



# Research and Innovation in Nutrition: A major health issue Milk products and innovative fermented ingredients for target populations: Focus on the PROLIFIC Project

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# Research and Innovation in Nutrition : A major health issue

# Milk products and innovative fermented ingredients for target populations : Focus on the PROLIFIC Project

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Yves LE LOIR

STLO - INRAE Institut Agro Rennes

# PROLIFIC

« May your diet be your first medicine »

ENS-  
Central Nervous  
System (CNS)  
interactions

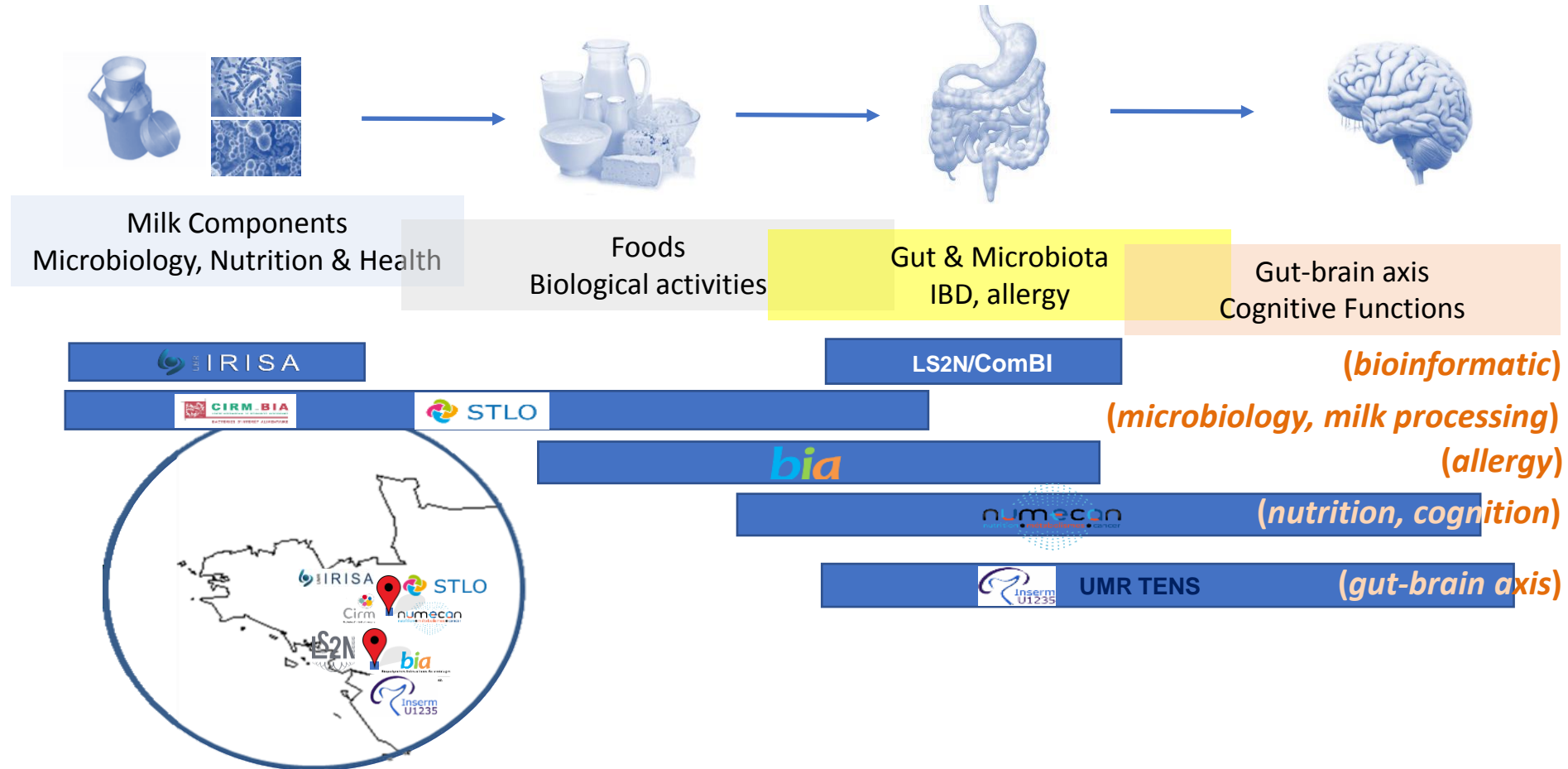


Lactic- and Propionic- Acid bacteria  
Metabolites of interest  
(SCFA, CLA, oligosaccharides, vitamins, etc.)

Food microbiota-intestinal  
epithelial barrier (IEB)  
interactions

IEB-Enteric nervous  
system (ENS) interactions

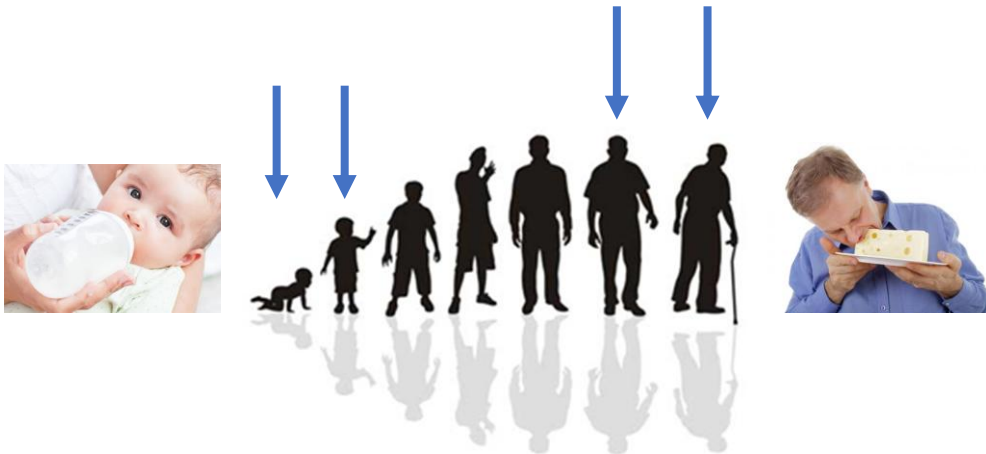
# Scientific continuum and expertise



## For which target populations?

The first **1000** days of life  
(0-6 months and 6 months-3 years)

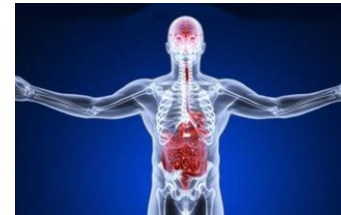
The **seniors**



## For which functionalities ?



Colonisation and homeostasis  
of gut microbiota



Cognitive development /  
Neurodegeneration



Inflammation  
Tolerance / Allergy

## Human resources

**5** PhD projects (*180 months*)

**4** post-docs (*60 months*)

**5** Contracts Technicians and Engineers (*90 months*)

## Funding

**13,9** M€ Full cost

**7,55** M€ funded by Bba Milk Valley

**1,86** M€ funded by Regions BZH and PDL

# Thank you for your attention



STLO



# Questions & Answers



# Two human milk synthetic bacterial community (SynCom) exhibited contrasted impacts *in vitro* on intestinal barrier and immune function

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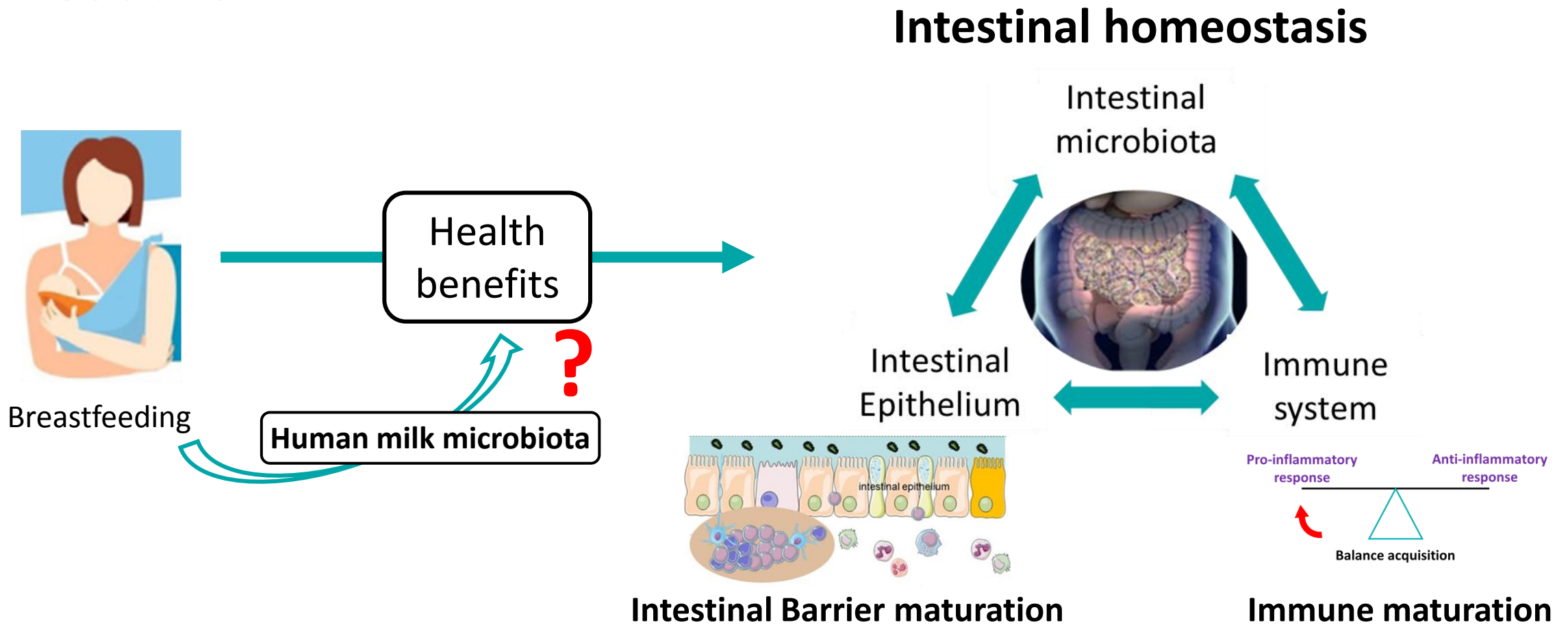


Charles LE BRAS  
STLO & NuMeCan





# Introduction



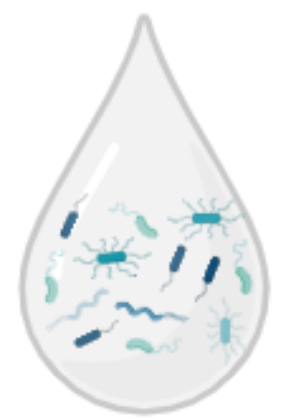
**Our hypothesis is that the microbiota of human breast milk contributes to the health benefits of breast milk**



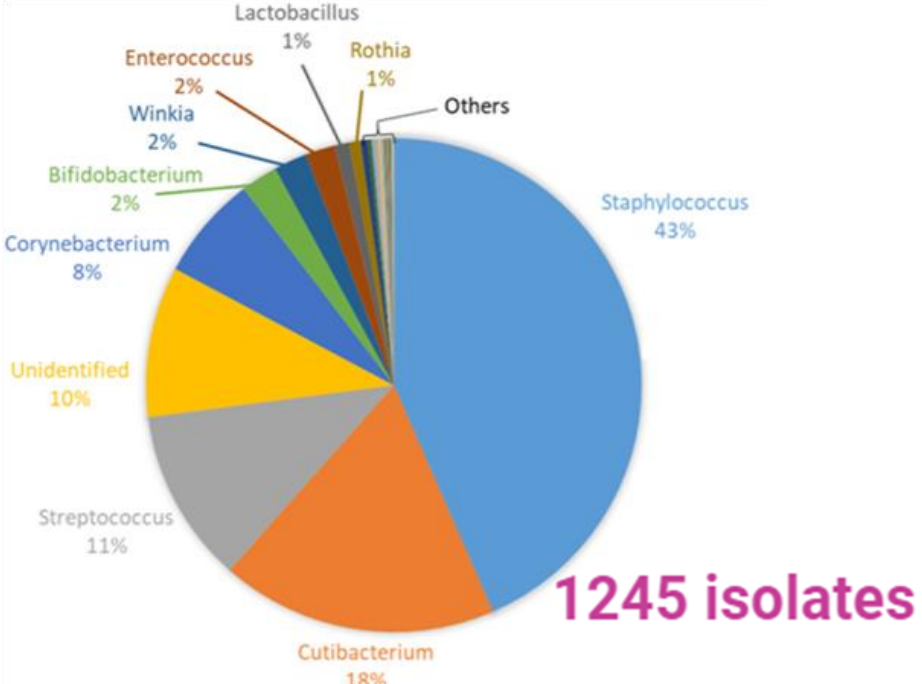


# Strategy

28 Donors

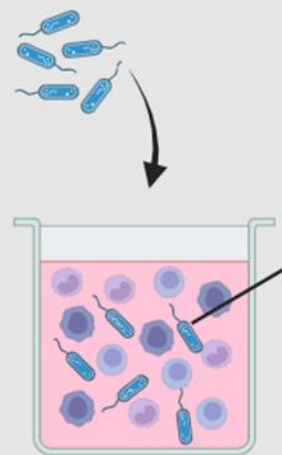


Bacterial collection



Preselection

**Human PBMC model**  
84 isolates



IL-10 and TNF- $\alpha$

**Quadricellular model**

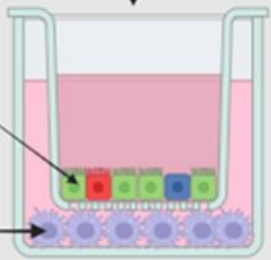
29 isolates

2 SynComs

OR

Enterocytes (Caco-2)  
Goblet cells (HT29-MTX)  
M cells

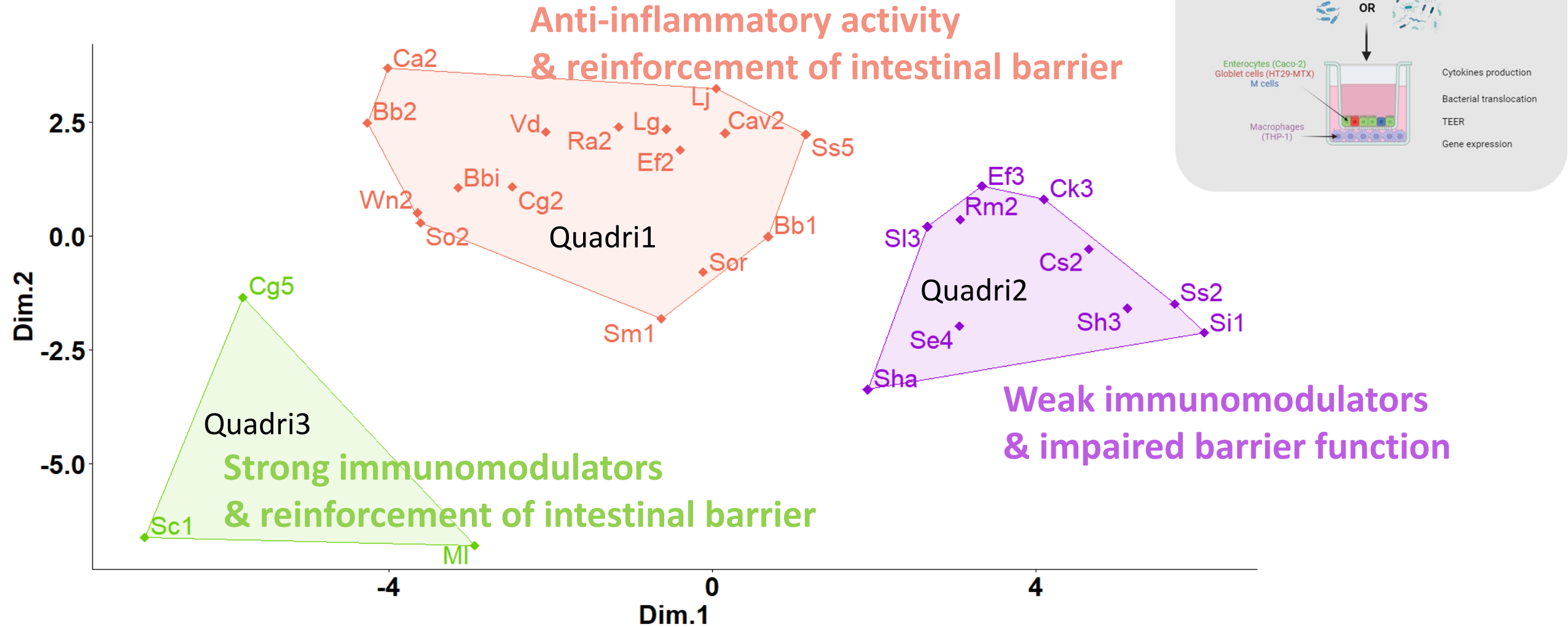
Macrophages (THP-1)



- Cytokines production
- Bacterial translocation
- TEER
- Gene expression

# Individual impact of HM bacteria on immune and barrier functions

Classification by *MultiDimensionate Scaling*



# Immune and barrier properties of the 2 SynComs

*sPLS-DA analysis*

Design of 2 Synthetic Communities :

- ➔ Mimicking HM microbiota
- ➔ With different functional properties

## SynCom AI

Anti-inflammatory

- Cutibacterium granulosum (Cg2)
- Staphylococcus haemolyticus (Sha)
- Winkia neuui (Wn2)
- Streptococcus infantis (Si1)
- Cutibacterium acnes (Ca2)
- Corynebacterium simulans (Cs2)
- Bifidobacterium breve (Bb1)
- Lactobacillus gasseri (Lg)

