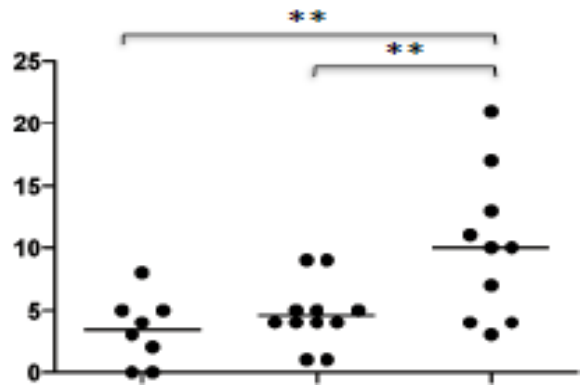




Système nerveux entérique

Lebouvier et al., *PlosOne*, 2010

Axial score



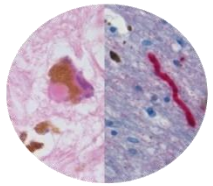
0 Moderate Severe

ENS Lewy pathology

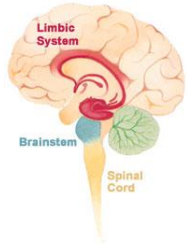
Role de l'α-synucléine dans la maladie de Parkinson

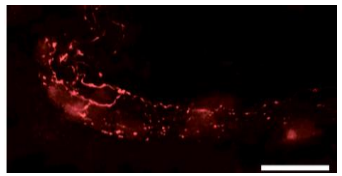
Protéinopathies

M Parkinson



α-synucléine

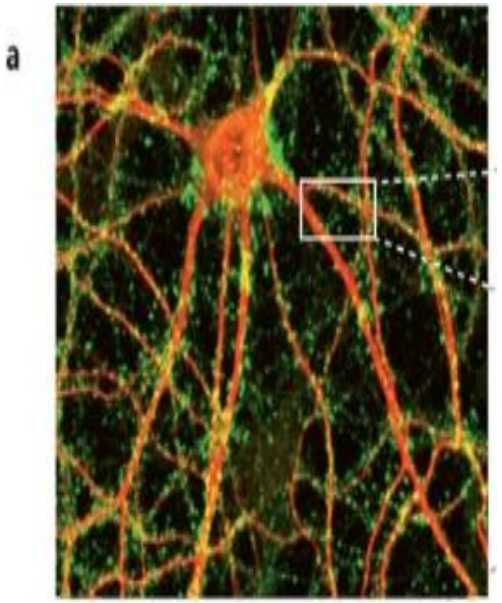




α-synucléine

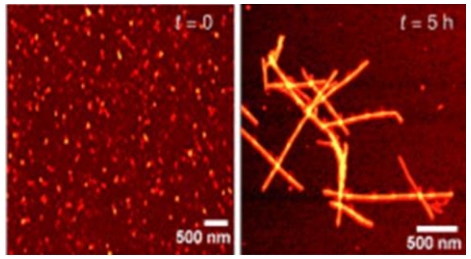
α-synucléine

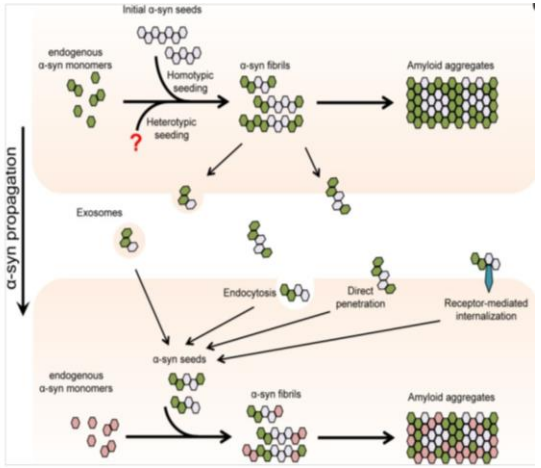
Rôle physiologique



Lashuel et al., *Nat Rev Neurosc,* 2013

Rôle pathologique





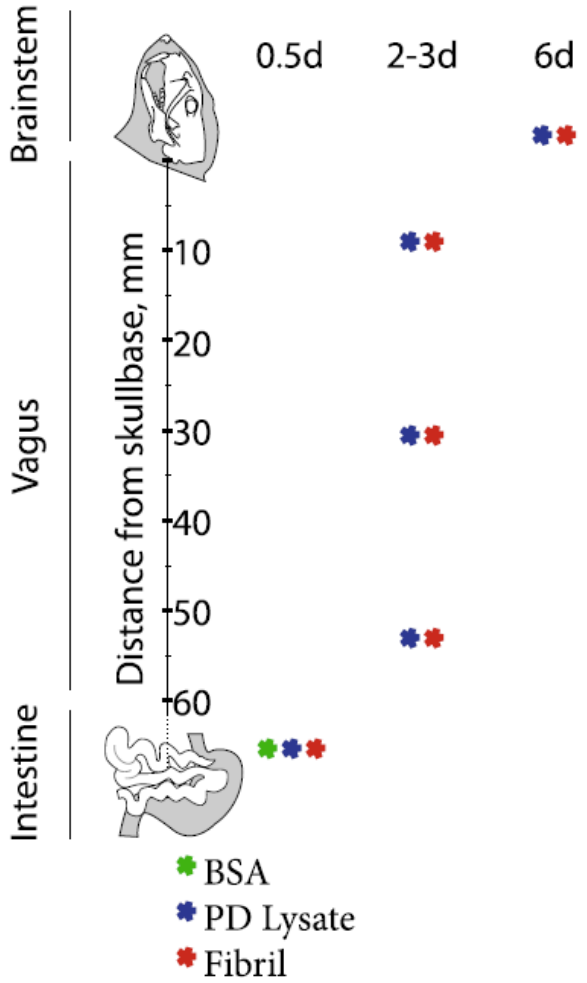
Oueslati et al, *Exp Neurol, 2014*

L'α-synucléine peut se propager du tube digestif vers le cerveau

Sprague Dawley

Injection (stomach-duodenum) :

1) Lysat de cerveau MP
2) Fibrilles d'α-synucléine
3) Albumine

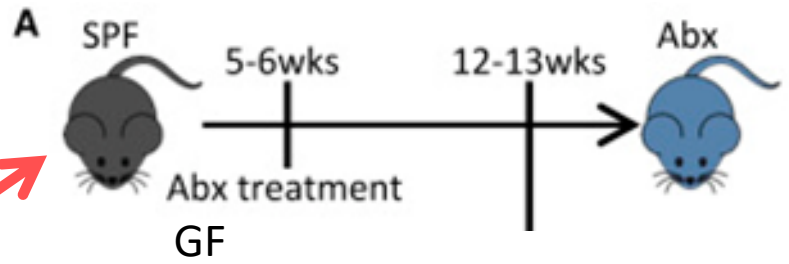


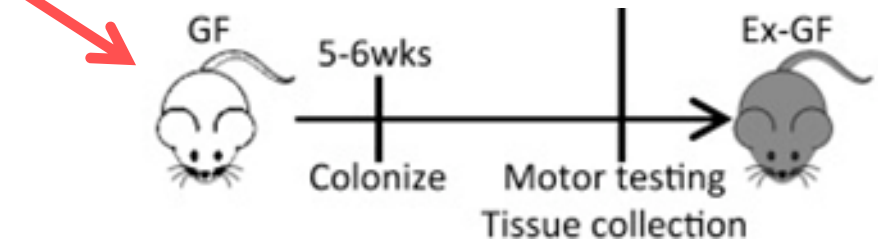
Holmqvist et al., *Acta Neuropathol,* 2014

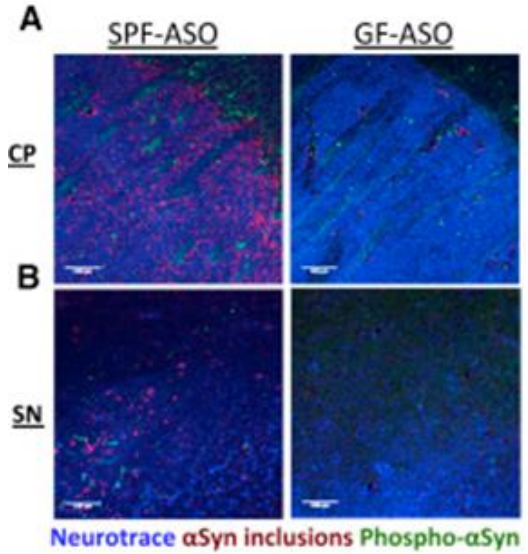
Le microbiote peut-il contribuer à l'évolution de la Maladie de Parkinson ?

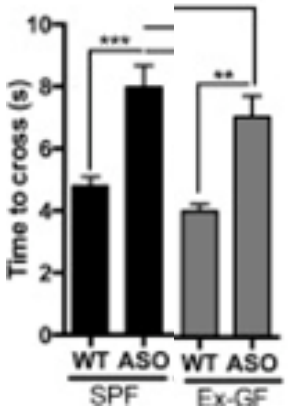
Thy1-hαSyn

Parkinson mice (ASO mice)





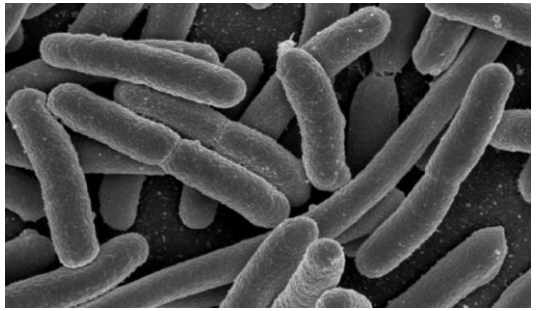




Sampson et al., *Cell*

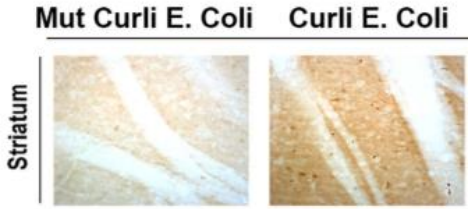
Des peptides d'origine bactérienne peuvent induire la formation d'aggrégats de synucléine dans le tube digestif et le cerveau

E Coli

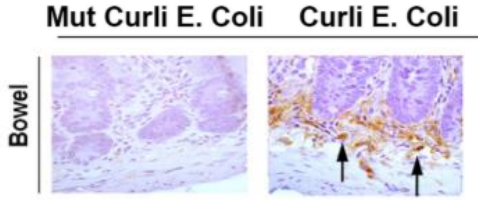


- Curli : peptides amyloides bactériens
- Formation de biofilm / colonisation de l'hote

Gavage hebdomadaire (2-3 mois) avec E Coli +/- curli

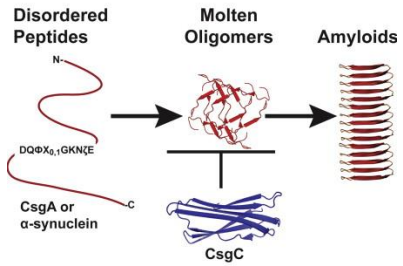


α-synucléine



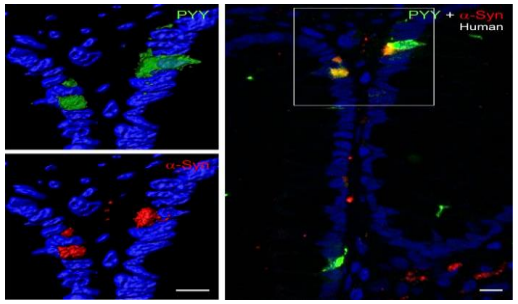
α-synucléine

Chen et al., *Scient Rep.*, 2016



Evans et al., *Mol Cell* 2015

Les cellules entéroendocrines : 'porte d'entrée' vers le cerveau?