## SynCom HI

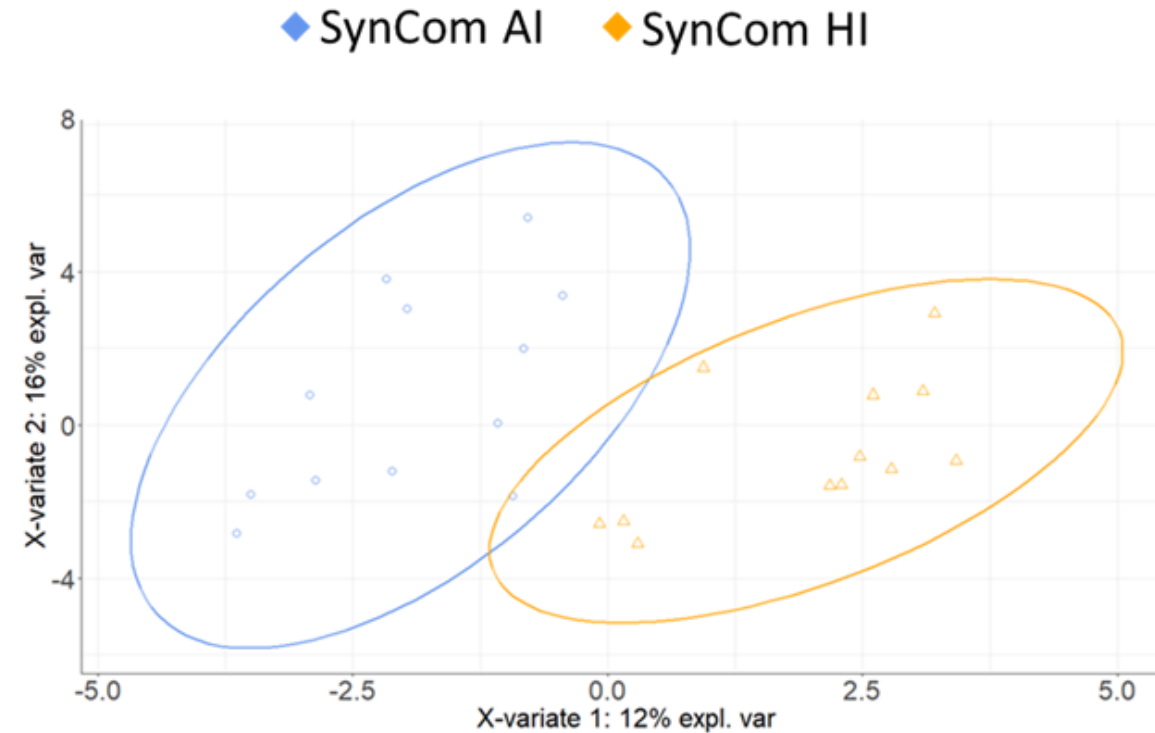
Strong immunomodulatory

- Cutibacterium granulosum (Cg5)
- Staphylococcus capitis (Sc1)
- Micrococcus luteus (Ml)
- Staphylococcus epidermidis (Se4)
- Streptococcus salivarius (Ss2)
- Corynebacterium kroppenstedtii (Ck3)
- Bifidobacterium breve (Bb2)
- Lactobacillus jensenii (Lj)

Anti-inflammatory

Common strains

- Rothia mucilaginosa (Rm2)
- Veillonella dispar (Vd)
- Bifidobacterium bifidum (Bbi)



- Contrasted immunomodulatory properties as expected from the assembly
- New properties that differed from those of the individual bacteria

# Conclusion

- The profile of HM bacterial SynComs reflected the coexistence of specific bacterial profiles that comprise the HM microbiota, leading to its role in driving gut homeostasis
- The functional properties of the HM bacterial community relied on a combination of strain-specific features rather than on the taxonomic composition itself



# Questions & Answers



# In silico modeling of host-lactic acid bacteria interactions at the Epithelial Intestinal Barrier

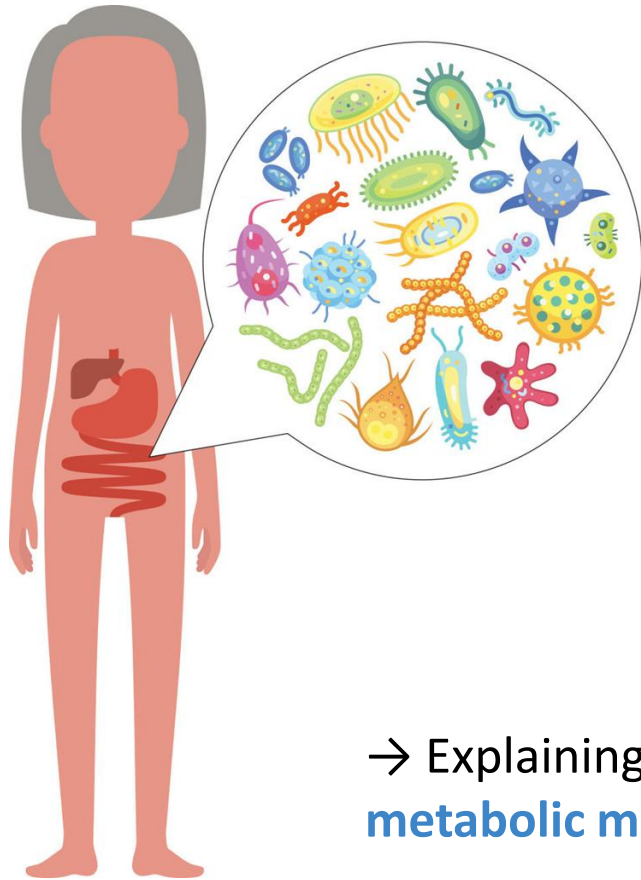
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Anna LAMBERT

**LS2N & TENS laboratories**

# The host - microbiota ecosystem

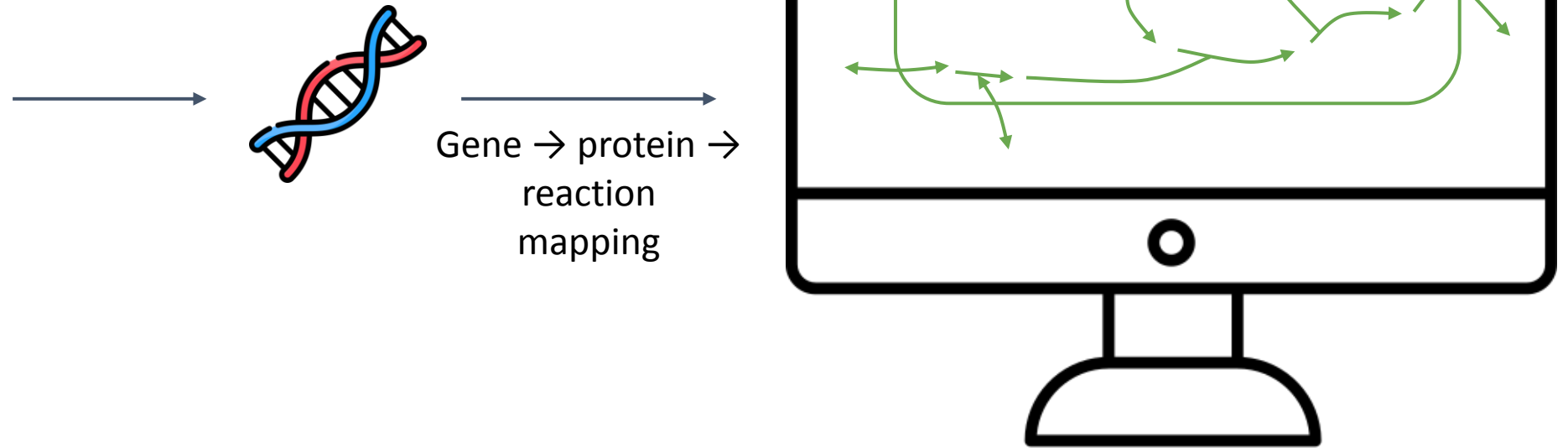


- The gut microbiota is a complex ecosystem
- It impacts our health in several ways, notably through metabolism (e.g. production of vitamins or butyrate)
- Mechanisms of action of many bacteria remains unclear

→ Explaining the influence of gut bacteria on the host using **computational metabolic models**



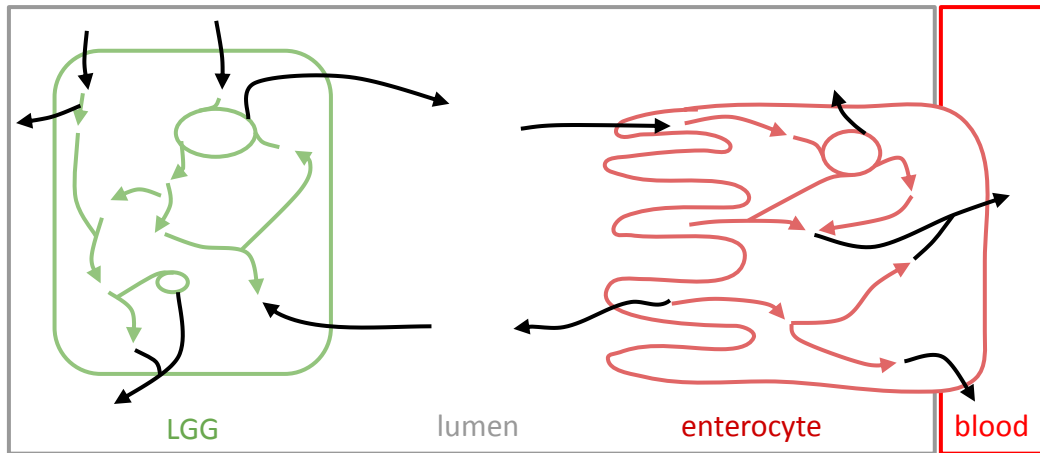
# Metabolic modeling



**Metabolic model** : Informatic reproduction of the metabolic network of an organism



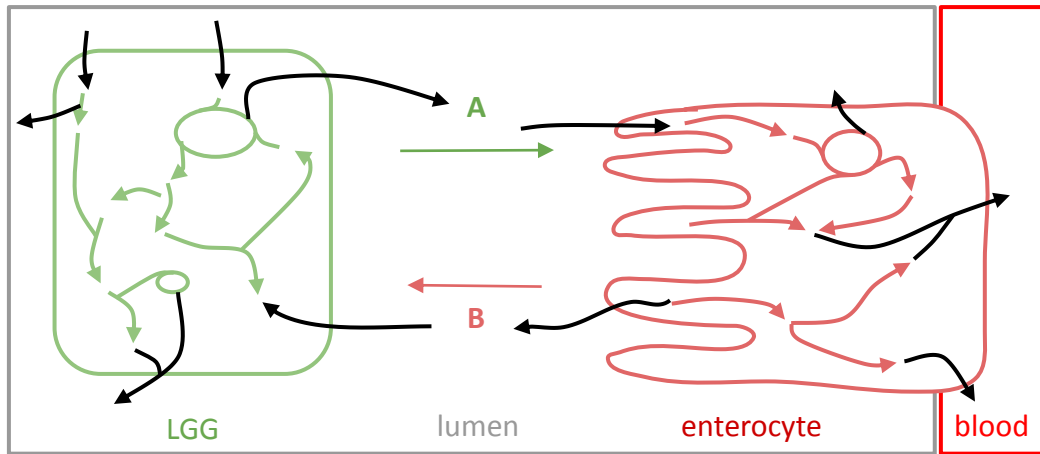
# Exploration of ecosystem interaction



- Interaction score  
(competition, neutrality, mutualism)

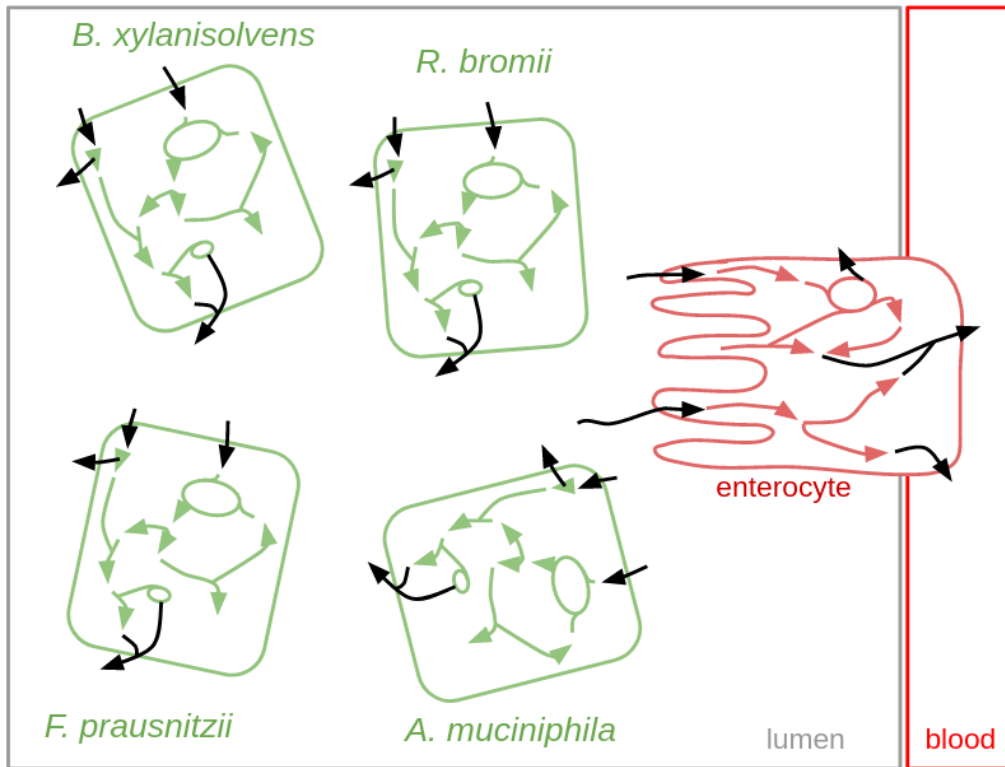


# Exploration of ecosystem interaction



- Interaction score (competition, neutrality, mutualism)
- Cross-fed metabolites

# Exploration of ecosystem interaction



- Interaction score (competition, neutrality, mutualism)
- Cross-fed metabolites
- Applied in larger ecosystems

# Questions & Answers



# Combined effects of propionic acid bacteria and n-6 polyunsaturated fatty acids on the intestinal barrier

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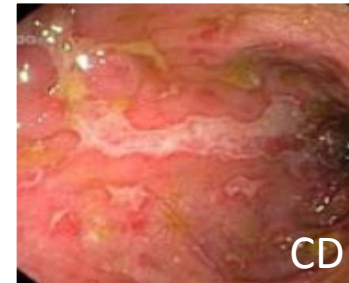


Marine MANTEL  
TENS & STLO laboratories

# Intestinal bowel disease (IBD)



Crohn's disease (CD) and Ulcerative colitis (UC)