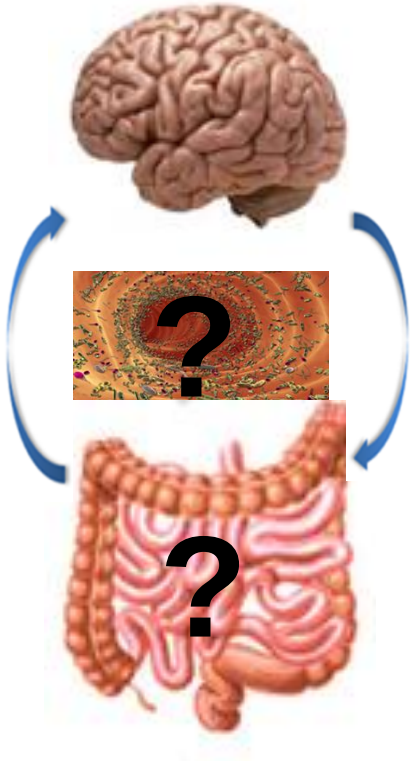
Human colon

Chandra et al., *JCI Insights, 2017*

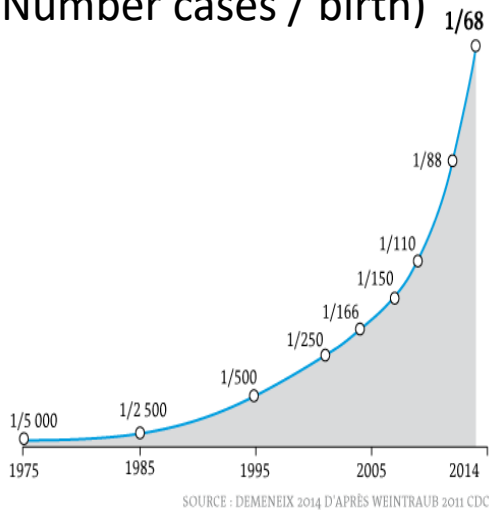
Les troubles du spectre autistiques sont-ils une pathologie de l'axe microbiote-intestin-cerveau ?

Autism Spectrum Disorders

- Altered social interactions
- Repetitive behaviors
- Language deficits



Autistic spectrum disorder
(Number cases / birth)

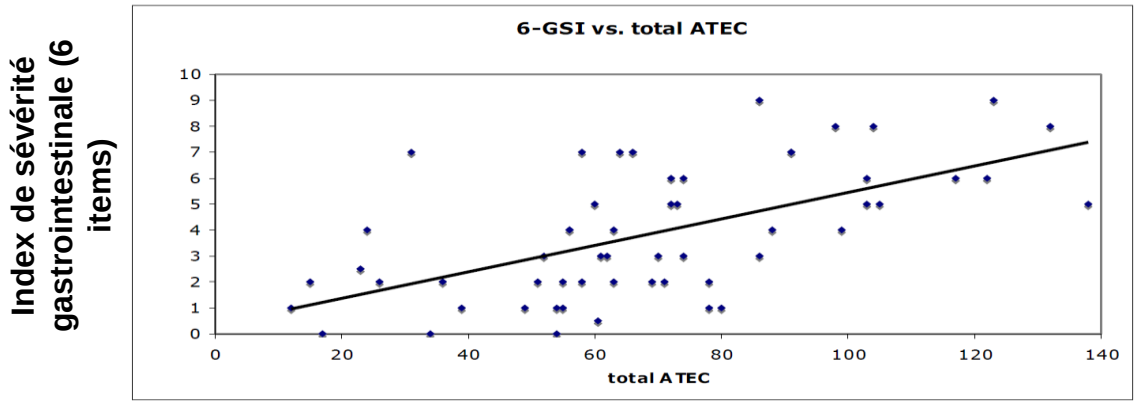


symptoms

- Diarrhea
- Bloating
- Constipation
- Abdominal pain
- Reflux

Nb of digestive symptoms*/ child	Children with ASD		Age-matched siblings	
0	19.8		70.5	
1	16.4		18.2	
2	24.1	64 %	4.5	11%
3	25		4.5	
>=4	14.7		2.3	

Horvath and Perman, Current Opinion in Pediatrics (2012)



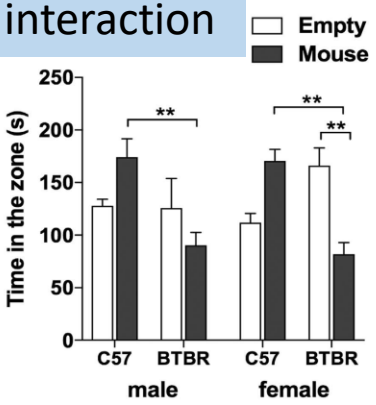
Adams et al. BMC Gastroenterology 2011

Score TSA (4 items)

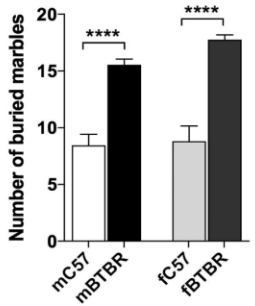
Modifications de l'axe microbiote-intestin-cerveau dans des modèles de TSA: modèle génétique

BTBR T+ Itpr3tf/J

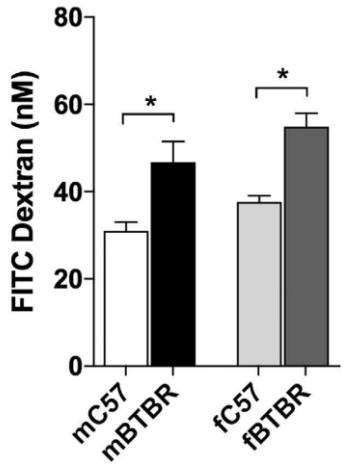
Social interaction



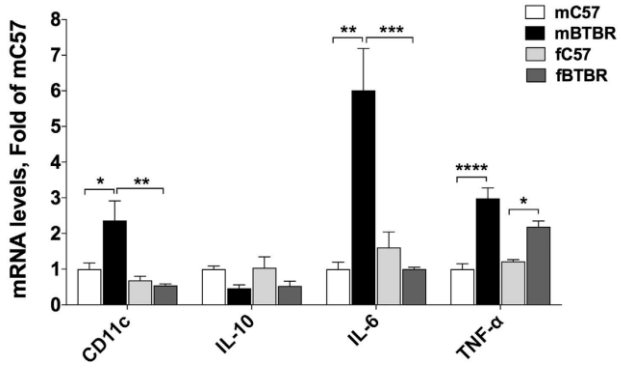
Repetitive behavior



Intestinal permeability

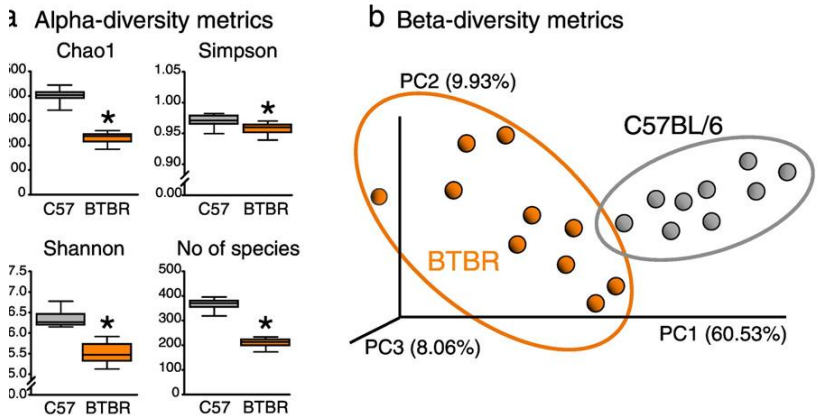


Intestinal inflammation



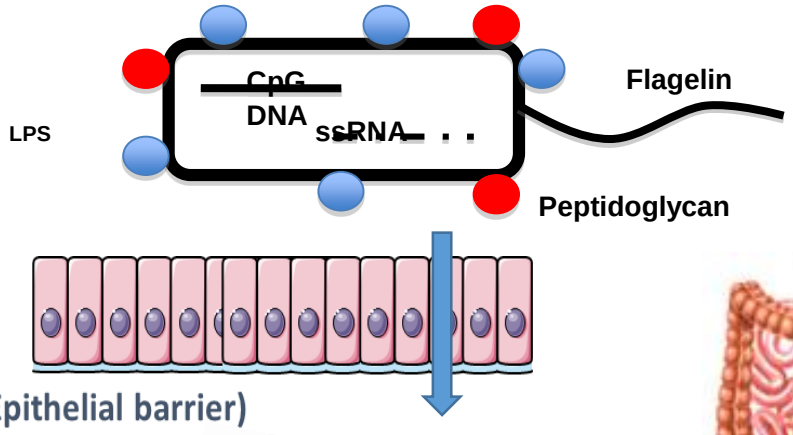
Coretti et al., *Scient Rep,* 2017

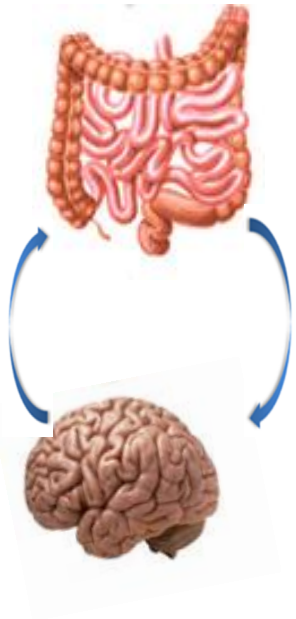
Loss of bacterial diversity



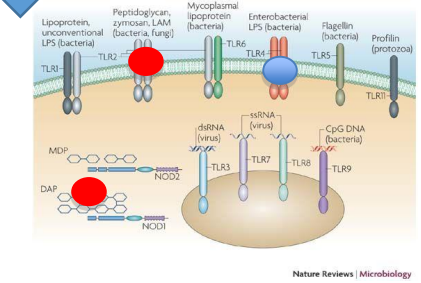
Golubeva et al., *EBioMedecine,* 2017

Mécanismes d'action des interactions microbiote intestin-cerveau : implication des peptidoglycans dans développement du cerveau