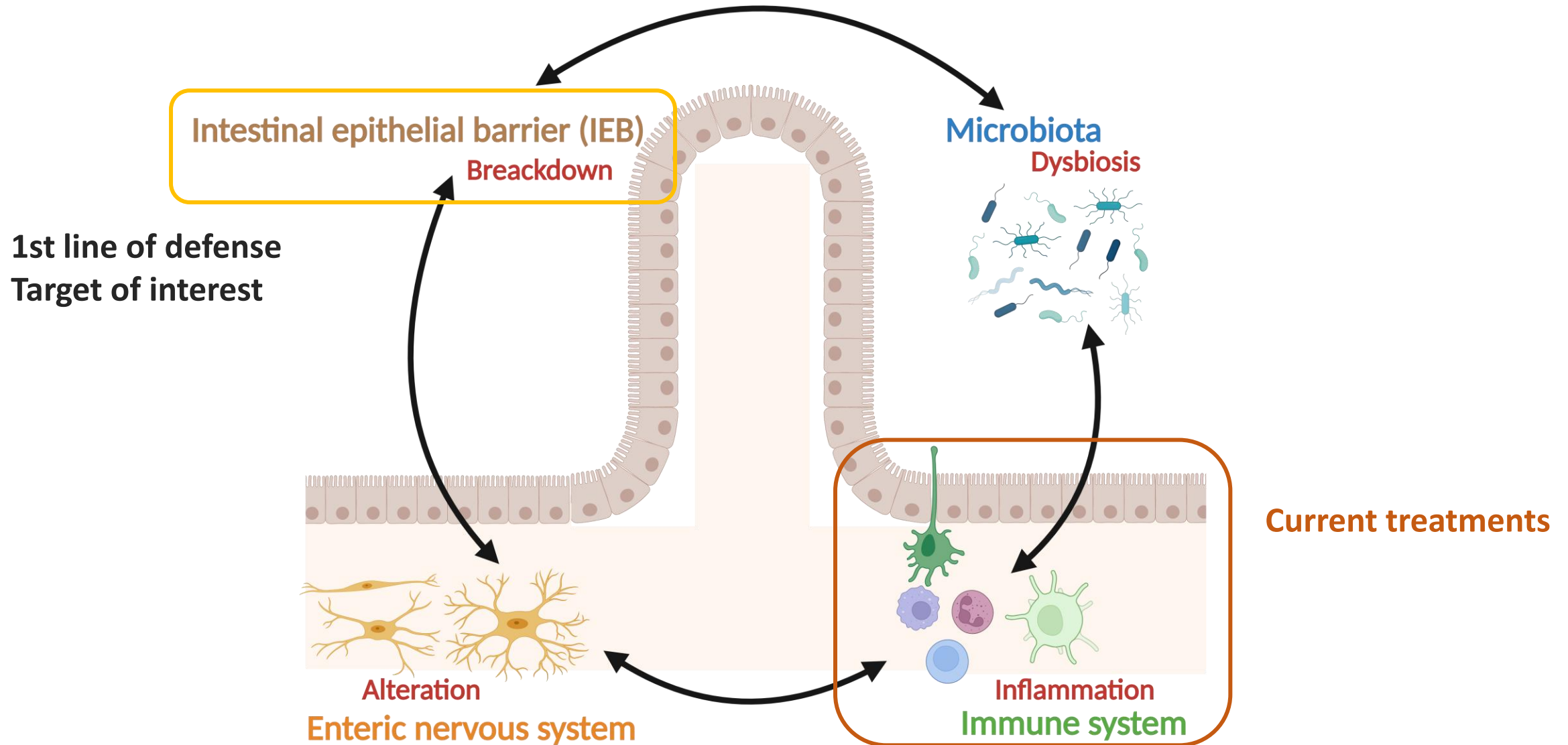


**Chronic inflammation.**

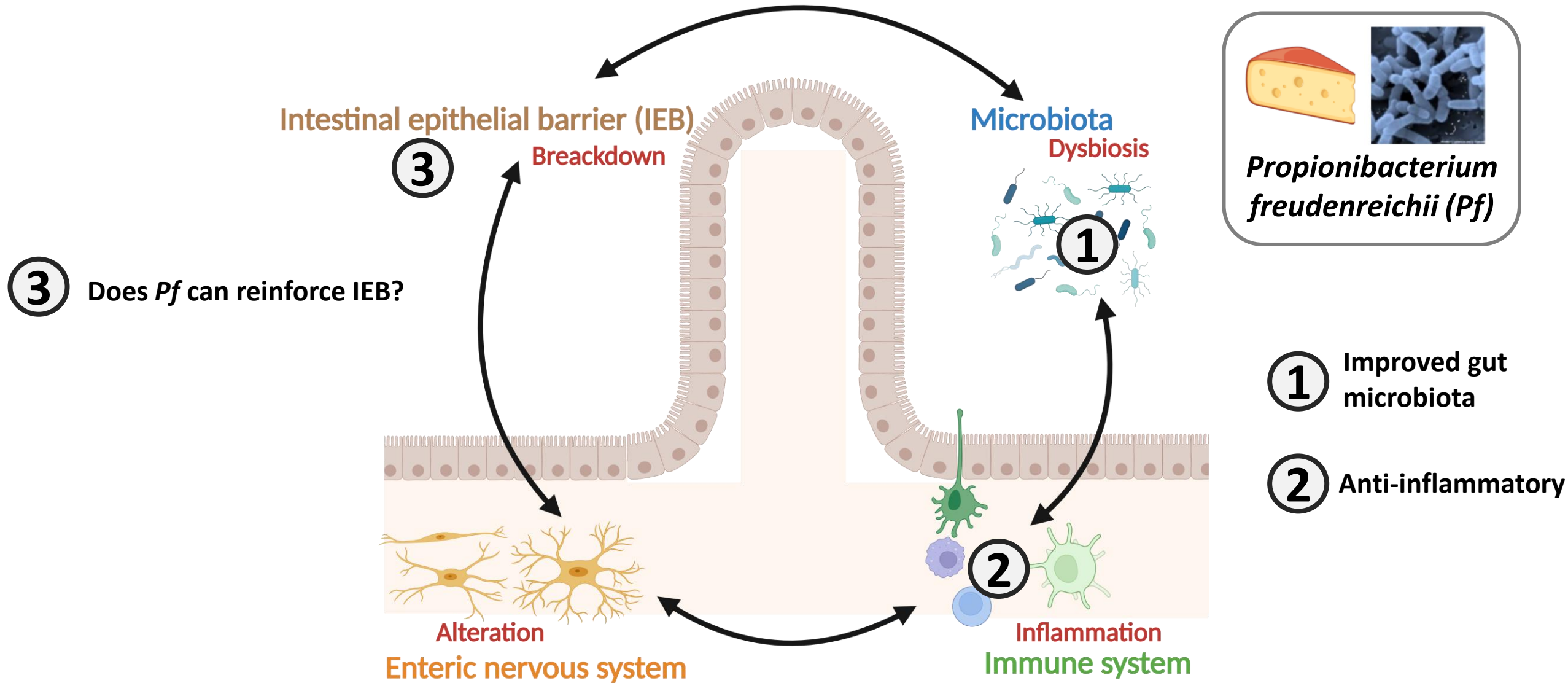
**No curative treatment!**



# Intestinal bowel disease (IBD)



# How to reinforce IEB?

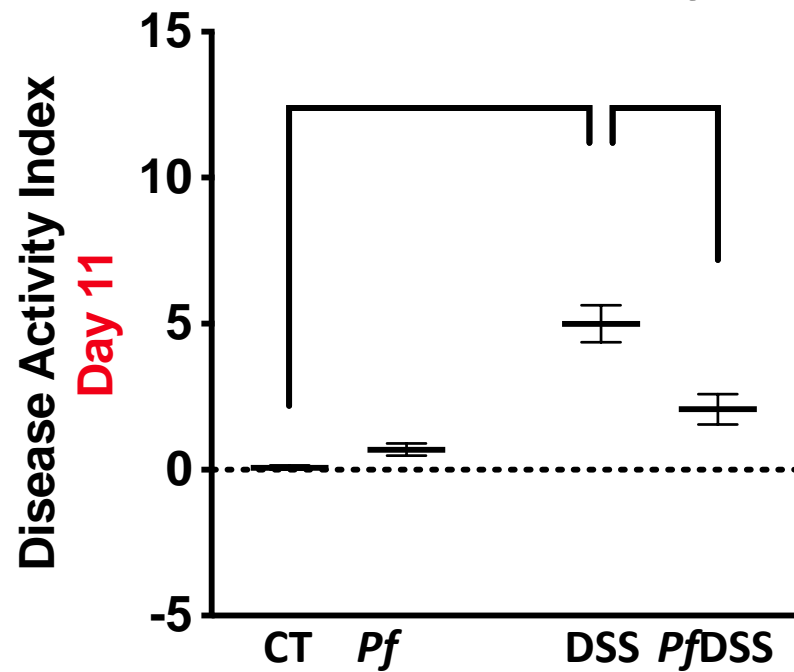


# *Pf* supplementation

## DSS-induced colitis



## Colitis severity

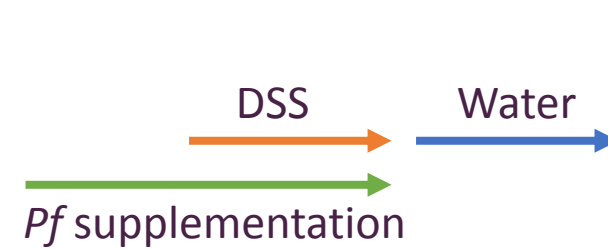
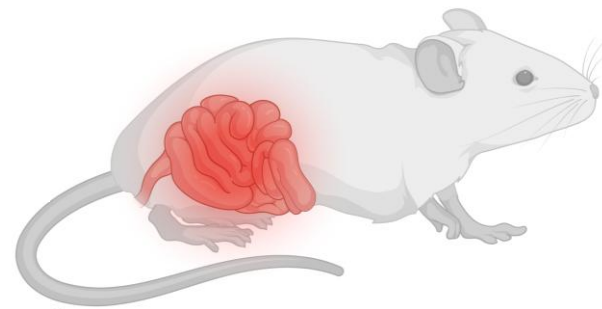


*Pf* prevents colitis severity induced by the DSS.

# *Pf* supplementation

## DSS-induced colitis

### Recovery protocol

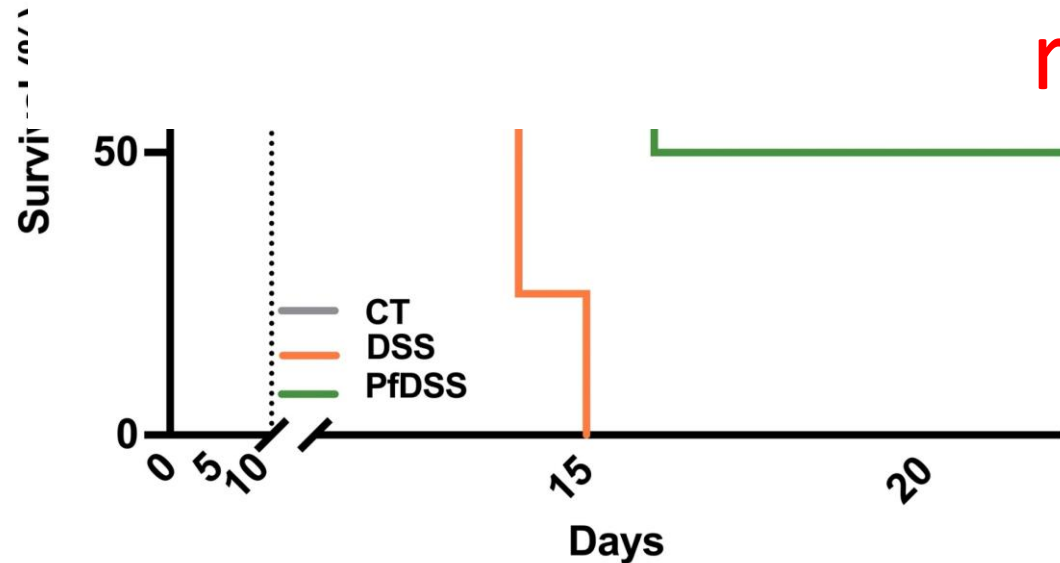


Day 11

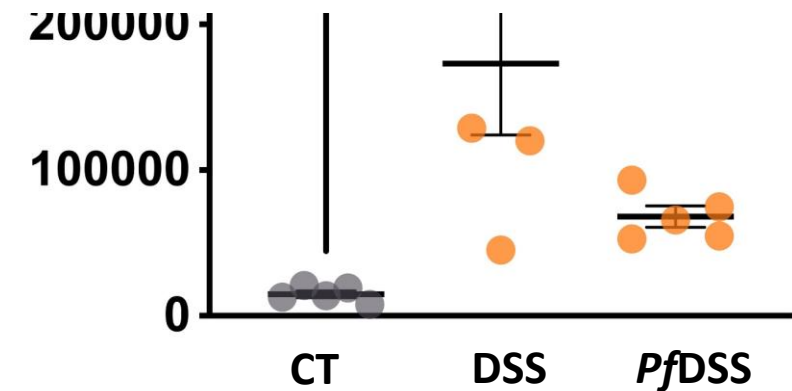
Survival

Intestinal permeability

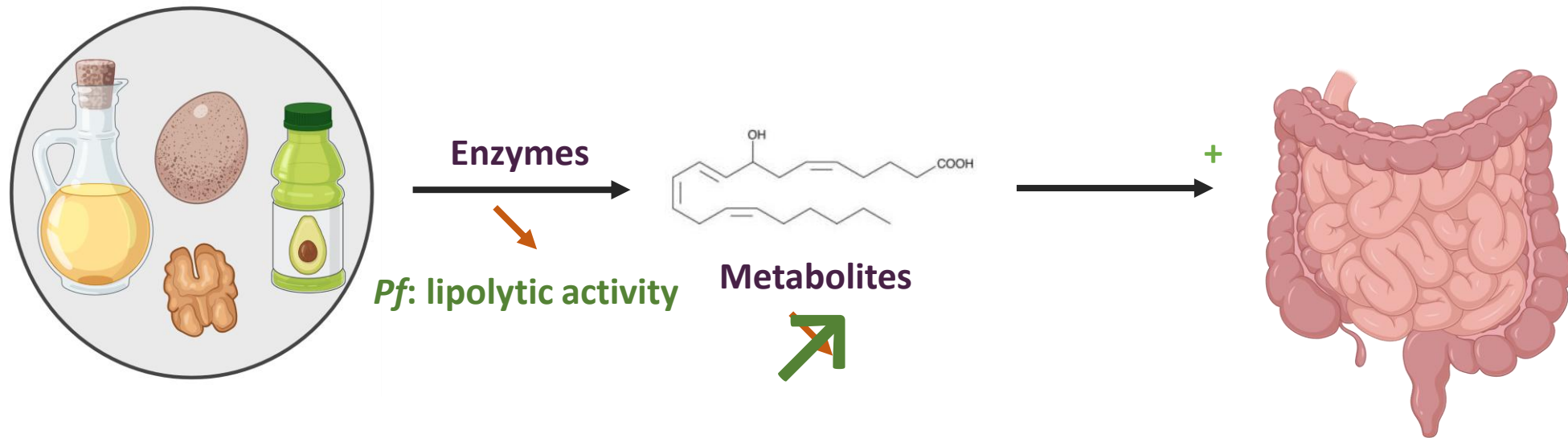
*Pf* decreases intestinal permeability and improves recovery.



Sulfonic acid  
abitar  
Day



# N-6 diet: good for the gut?



**Disruption of n-6 metabolism in IBD patients.**

Combine protective effects of n-6 enriched diet and *Pf*?

*Pf* supplementation  
N-6 enriched diet

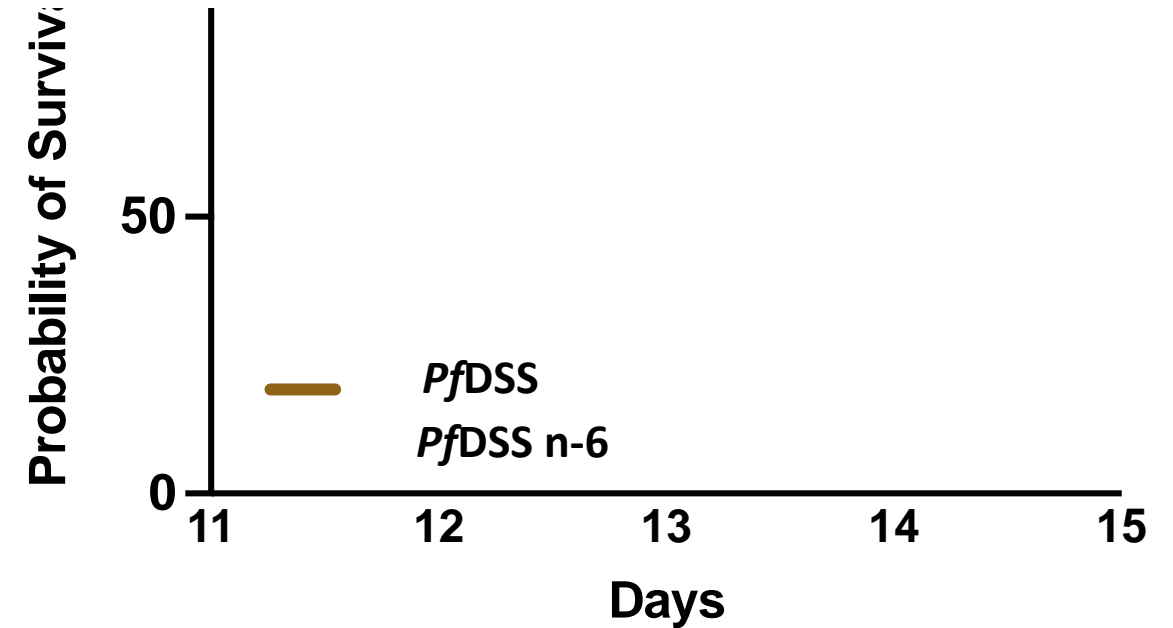
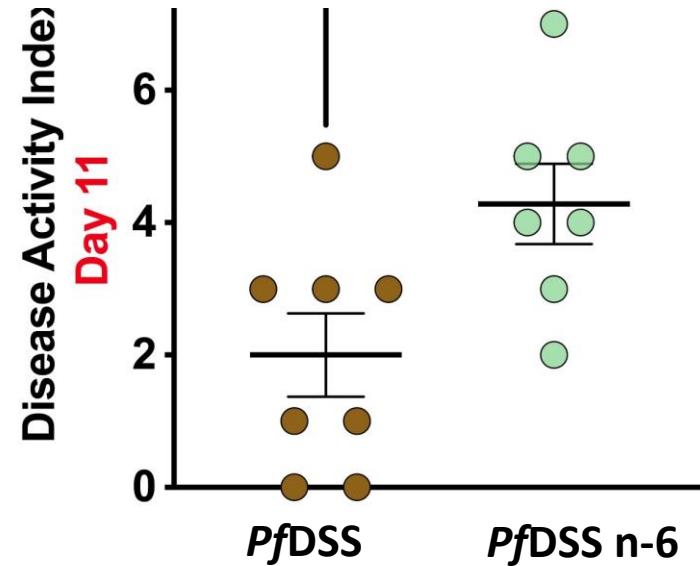
Recovery protocol



Colitis severity

Survival

N-6 enriched diet abrogates *Pf* protective effects.



# Take home message

- 1) *Pf* reinforces IEB
- 2) *Pf* improves recovery and inhibits colitis
- 3) N-6 enriched diet abrogates *Pf* protective effects

Taking the patient's nutritional profile into account is essential  
when integrating probiotics !