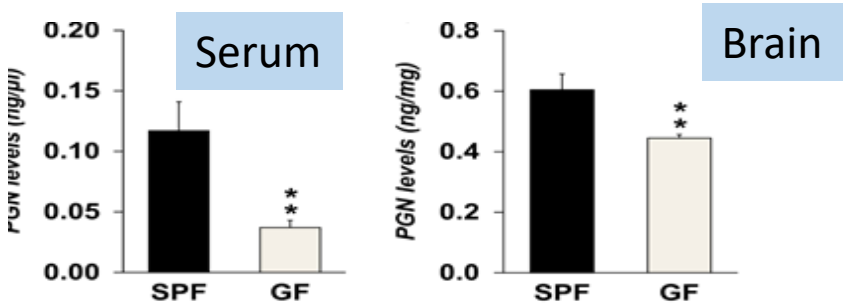




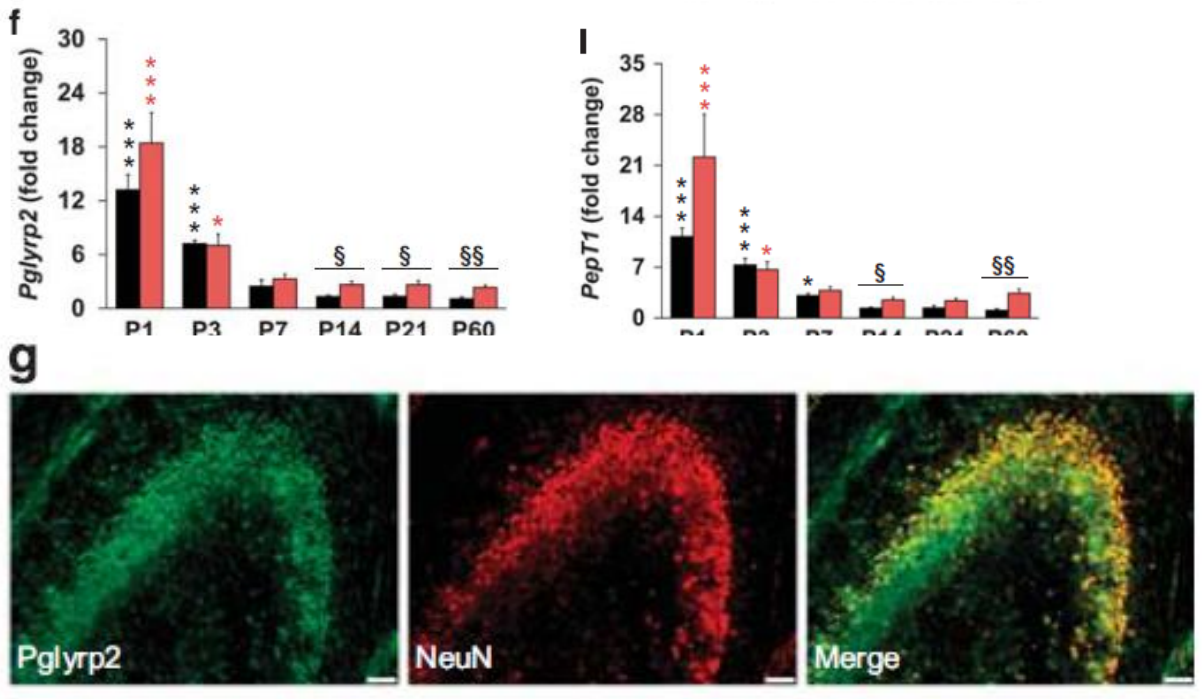
CNS neurons ?



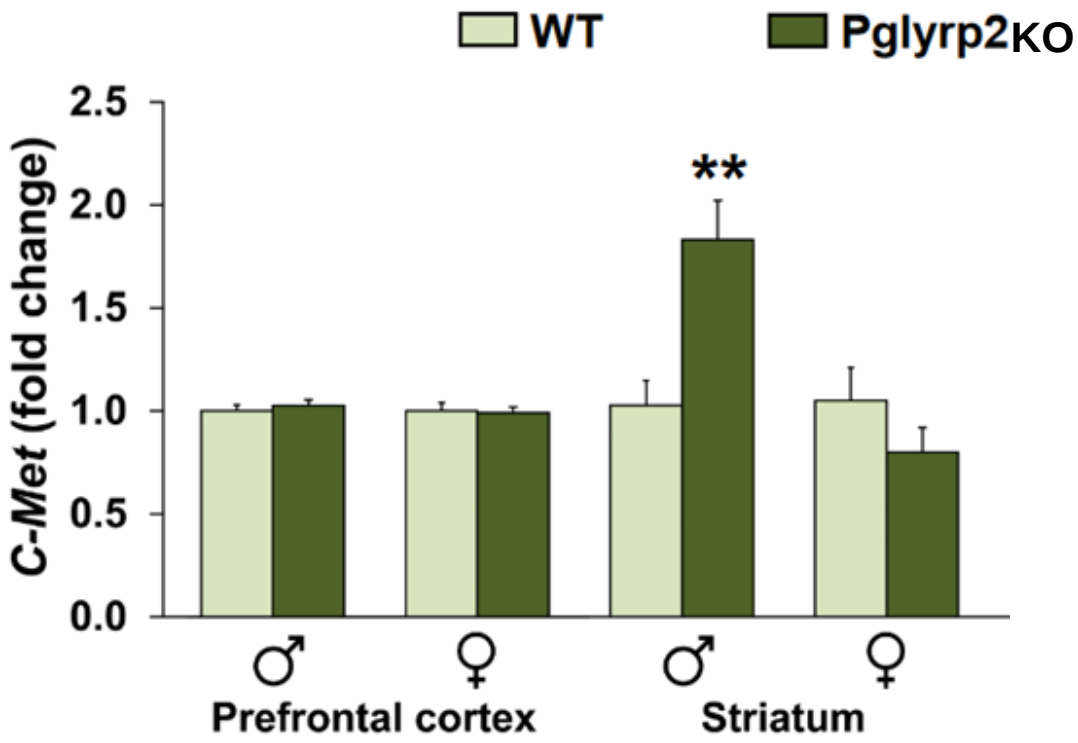
Arentsen et al., *Mol Psych*, 2017

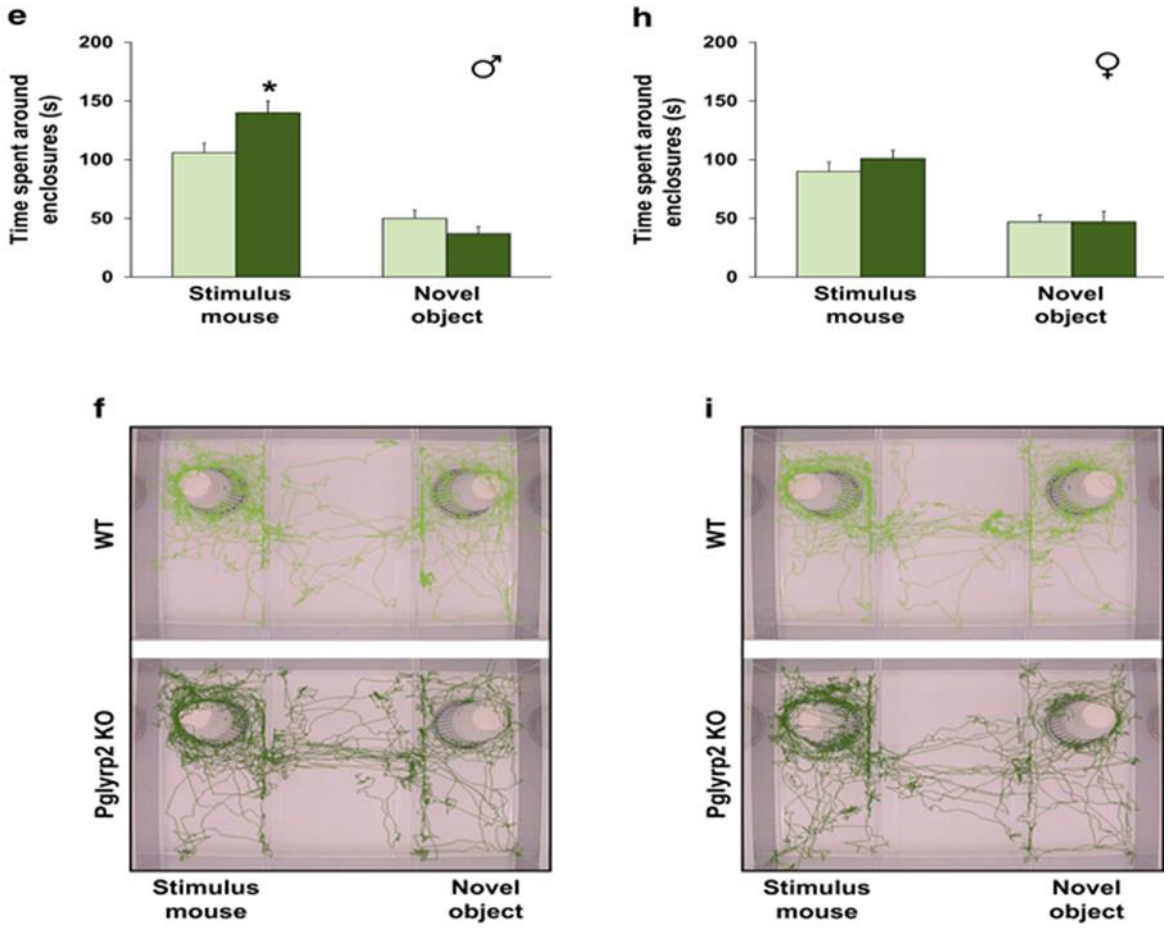


Age dependent expression of PG recognition proteins/transporters



Mécanismes d’action des interactions microbiote intestin-cerveau : implication des peptidoglycans dans développement du cerveau

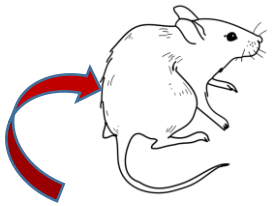




Arentsen et al., *Mol Psych*, 2017

Modifications de l'axe microbiote-intestin-cerveau dans des modèles de TSA : modèle d'activation immunitaire maternel

Pregnant mice

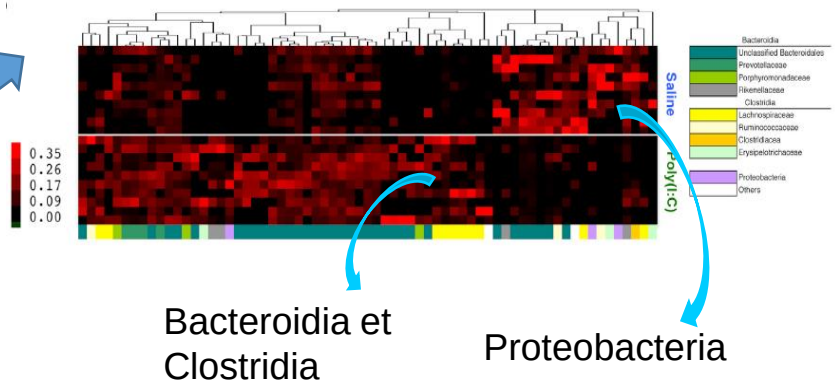


Immune activation
(viral mimic: poly (I:C))

Progeny

- **↗ stereotypic behavior**
- **↘ social interactions**

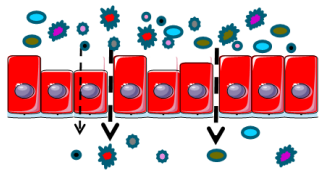
Dysbiosis

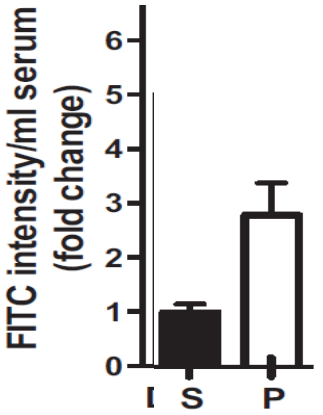


Bacteroidia et Clostridia

Proteobacteria

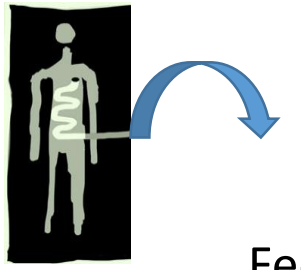
↗ gut permeability



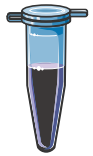


Hsia et al.,*Cell, 2013*

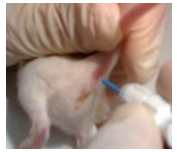
Le microbiote de patients atteints de TSA induit des altérations des fonctions digestives et du SNE