# Questions & Answers



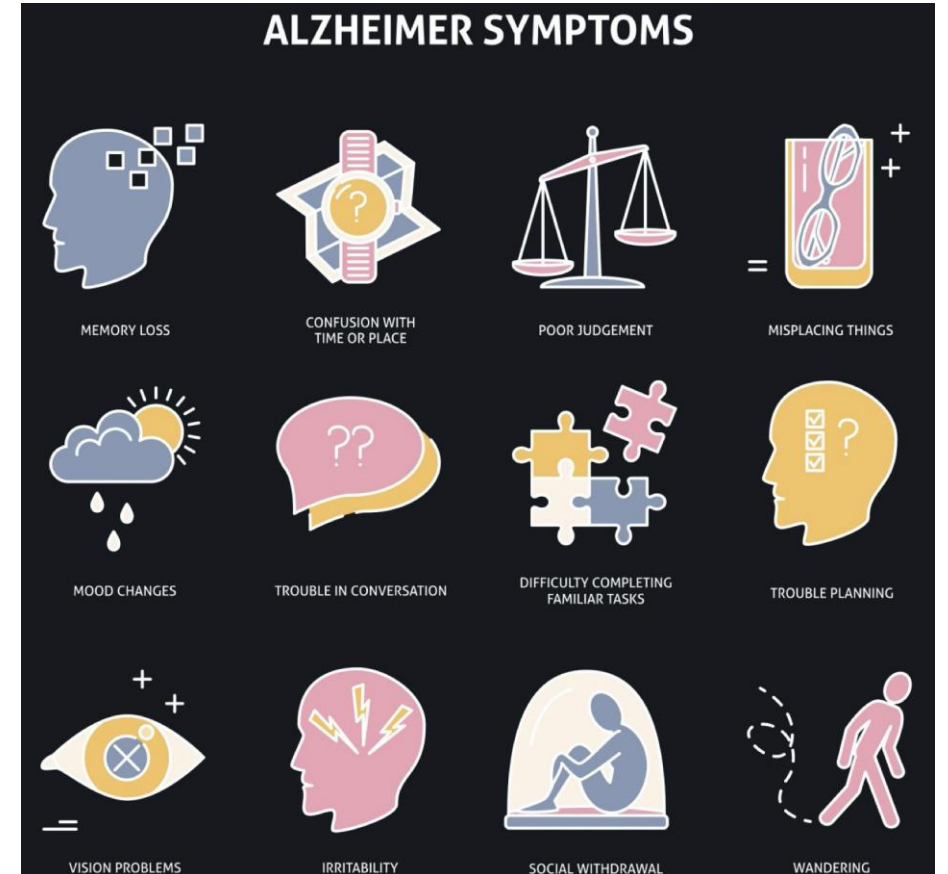
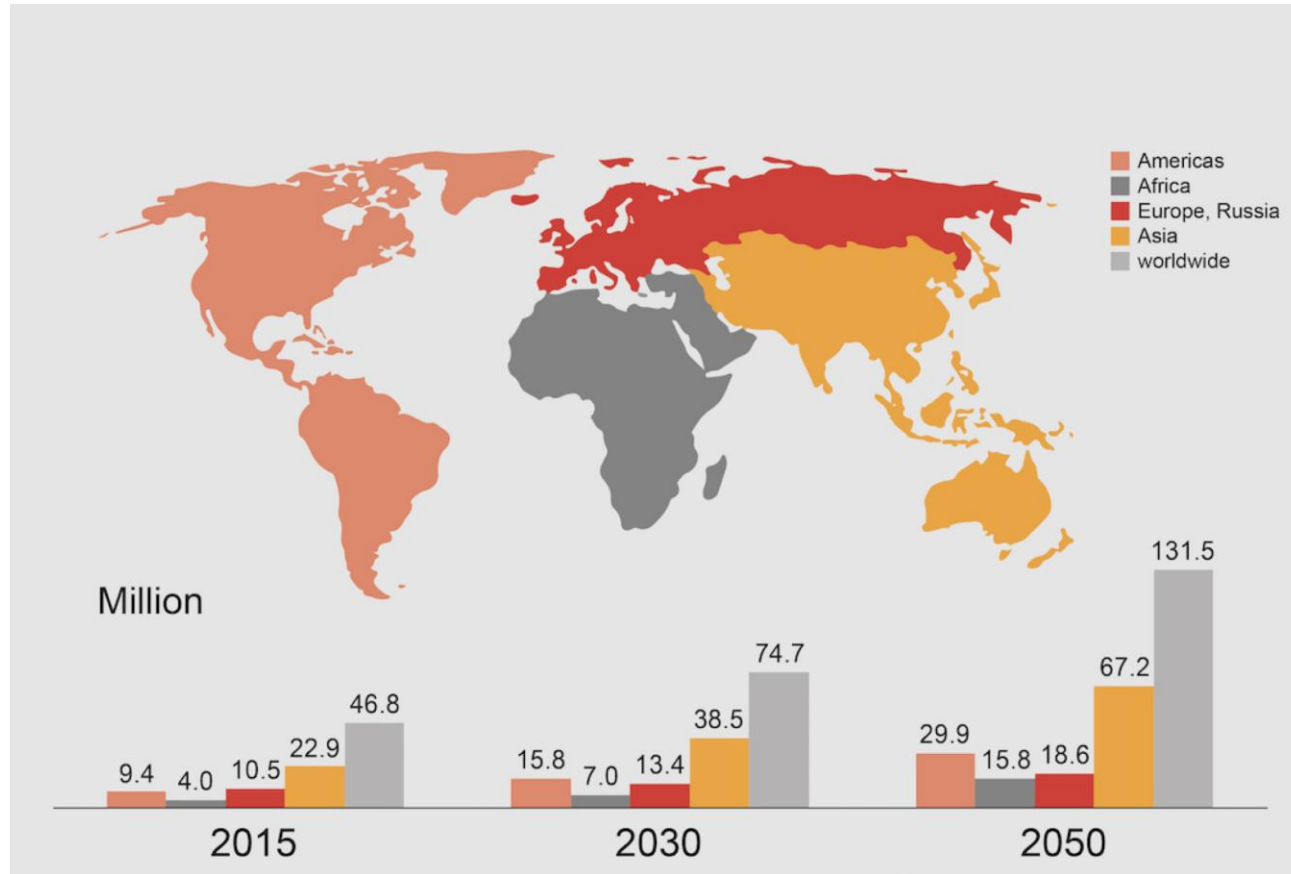
# What are the beneficial effects of bacterial metabolites on cognitive and digestive functions in Alzheimer's disease ?

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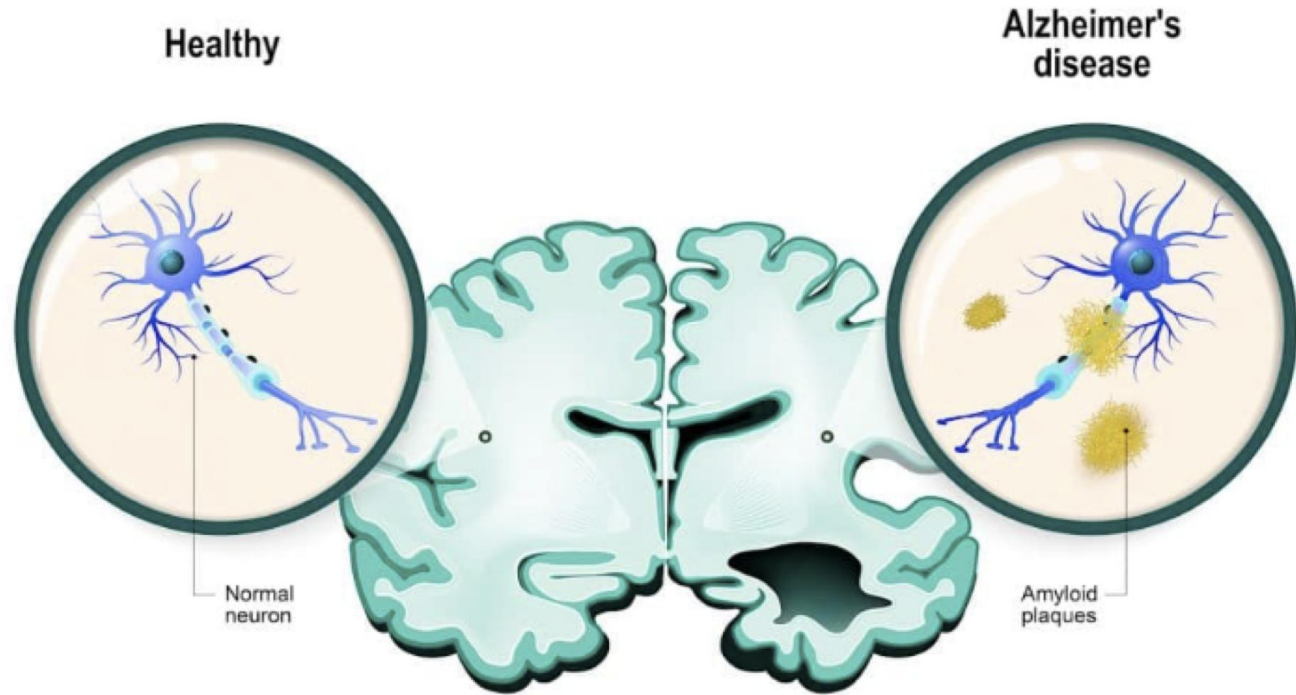
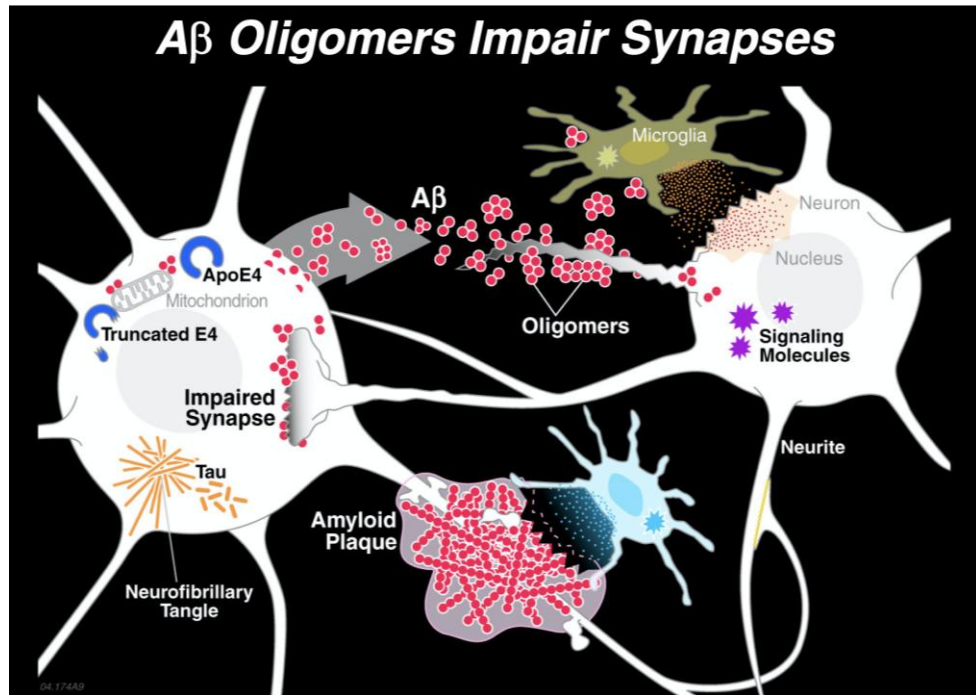


Rodrigue BROSSAUD  
**TENS & STLO laboratories**

# Alzheimer's disease : epidemiology and symptoms

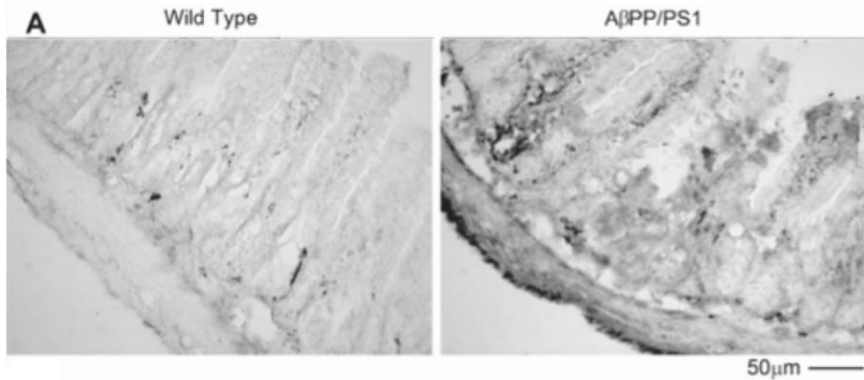


# Alzheimer's disease : Amyloid- $\beta$ toxicity

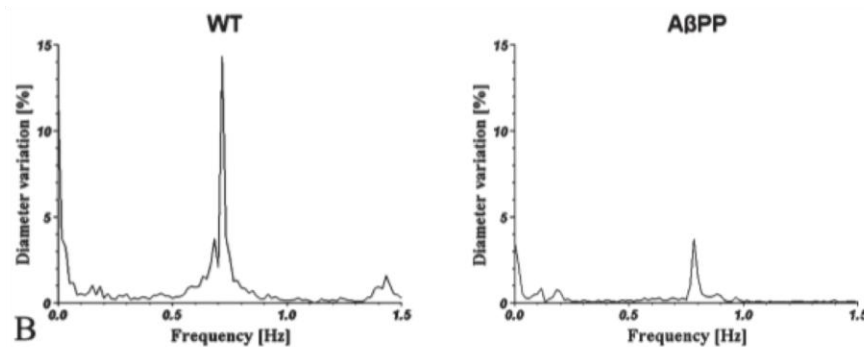


# Alzheimer's disease : A gut-brain disease ?

## Animal models

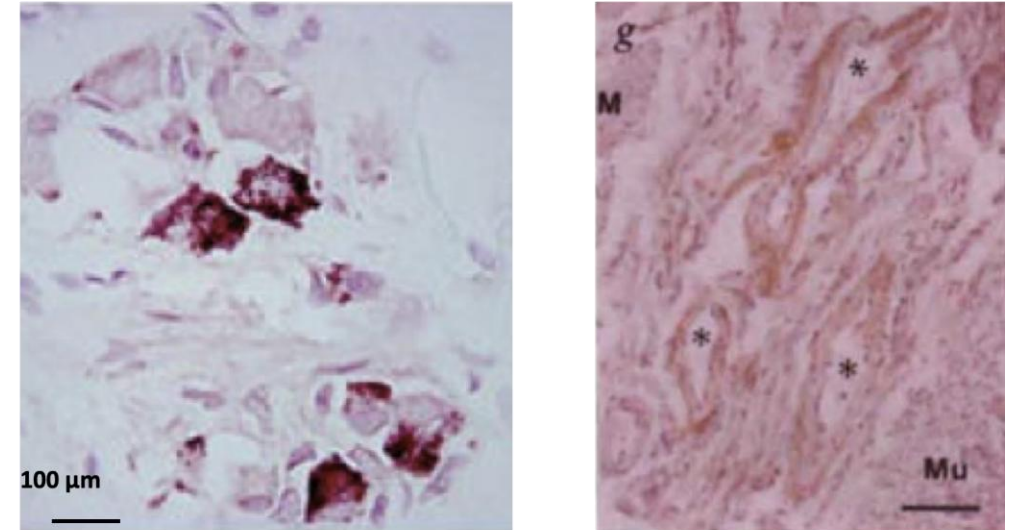


- Intestinal amyloid aggregates  
(Puig et al., 2015)



- Impairments of digestive motricity  
(Semar et al., 2013)

## Humans



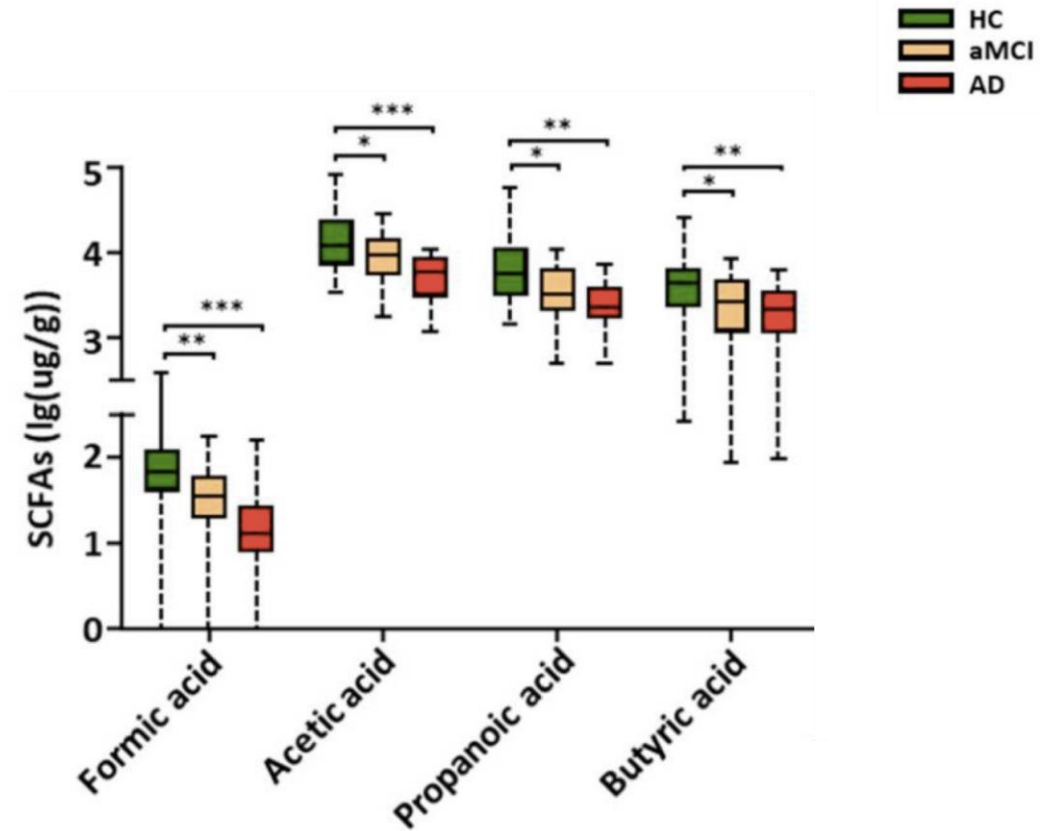
- Intestinal amyloid aggregates  
(Joachim et al., 1989 ; Puig et al., 2015)

# Alzheimer's disease : A gut-brain disease ?

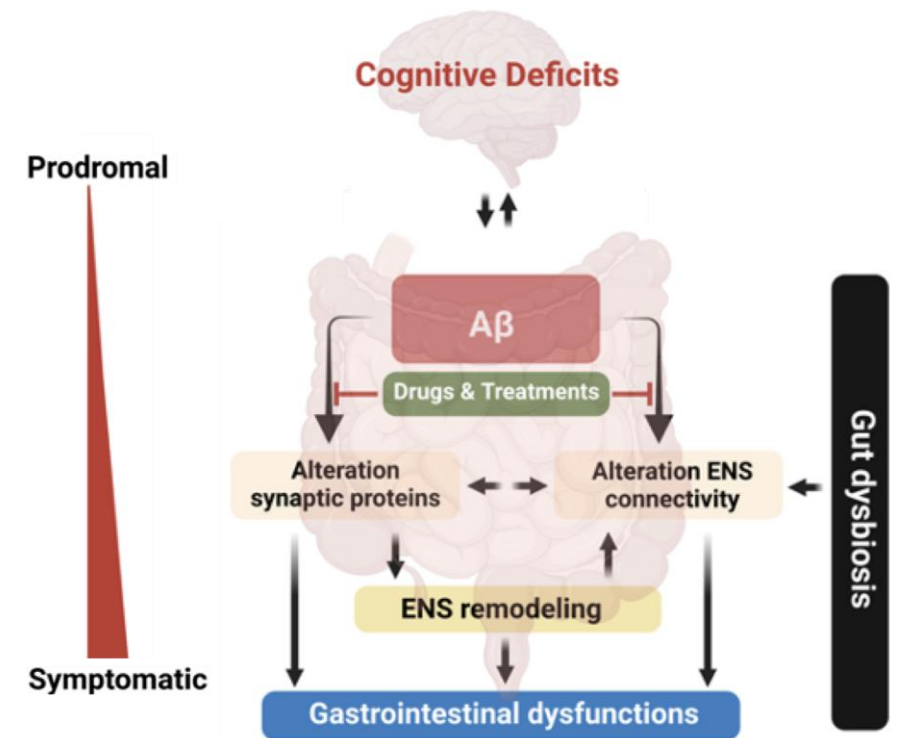
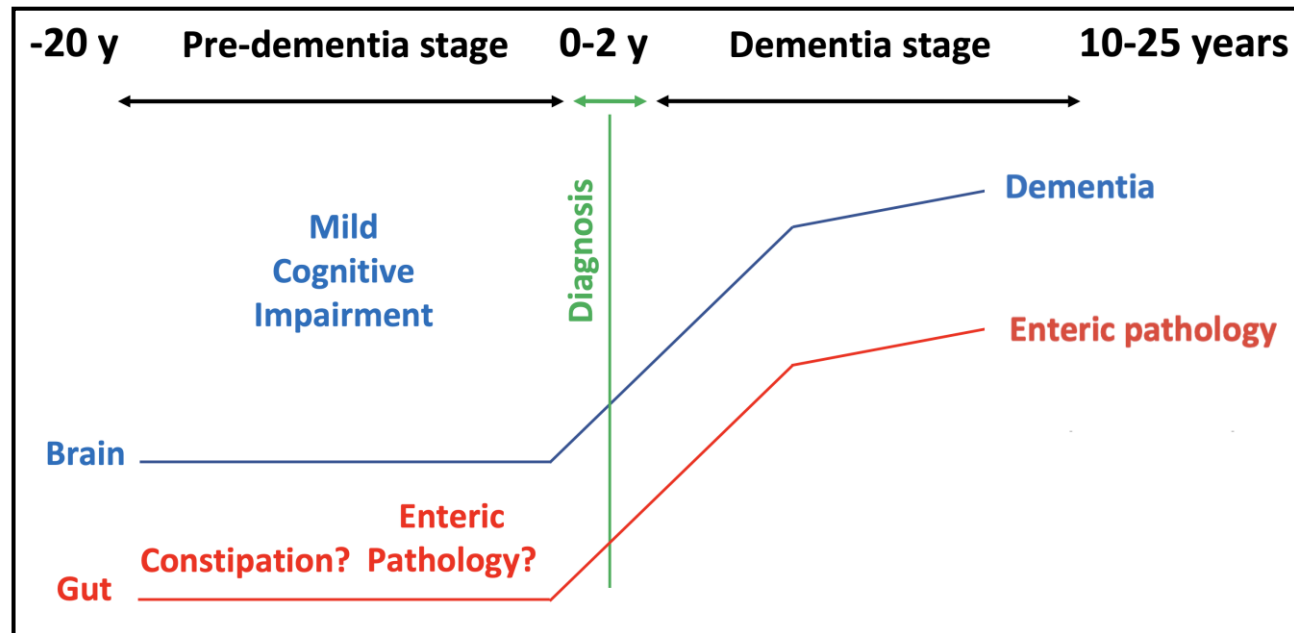
	Diagnosis within 0-2 years				Diagnosis within 2-10 years			
	UK		France		UK		France	
	OR (corrected 95% CI)	Corrected p value	OR (corrected 95% CI)	Corrected p value	OR (corrected 95% CI)	Corrected p value	OR (corrected 95% CI)	Corrected p value
Major depressive disorder, F32	2.14 (1.77-2.59)	<0.0001	3.41 (3.04-3.84)	<0.0001	1.34 (1.15-1.56)	<0.0001	1.73 (1.45-2.07)	<0.0001
Anxiety, F41	2.02 (1.69-2.41)	<0.0001	1.93 (1.71-2.17)	<0.0001	1.36 (1.18-1.56)	<0.0001	1.5 (1.26-1.78)	<0.0001
Reaction to severe stress and adjustment disorders, F43	2.34 (1.76-3.11)	<0.0001	2.1 (1.61-2.75)	<0.0001	1.4 (1.12-1.77)	<0.0001	1.83 (1.36-2.46)	<0.0001
Hearing loss, H91	1.28 (1.07-1.52)	0.0001	1.95 (1.35-2.82)	<0.0001	1.19 (1.04-1.36)	0.0006	1.51 (1.01-2.26)	0.033
Constipation, K59	1.41 (1.23-1.63)	<0.0001	1.66 (1.47-1.87)	<0.0001	1.31 (1.16-1.49)	<0.0001	1.59 (1.33-1.89)	<0.0001
Spondylosis, M47	1.25 (0.93-1.69)	0.933	1.45 (1.22-1.72)	<0.0001	1.26 (1.05-1.5)	0.0005	1.62 (1.32-1.98)	<0.0001
Memory loss symptom, R41	31.5 (24.18-41.05)	<0.0001	16.5 (10.39-26.19)	<0.0001	7.63 (5.95-9.79)	<0.0001	4.41 (2.3-8.48)	<0.0001
Malaise and fatigue, R53	1.36 (1.17-1.58)	<0.0001	1.78 (1.59-2.0)	<0.0001	1.23 (1.08-1.39)	<0.0001	1.59 (1.36-1.86)	<0.0001
Syncope and collapse, R55	1.95 (1.53-2.48)	<0.0001	2.49 (1.68-3.69)	<0.0001	1.23 (1.01-1.5)	0.034	1.57 (1.06-2.34)	0.007
Abnormal weight loss, R63	2.1 (1.68-2.62)	<0.0001	3.12 (2.41-4.02)	<0.0001	1.47 (1.22-1.77)	<0.0001	1.88 (1.35-2.62)	<0.0001

Both CIs and p values were corrected for multiple comparisons. OR=odds ratio. \*Cannot be calculated because an insufficient number of presentations w

**Table 2: ORs for all variables individually associated with a future diagnosis of Alzheimer's disease in the 2-10 years before diagnosis**



- Early GI disorders in AD patients (*Nedelec et al., 2022*)
- Early GI disorders ↗ the risk of developing severe AD (*Nakase et al., 2022*)
- Dysbiosis of intestinal microbiota in AD patients (*Liu et al., 2019*)
- Alteration in the composition of metabolites in AD patients (*Wu et al., 2021*)



**What are the beneficial effects of bacterial metabolites on cognitive and digestive functions in Alzheimer's disease ?**

**Are there early digestive impairments in Alzheimer's mouse model ?**



# Are there early digestive impairments in Alzheimer's mouse model ?

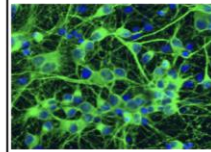
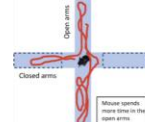
*In vivo* tests  
+ Sacrifice  
(2-month-old group)

*In vivo* tests  
+ Sacrifice  
(6-month-old group)

**Digestive characterization**  
TTT & FPO

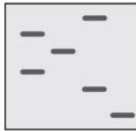


**Cognitive characterization**  
Open field & NOR



**IHC**

Neuronal density & connectivity  
*Aβ* deposits  
(*Aβ*, *Hu*, *Tuj*)



**Western-Blot**

Neuronal connectivity  
(*EphB2*, *SAPs*)

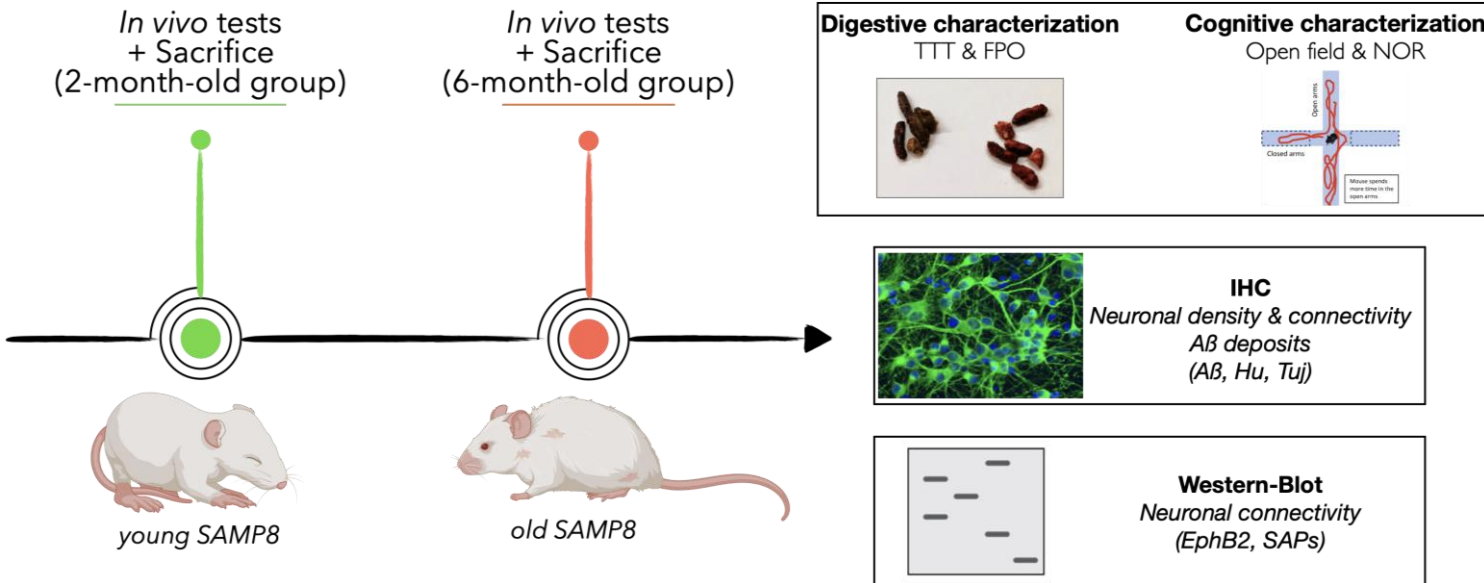


young SAMP8



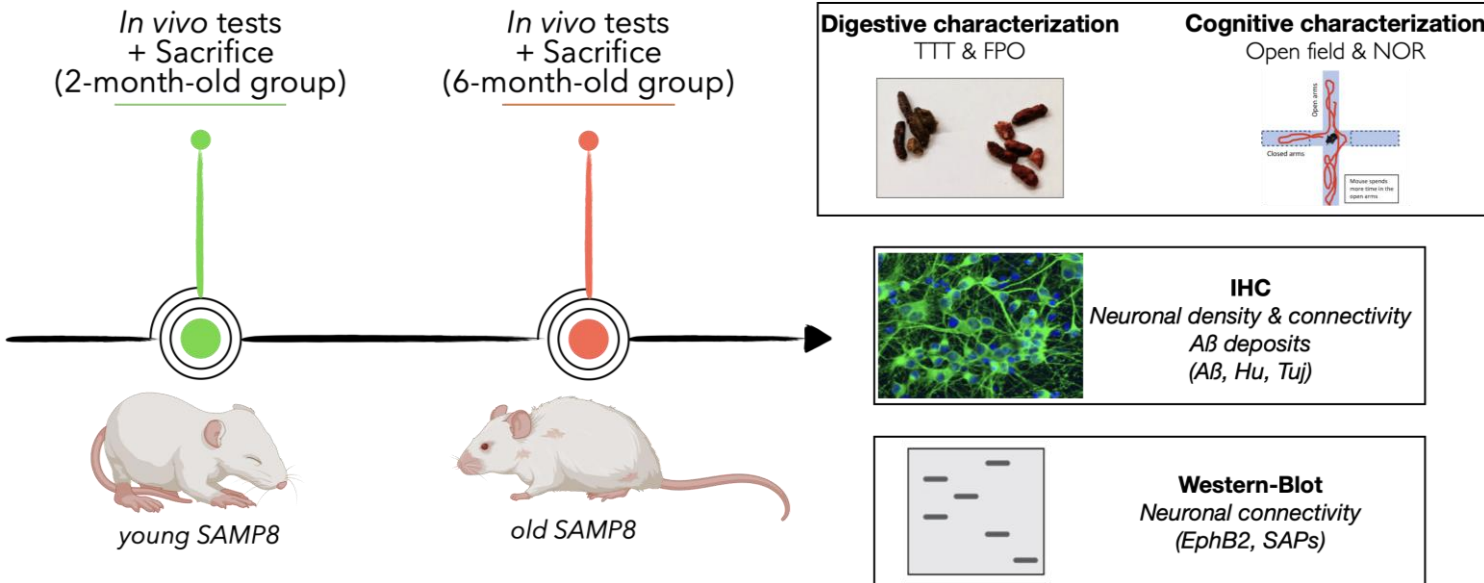
old SAMP8

# Are there early digestive impairments in Alzheimer's mouse model ?



- Constipation and alterations in transit velocity as early as 2 months of age (*in vivo*)
- Memory impairments only appear only from the age of 6 months (*in vivo*)
- Amyloid- $\beta$  deposits in the gut at 2 months of age and only from the age of 6 months in the brain (*ex vivo*)
- Synaptic alterations in the ENS at 2 months of age, while they appear in the brain at the age of 6 months (*in vitro*)

# Are there early digestive impairments in Alzheimer's mouse model ?



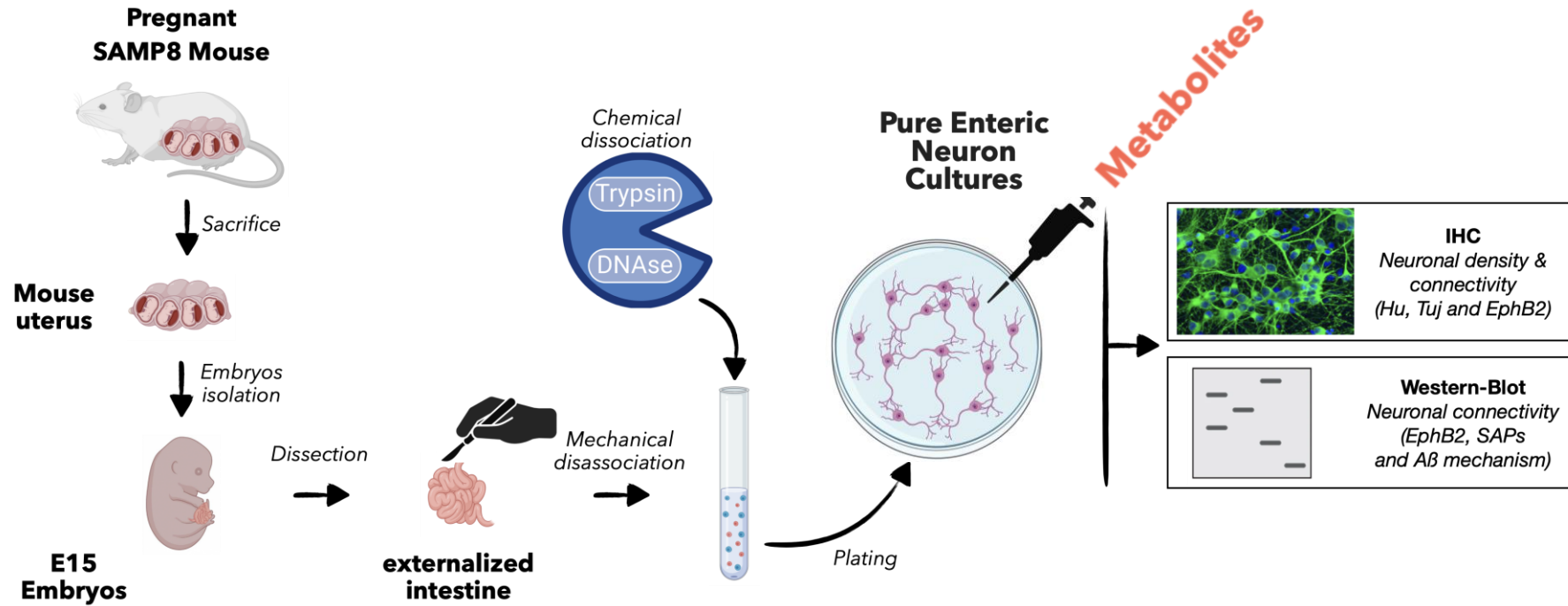
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**There are early digestive impairments in SAMP8 mouse**