TSA / Ct



Fecal Supernatant

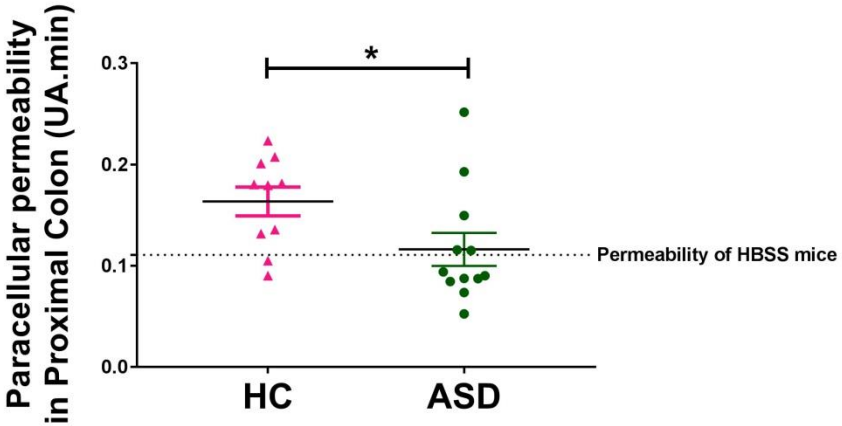


Enemas with FS in Ab treated mice

Measurement of gut and ENS functions *(in vivo and ex vivo)*

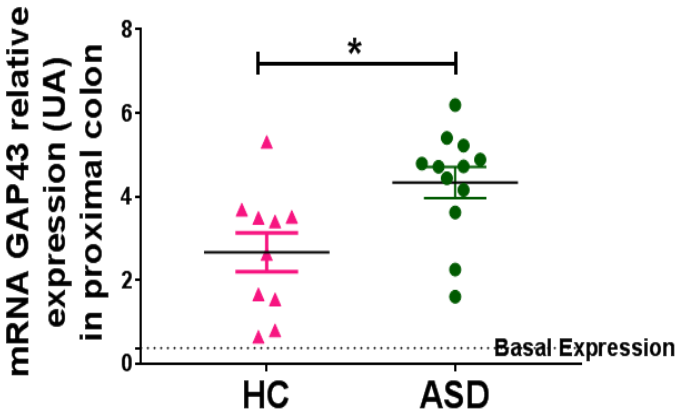
Ussing Chamber

Paracellular permeability



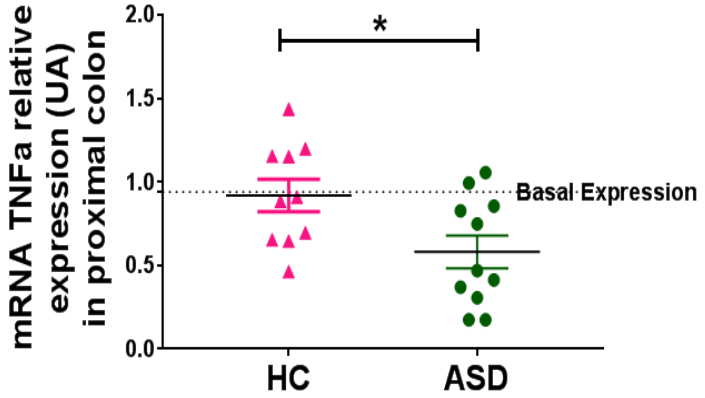
Neuronal Connectivity

GAP43 mRNA expression



Inflammation

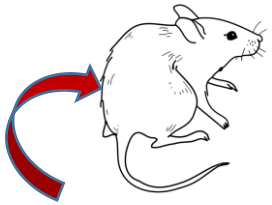
TNFα mRNA expression



Gonzales et al., *Neurogastr Mot,* 2018 Abstract

Cibler les fonctions digestives (et le microbiote): nouvel objectif thérapeutique dans les TSA?

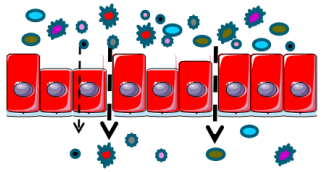
Pregnant mice

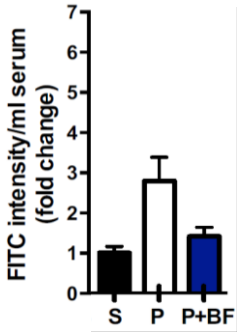


Immune activation
(viral mimic: poly (I:C))

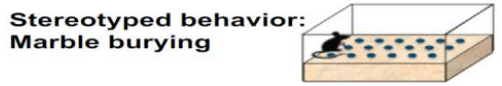
bacteroides fragilis
(anti-inflammatory effects)

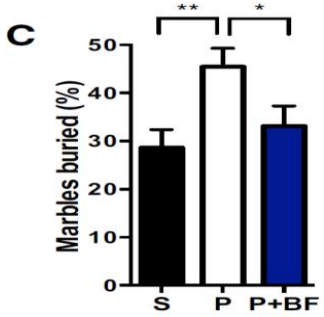
Restauration of intestinal pemeability





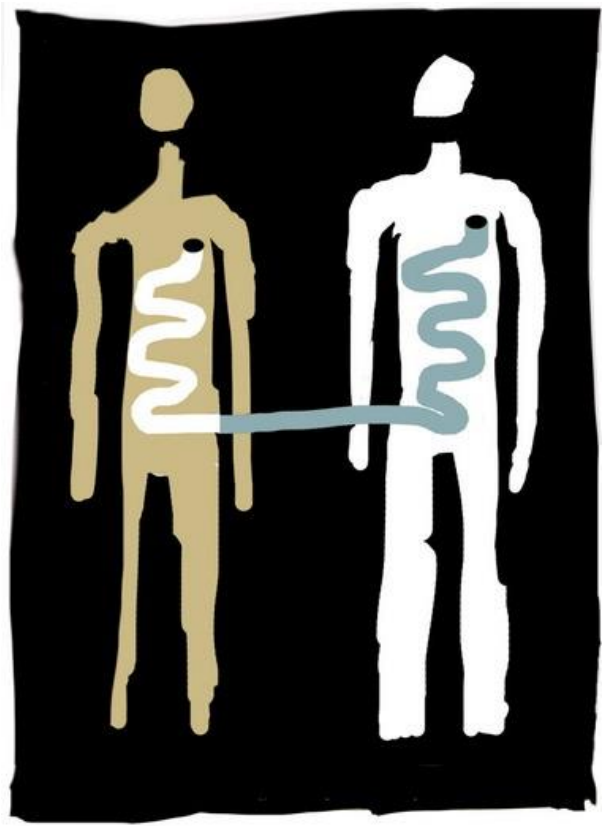
↘ stereotypic behavior





Hsia et al.,*Cell, 2013*

Cibler les fonctions digestives (et le microbiote): des souris vers l'homme ?