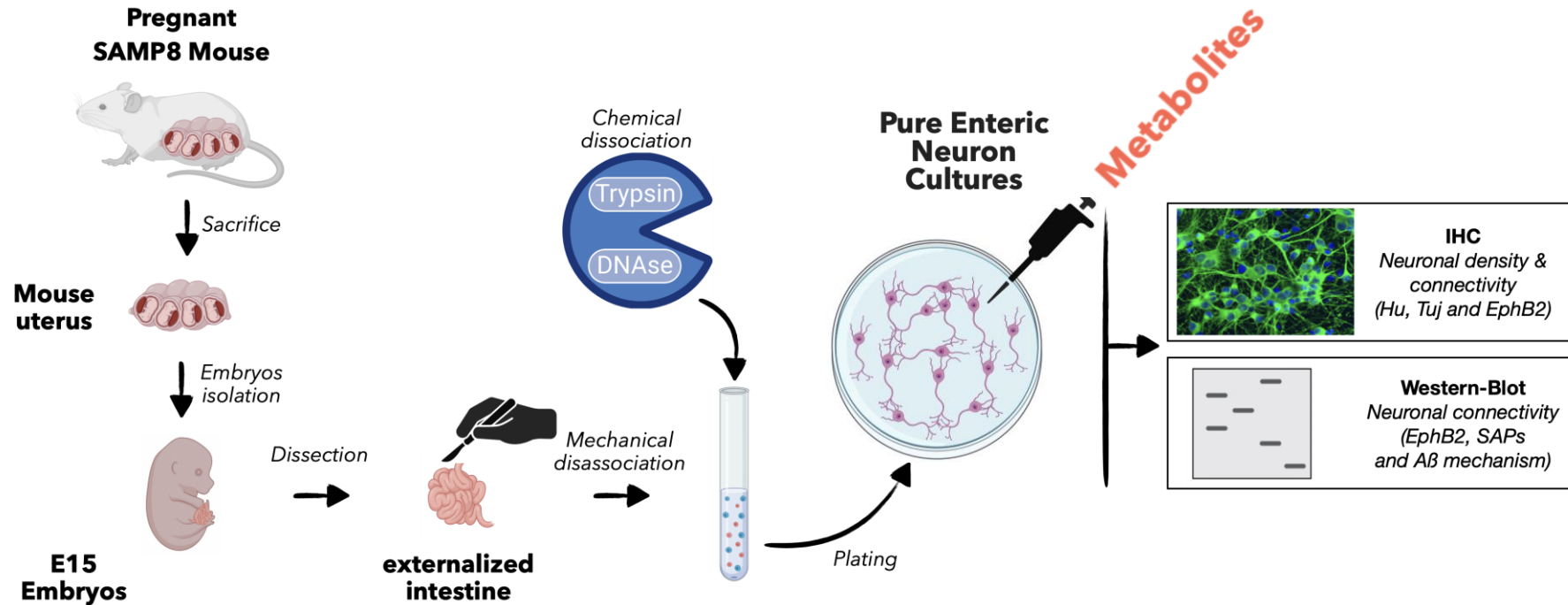
**Which metabolites are capable of improving the enteric neuronal connectivity ?**



# Which metabolites are capable of improving the enteric neuronal connectivity ?



# Which metabolites are capable of improving the enteric neuronal connectivity ?



METABOLITE	BENEFICIAL EFFECTS ?
Acétate	NO
Propionate	NO
Butyrate	YES
Lactate	NO
GABA	NO
Spermine	NO
Spermidine	NO
Kynurénine	NO
Vitamine B9	NO
Vitamine B12	NO

**Butyrate treatment improves the enteric neuronal connectivity *in vitro***

**Could butyrate enhance cognitive and digestive functions in Alzheimer's mouse model ?**



# Could butyrate enhance cognitive and digestive functions in Alzheimer's mouse model ?

*In vivo* tests  
+ Sacrifice  
(2-month-old group)

*In vivo* tests  
+ Sacrifice  
(6-month-old group)

21-day-old  
weaned mouse

young SAMP8

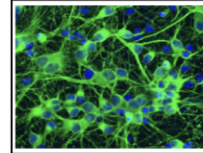
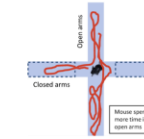
old SAMP8

Butyrate supplementation

**Digestive characterization**  
TTT & FPO



**Cognitive characterization**  
Open field & NOR



**IHC**  
Neuronal density & connectivity  
 $A\beta$  deposits  
( $A\beta$ , Hu, Tuj)



**Western-Blot**  
Neuronal connectivity  
(EphB2, SAPs)

# Could butyrate enhance cognitive and digestive functions in Alzheimer's mouse model ?

*In vivo* tests  
+ Sacrifice  
(2-month-old group)

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21-day-old  
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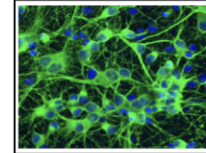
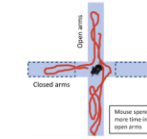
old SAMP8

Butyrate supplementation

**Digestive characterization**  
TTT & FPO



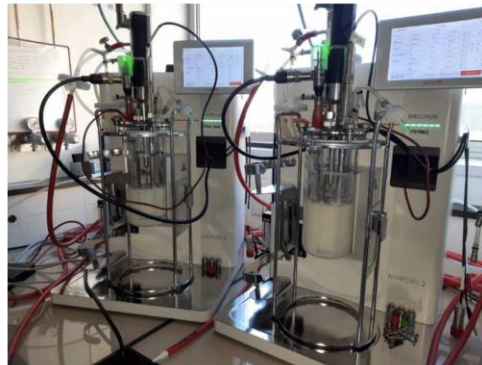
**Cognitive characterization**  
Open field & NOR



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Neuronal density & connectivity  
 $A\beta$  deposits  
( $A\beta$ , Hu, Tuj)



**Western-Blot**  
Neuronal connectivity  
(EphB2, SAPs)



Dr. Hélène Falentin



Marina Giblaine

Butyrate production through milk fermentation  
using a bacterial consortium

# Could butyrate enhance cognitive and digestive functions in Alzheimer's mouse model ?

*In vivo* tests  
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21-day-old  
weaned mouse

young SAMP8

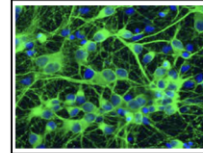
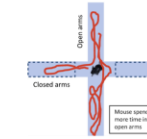
old SAMP8

Butyrate supplementation

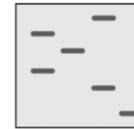
**Digestive characterization**  
TTT & FPO



**Cognitive characterization**  
Open field & NOR



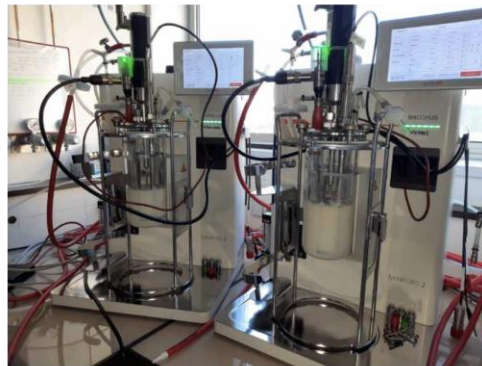
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Work in progress ...



Dr. Hélène Falentin



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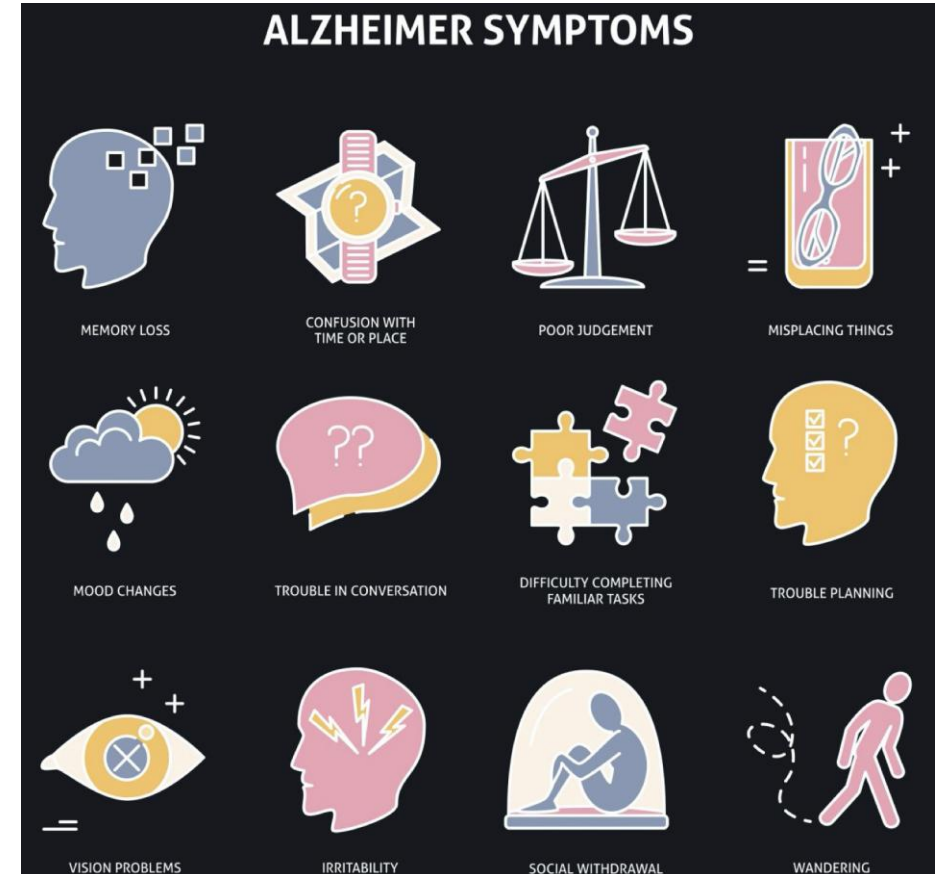
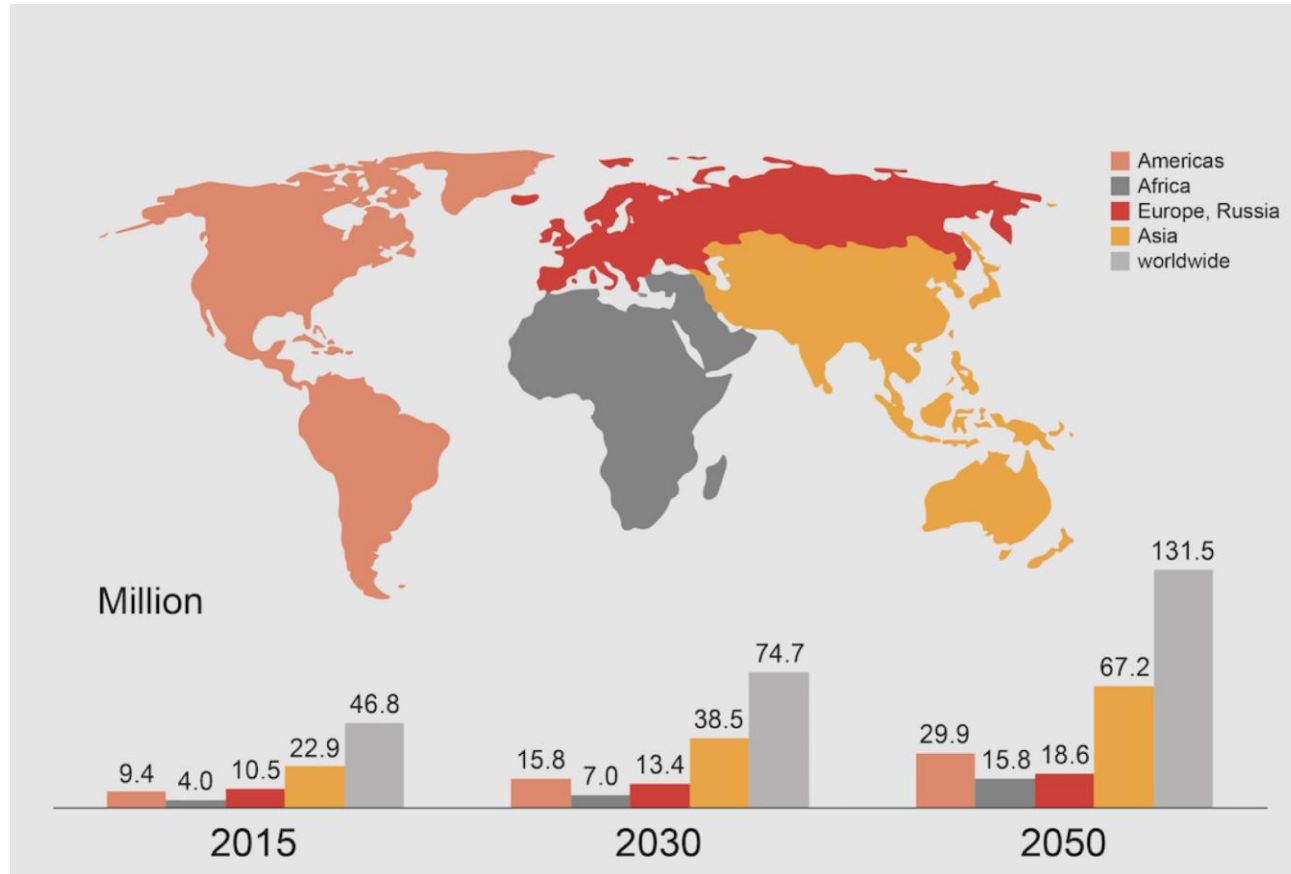
# What are the beneficial effects of bacterial metabolites on cognitive and digestive functions in Alzheimer's disease ?

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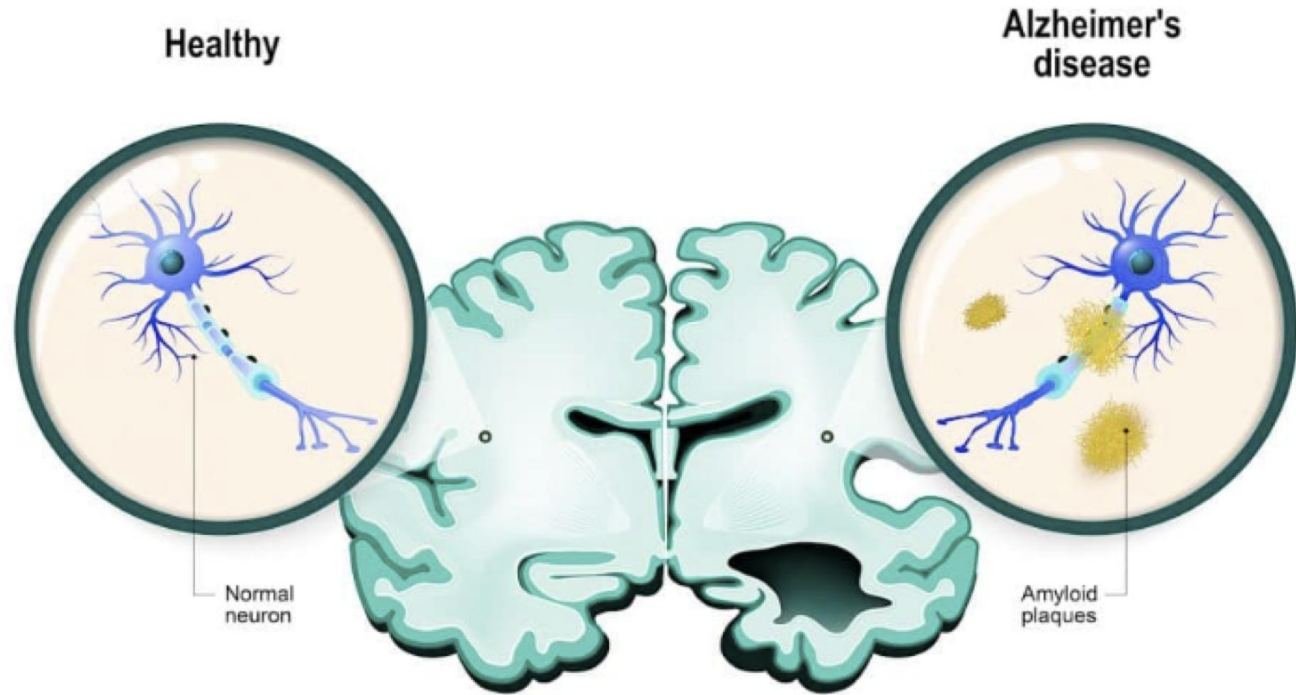
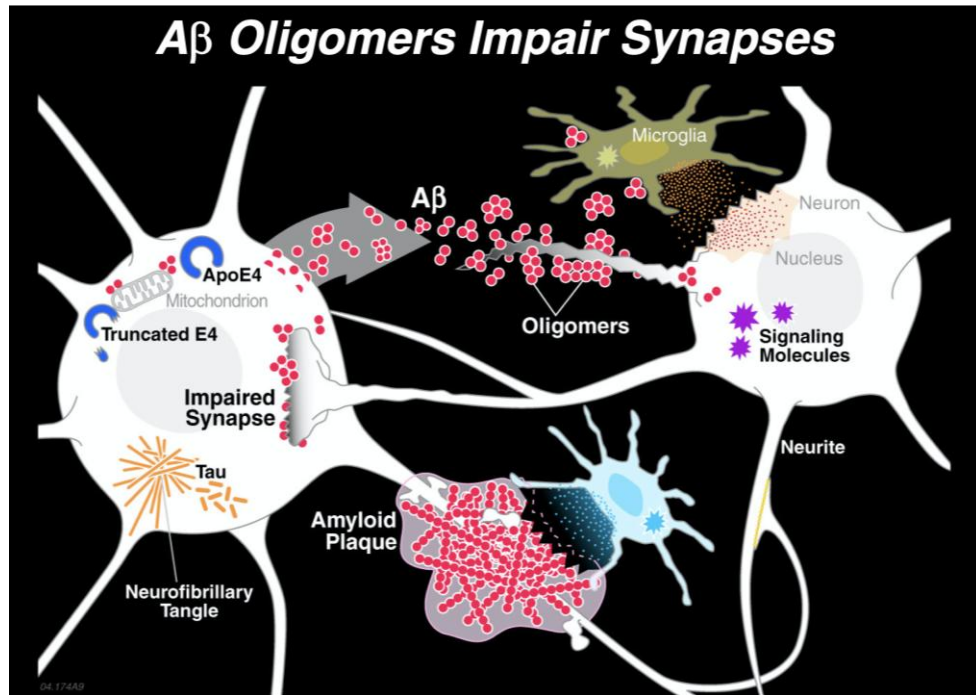


Rodrigue BROSSAUD  
**TENS & STLO laboratories**

# Alzheimer's disease : epidemiology and symptoms

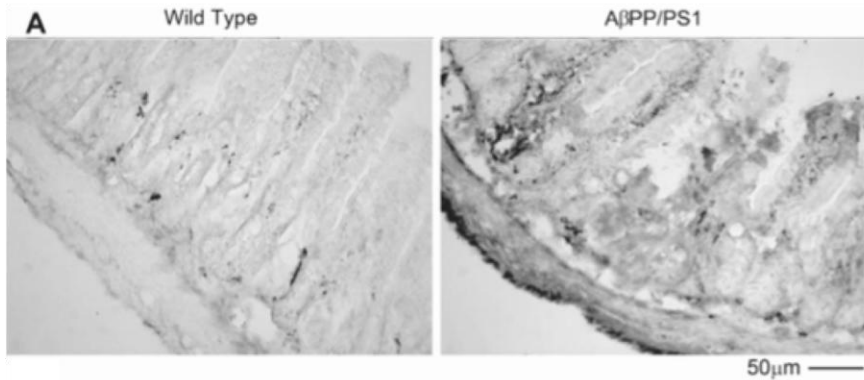


# Alzheimer's disease : Amyloid- $\beta$ toxicity

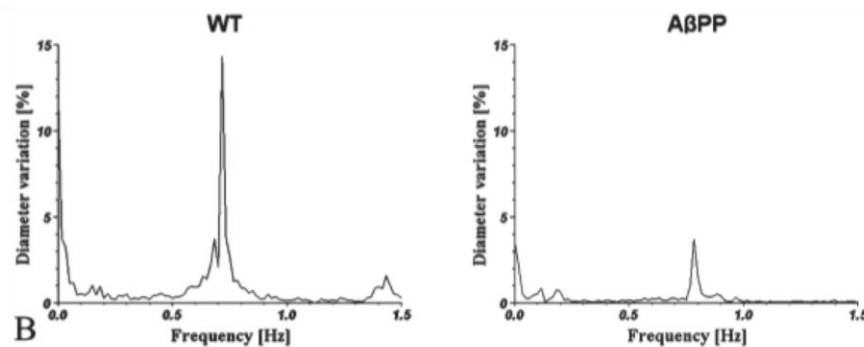


# Alzheimer's disease : A gut-brain disease ?

## Animal models

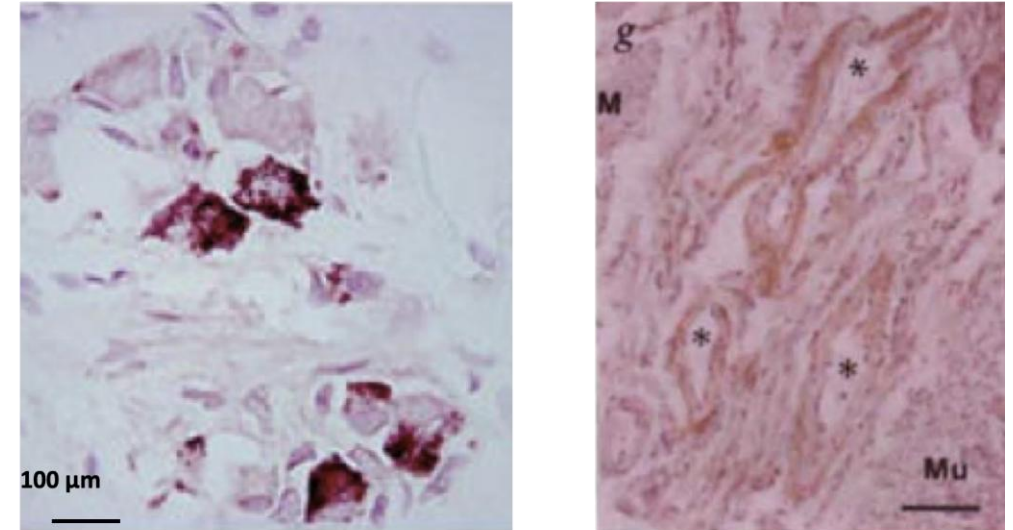


- Intestinal amyloid aggregates  
(Puig et al., 2015)



- Impairments of digestive motricity  
(Semar et al., 2013)

## Humans



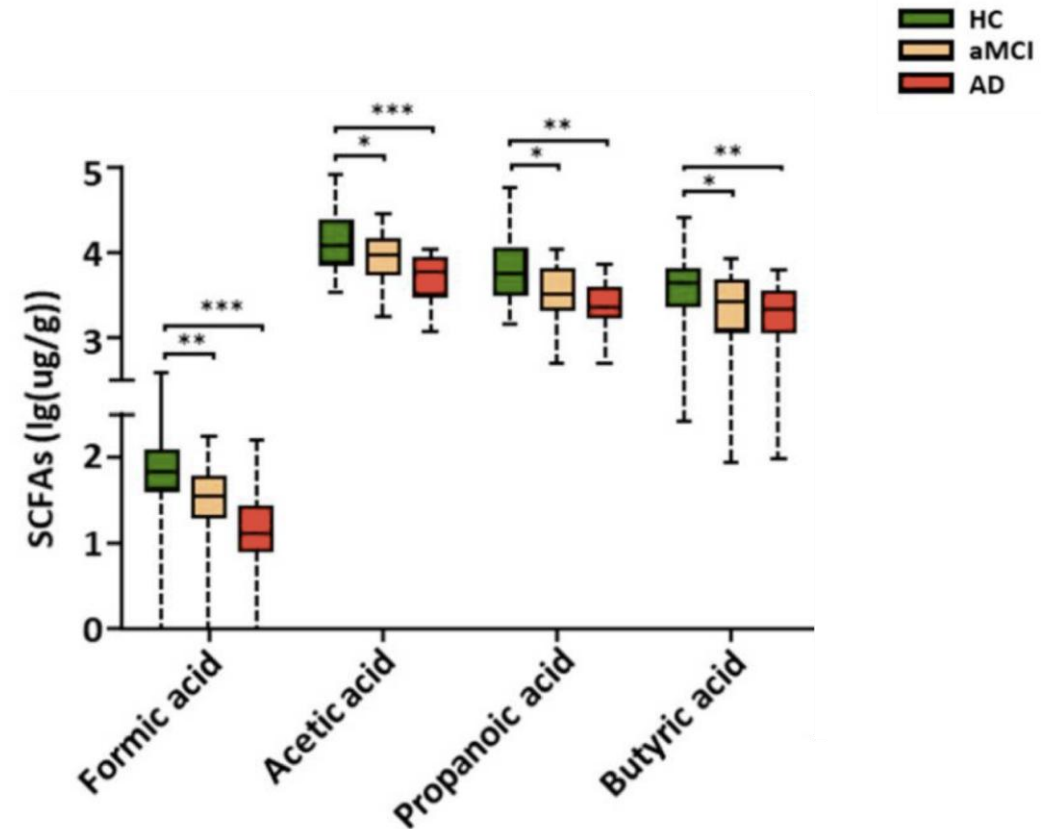
- Intestinal amyloid aggregates  
(Joachim et al., 1989 ; Puig et al., 2015)

# Alzheimer's disease : A gut-brain disease ?

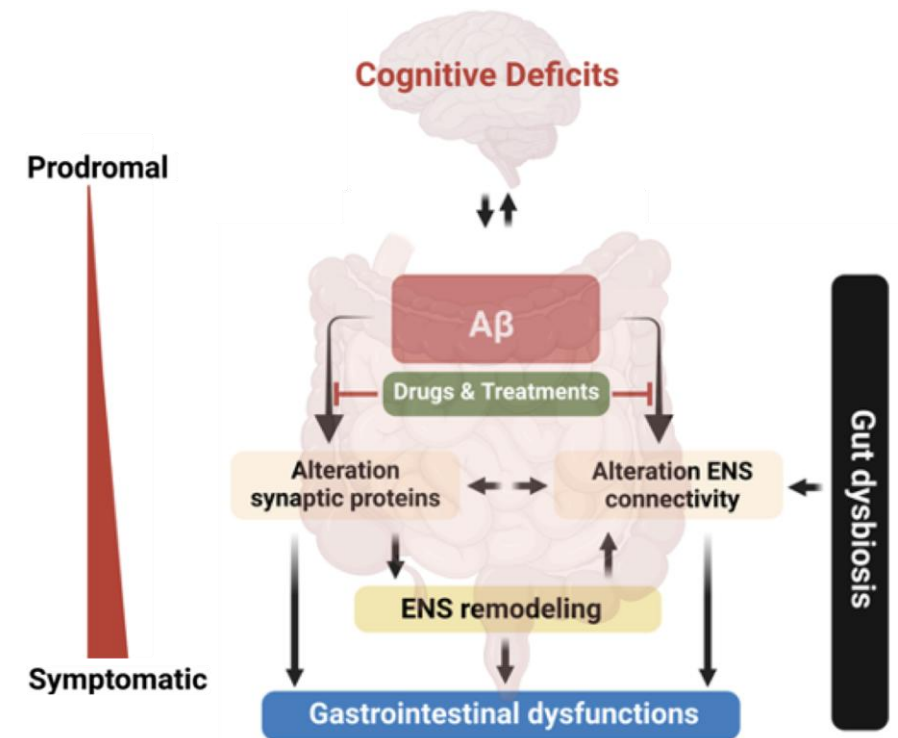
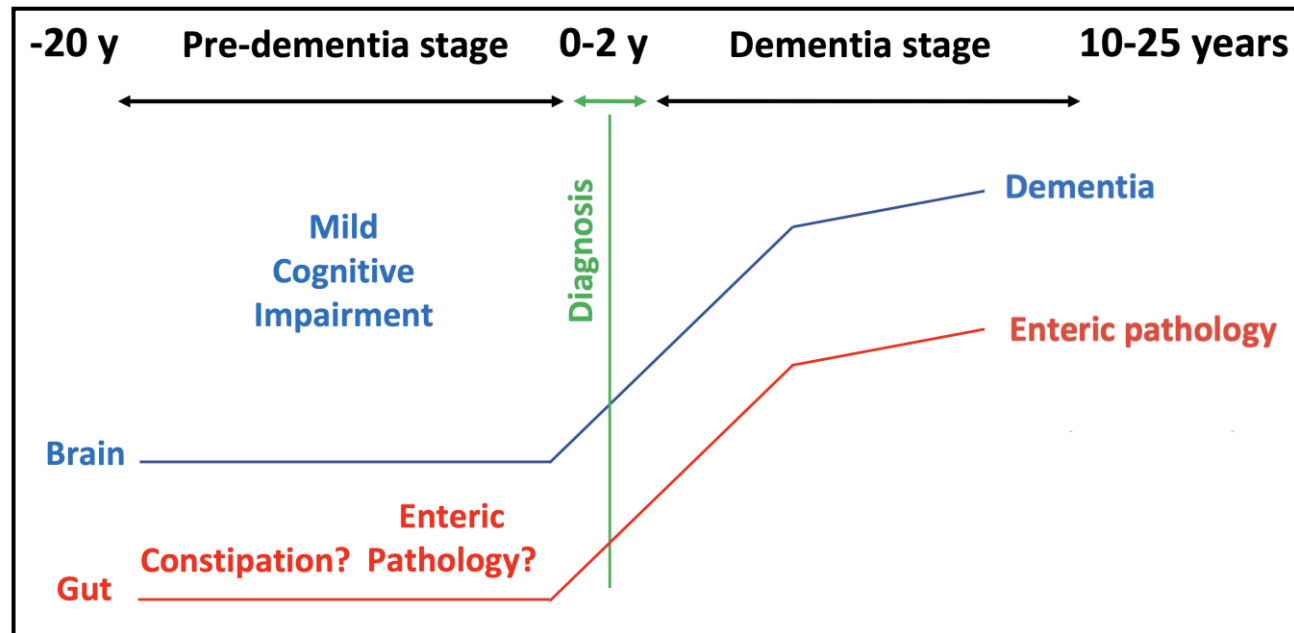
	Diagnosis within 0–2 years				Diagnosis within 2–10 years			
	UK		France		UK		France	
	OR (corrected 95% CI)	Corrected p value	OR (corrected 95% CI)	Corrected p value	OR (corrected 95% CI)	Corrected p value	OR (corrected 95% CI)	Corrected p value
Major depressive disorder, F32	2.14 (1.77–2.59)	<0.0001	3.41 (3.04–3.84)	<0.0001	1.34 (1.15–1.56)	<0.0001	1.73 (1.45–2.07)	<0.0001
Anxiety, F41	2.02 (1.69–2.41)	<0.0001	1.93 (1.71–2.17)	<0.0001	1.36 (1.18–1.56)	<0.0001	1.5 (1.26–1.78)	<0.0001
Reaction to severe stress and adjustment disorders, F43	2.34 (1.76–3.11)	<0.0001	2.1 (1.61–2.75)	<0.0001	1.4 (1.12–1.77)	<0.0001	1.83 (1.36–2.46)	<0.0001
Hearing loss, H91	1.28 (1.07–1.52)	0.0001	1.95 (1.35–2.82)	<0.0001	1.19 (1.04–1.36)	0.0006	1.51 (1.01–2.26)	0.033
Constipation, K59	1.41 (1.23–1.63)	<0.0001	1.66 (1.47–1.87)	<0.0001	1.31 (1.16–1.49)	<0.0001	1.59 (1.33–1.89)	<0.0001
Spondylosis, M47	1.25 (0.93–1.69)	0.933	1.45 (1.22–1.72)	<0.0001	1.26 (1.05–1.5)	0.0005	1.62 (1.32–1.98)	<0.0001
Memory loss symptom, R41	31.5 (24.18–41.05)	<0.0001	16.5 (10.39–26.19)	<0.0001	7.63 (5.95–9.79)	<0.0001	4.41 (2.3–8.48)	<0.0001
Malaise and fatigue, R53	1.36 (1.17–1.58)	<0.0001	1.78 (1.59–2.0)	<0.0001	1.23 (1.08–1.39)	<0.0001	1.59 (1.36–1.86)	<0.0001
Syncope and collapse, R55	1.95 (1.53–2.48)	<0.0001	2.49 (1.68–3.69)	<0.0001	1.23 (1.01–1.5)	0.034	1.57 (1.06–2.34)	0.007
Abnormal weight loss, R63	2.1 (1.68–2.62)	<0.0001	3.12 (2.41–4.02)	<0.0001	1.47 (1.22–1.77)	<0.0001	1.88 (1.35–2.62)	<0.0001

Both CIs and p values were corrected for multiple comparisons. OR=odds ratio. \*Cannot be calculated because an insufficient number of presentations w

**Table 2: ORs for all variables individually associated with a future diagnosis of Alzheimer's disease in the 2–10 years before diagnosis**



- Early GI disorders in AD patients (*Nedelec et al., 2022*)
- Early GI disorders ↗ the risk of developing severe AD (*Nakase et al., 2022*)
- Dysbiosis of intestinal microbiota in AD patients (*Liu et al., 2019*)
- Alteration in the composition of metabolites in AD patients (*Wu et al., 2021*)



**What are the beneficial effects of bacterial metabolites on cognitive and digestive functions in Alzheimer's disease ?**

**Are there early digestive impairments in Alzheimer's mouse model ?**



# Are there early digestive impairments in Alzheimer's mouse model ?

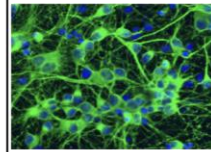
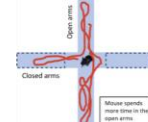
*In vivo* tests  
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**Digestive characterization**  
TTT & FPO



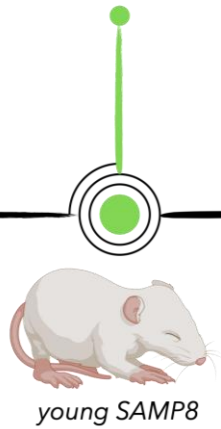
**Cognitive characterization**  
Open field & NOR



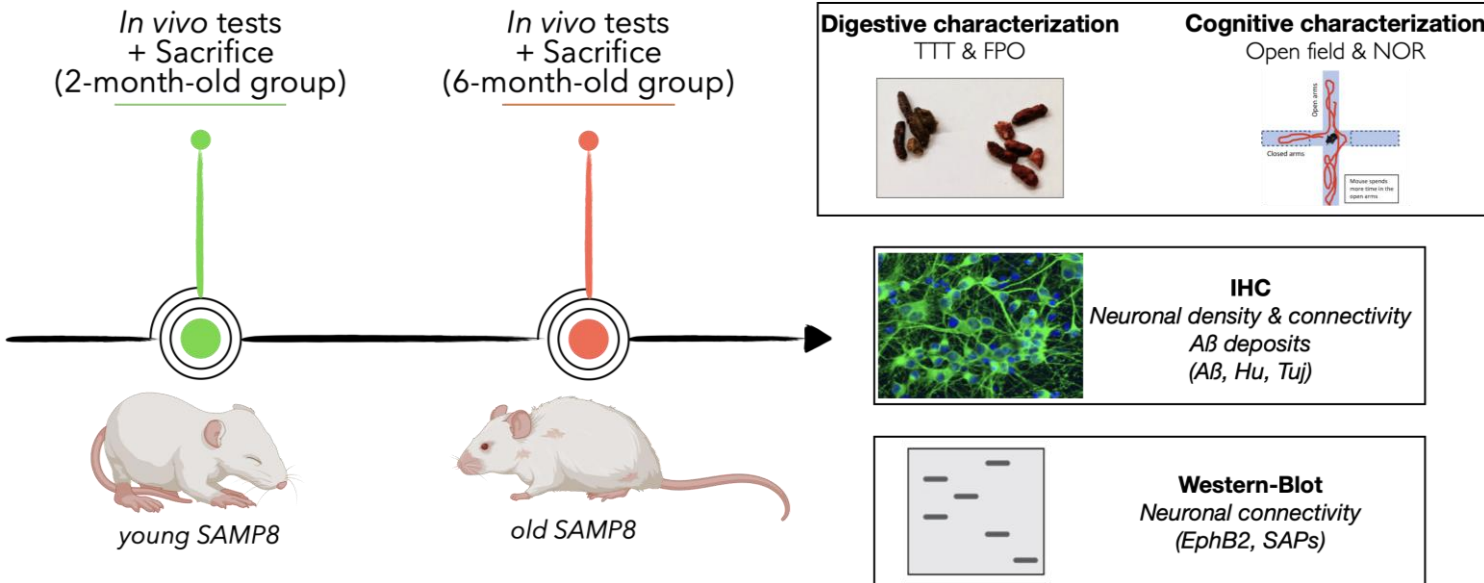
**IHC**  
Neuronal density & connectivity  
*Aβ* deposits  
(*Aβ*, *Hu*, *Tuj*)