Kang *et al. Microbiome* (2017) 5:10
DOI 10.1186/s40168-016-0225-7

Microbiome

RESEARCH Open Access

Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study

Dae-Wook Kang[1†], James B. Adams[2†], Ann C. Gregory[3,15†], Thomas Borody[4], Lauren Chittick[5,15], Alessio Fasano[6], Alexander Khoruts[7,8,9], Elizabeth Geis[2], Juan Maldonado[1], Sharon McDonough-Means[10], Elena L. Pollard[2], Simon Roux[5,15], Michael J. Sadowsky[8,11], Karen Schwarzberg Lipson[12], Matthew B. Sullivan[3,5,15,16*], J. Gregory Caporaso[12,13*] and Rosa Krajmalnik-Brown[1,14*]

Abstract

Background: Autism spectrum disorders (ASD) are complex neurobiological disorders that impair social interactions and communication and lead to restricted, repetitive, and stereotyped patterns of behavior, interests, and activities. The causes of these disorders remain poorly understood, but gut microbiota, the 10^{13} bacteria in the human intestines, have been implicated because children with ASD often suffer gastrointestinal (GI) problems that correlate with ASD severity. Several previous studies have reported abnormal gut bacteria in children with ASD. The gut microbiome-ASD connection has been tested in a mouse model of ASD, where the microbiome was mechanistically linked to abnormal metabolites and behavior. Similarly, a study of children with ASD found that oral non-absorbable antibiotic treatment improved GI and ASD symptoms, albeit temporarily. Here, a small open-label clinical trial evaluated the impact of Microbiota Transfer Therapy (MTT) on gut microbiota composition and GI and ASD symptoms of 18 ASD-diagnosed children.

Results: MTT involved a 2-week antibiotic treatment, a bowel cleanse, and then an extended fecal microbiota transplant (FMT) using a high initial dose followed by daily and lower maintenance doses for 7–8 weeks. The Gastrointestinal Symptom Rating Scale revealed an approximately 80% reduction of GI symptoms at the end of treatment, including significant improvements in symptoms of constipation, diarrhea, indigestion, and abdominal pain. Improvements persisted 8 weeks after treatment. Similarly, clinical assessments showed that behavioral ASD symptoms improved significantly and remained improved 8 weeks after treatment ended. Bacterial and phagedeep sequencing analyses revealed successful partial engraftment of donor microbiota and beneficial changes in the gut environment. Specifically, overall bacterial diversity and the abundance of *Bifidobacterium*, *Prevotella*, and *Desulfovibrio* among other taxa increased following MTT, and these changes persisted after treatment stopped (followed for 8 weeks).

Conclusions: This exploratory, extended-duration treatment protocol thus appears to be a prc the gut microbiome and virome and improve GI and behavioral symptoms of ASD. Improvem symptoms, and the microbiome all persisted for at least 8 weeks after treatment ended, sugge

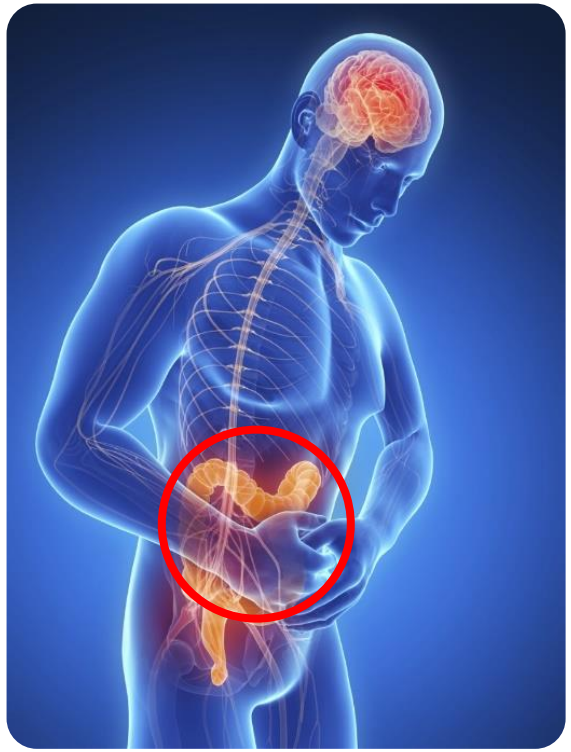
(Continued on next page)

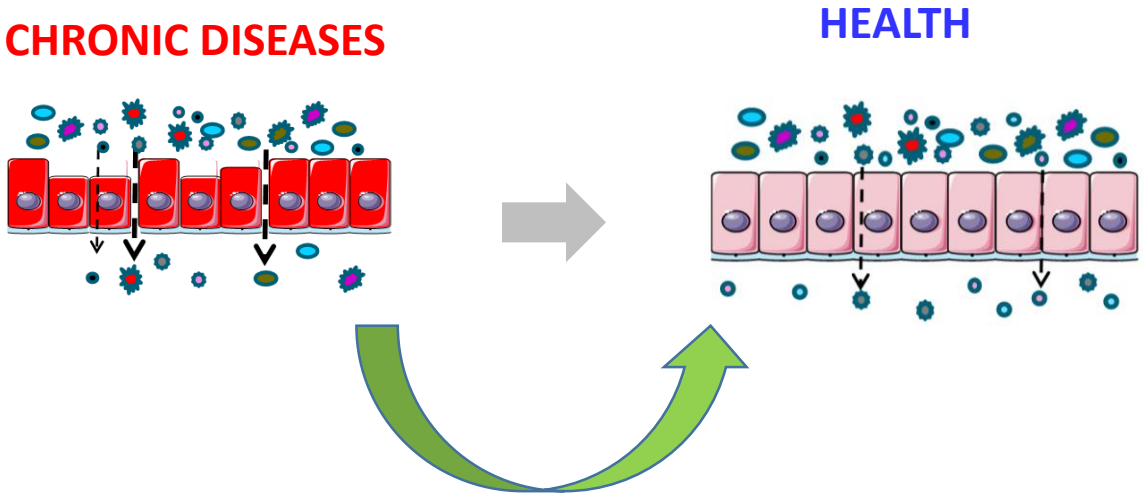
Gastroenterology 2017;152:799–811

Efficacy of Sterile Fecal Filtrate Transfer for Treating Patients With *Clostridium difficile* Infection

Stephan J. Ott,[1,*] **Georg H. Waetzig**,[2,*] **Ateequr Rehman**,[3,*] Jacqueline Moltzau-Anderson,[3,4] Richa Bharti,[3] Juris A. Grasis,[5] Liam Cassidy,[6] Andreas Tholey,[6] Helmut Fickenscher,[7] Dirk Seegert,[2] Philip Rosenstiel,[3,§] and Stefan Schreiber[1,3,§]

Cibler le tube digestif pour prévenir ou traiter les pathologies chroniques de l'intestin et du cerveau?





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J Doré