**Western-Blot**  
Neuronal connectivity  
(*EphB2*, *SAPs*)

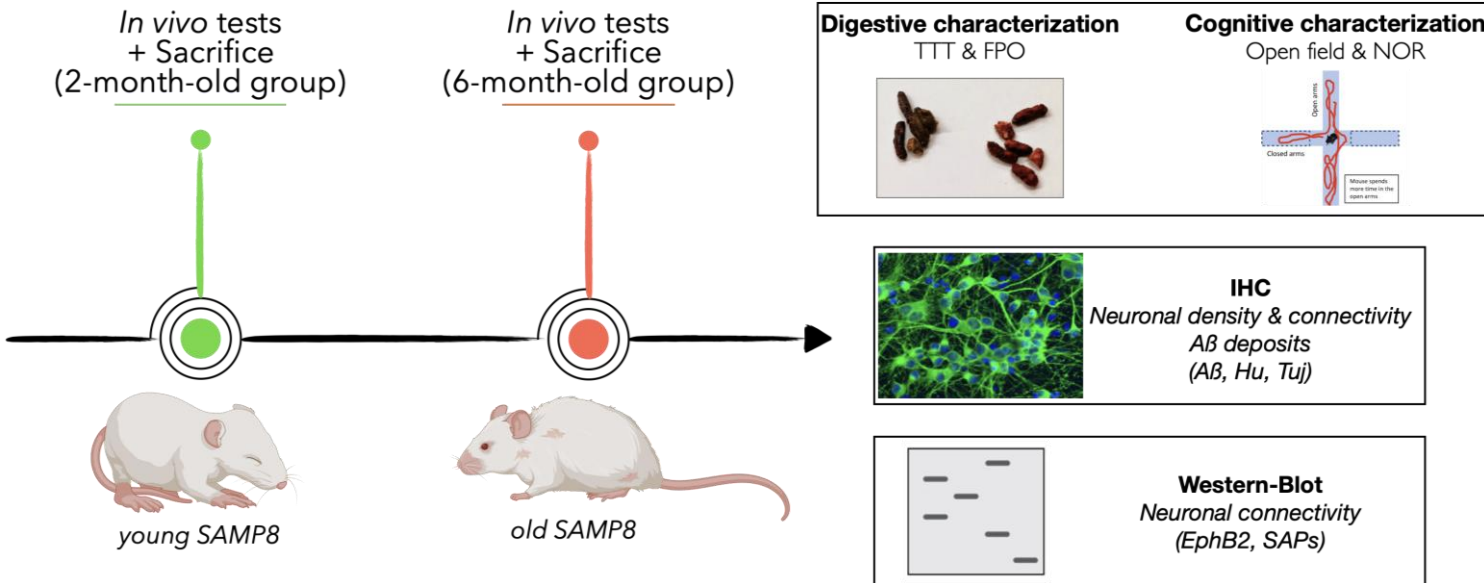


# Are there early digestive impairments in Alzheimer's mouse model ?



- Constipation and alterations in transit velocity as early as 2 months of age (*in vivo*)
- Memory impairments only appear only from the age of 6 months (*in vivo*)
- Amyloid- $\beta$  deposits in the gut at 2 months of age and only from the age of 6 months in the brain (*ex vivo*)
- Synaptic alterations in the ENS at 2 months of age, while they appear in the brain at the age of 6 months (*in vitro*)

# Are there early digestive impairments in Alzheimer's mouse model ?



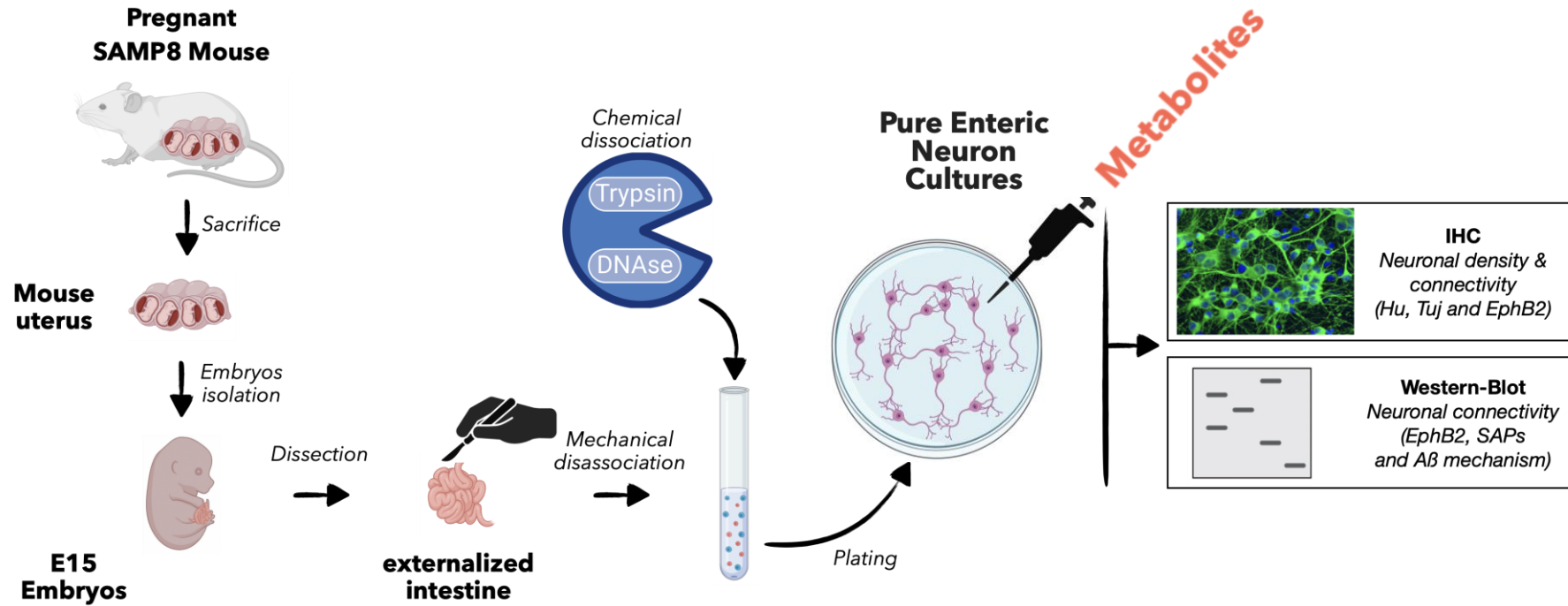
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**There are early digestive impairments in SAMP8 mouse**

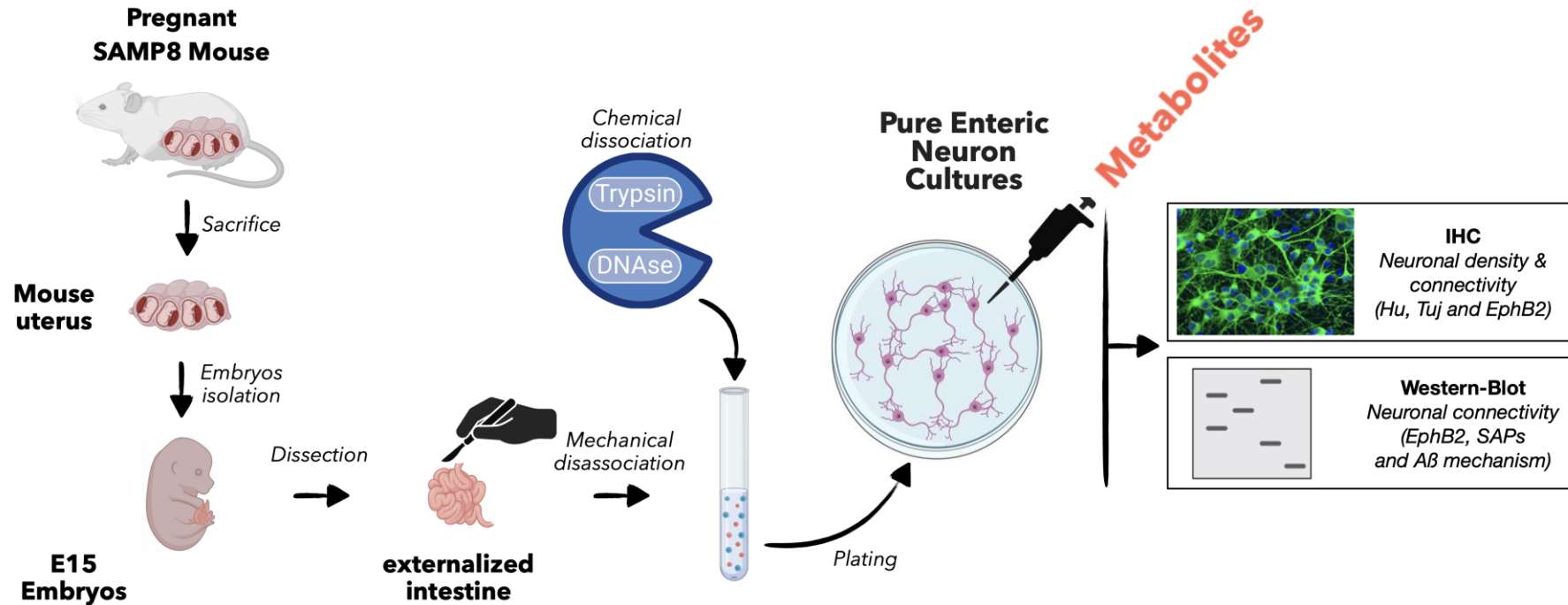
**Which metabolites are capable of improving the enteric neuronal connectivity ?**



# Which metabolites are capable of improving the enteric neuronal connectivity ?



# Which metabolites are capable of improving the enteric neuronal connectivity ?



METABOLITE	BENEFICIAL EFFECTS ?
Acétate	NO
Propionate	NO
Butyrate	YES
Lactate	NO
GABA	NO
Spermine	NO
Spermidine	NO
Kynurénine	NO
Vitamine B9	NO
Vitamine B12	NO

**Butyrate treatment improves the enteric neuronal connectivity *in vitro***

**Could butyrate enhance cognitive and digestive functions in Alzheimer's mouse model ?**



# Could butyrate enhance cognitive and digestive functions in Alzheimer's mouse model ?

*In vivo* tests  
+ Sacrifice  
(2-month-old group)

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21-day-old  
weaned mouse

young SAMP8

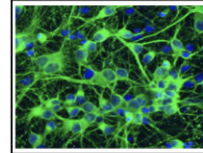
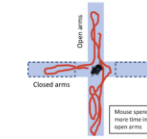
old SAMP8

Butyrate supplementation

**Digestive characterization**  
TTT & FPO



**Cognitive characterization**  
Open field & NOR



**IHC**  
Neuronal density & connectivity  
 $A\beta$  deposits  
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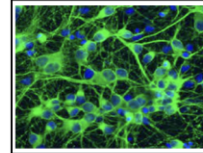
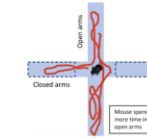
old SAMP8

Butyrate supplementation

**Digestive characterization**  
TTT & FPO



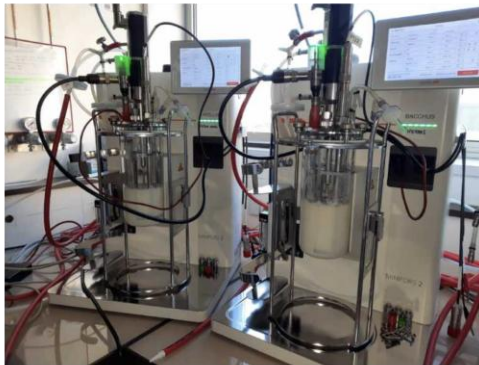
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Open field & NOR



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Neuronal density & connectivity  
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**Western-Blot**  
Neuronal connectivity  
(EphB2, SAPs)



Dr. Hélène Falentin



Marina Giblaine

Dairy product enriched with butyrate

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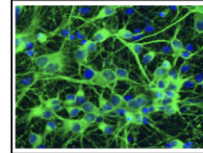
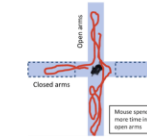
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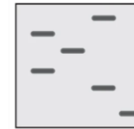
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**Cognitive characterization**  
Open field & NOR



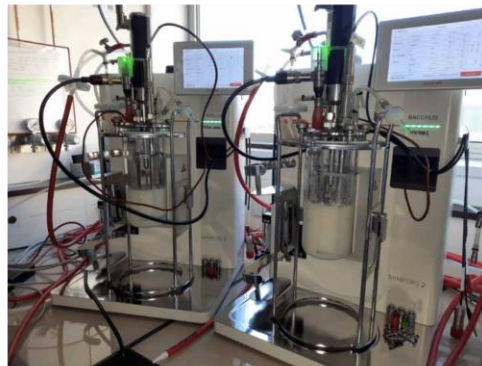
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Neuronal connectivity  
(EphB2, SAPs)



Work in progress ...



Dr. Hélène Falentin



Marina Giblaine

Butyrate production through milk fermentation  
using a bacterial consortium

# Questions & Answers



# Fermentation as a lever for improving Infant Formulas : Design of a fermented formula improving brain development in newborns

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Sarah BLANCHET

Directed by Sophie BLAT and by Sergine  
EVEN



# Context



## Human milk

→ Optimal post-natal nutrition for the newborn.



# Context



**Human milk**



**Infant Formula**



# Context



**Human milk**



**Infant Formula**

Meet the nutritional needs of the newborn by:

Macronutrients : Proteins, Carbohydrates, Lipids

Micronutrients : Minerals, vitamins

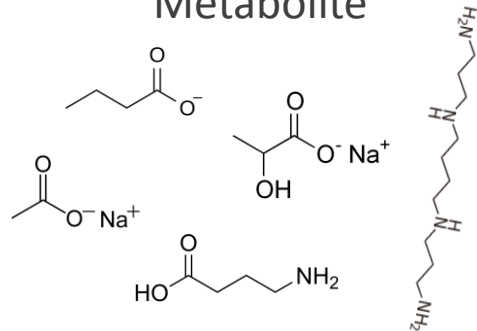


# Context



## Human milk

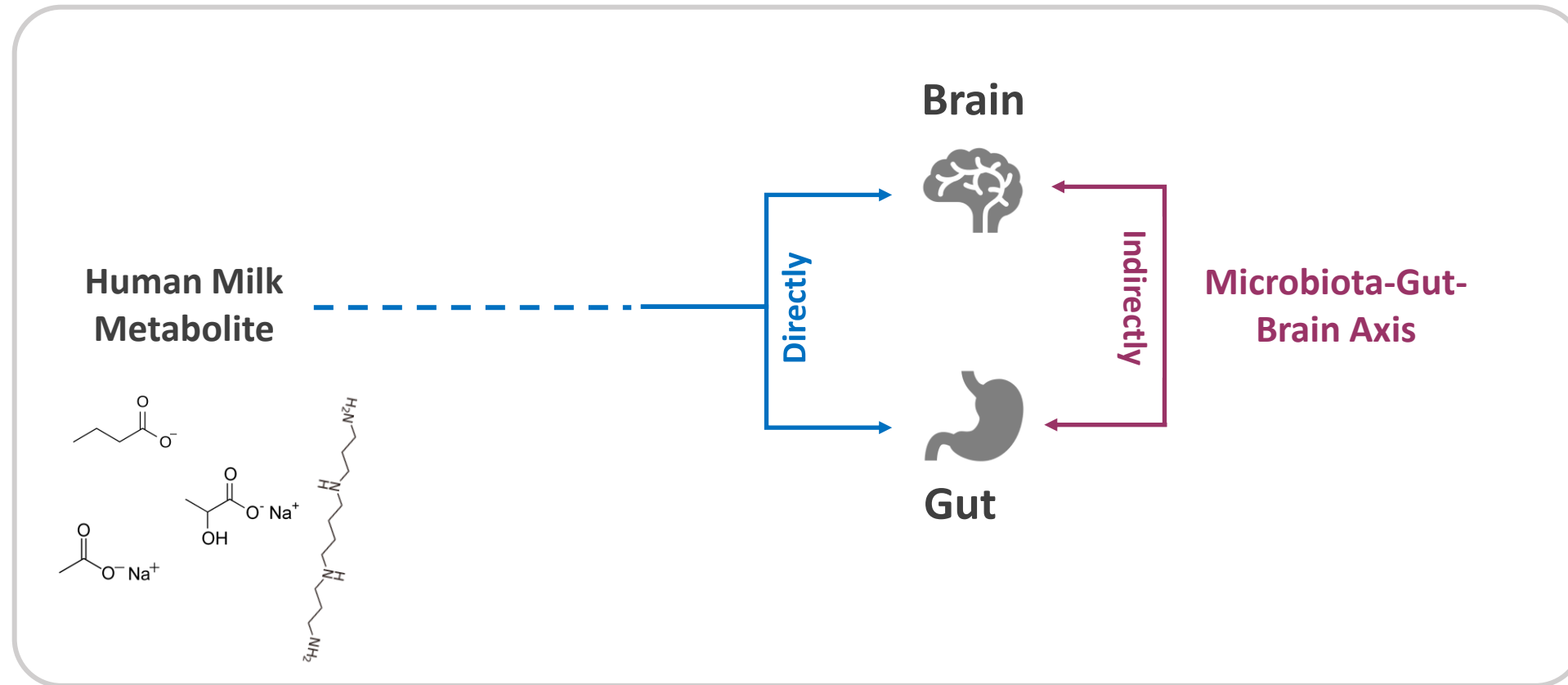
Human Milk  
Metabolite



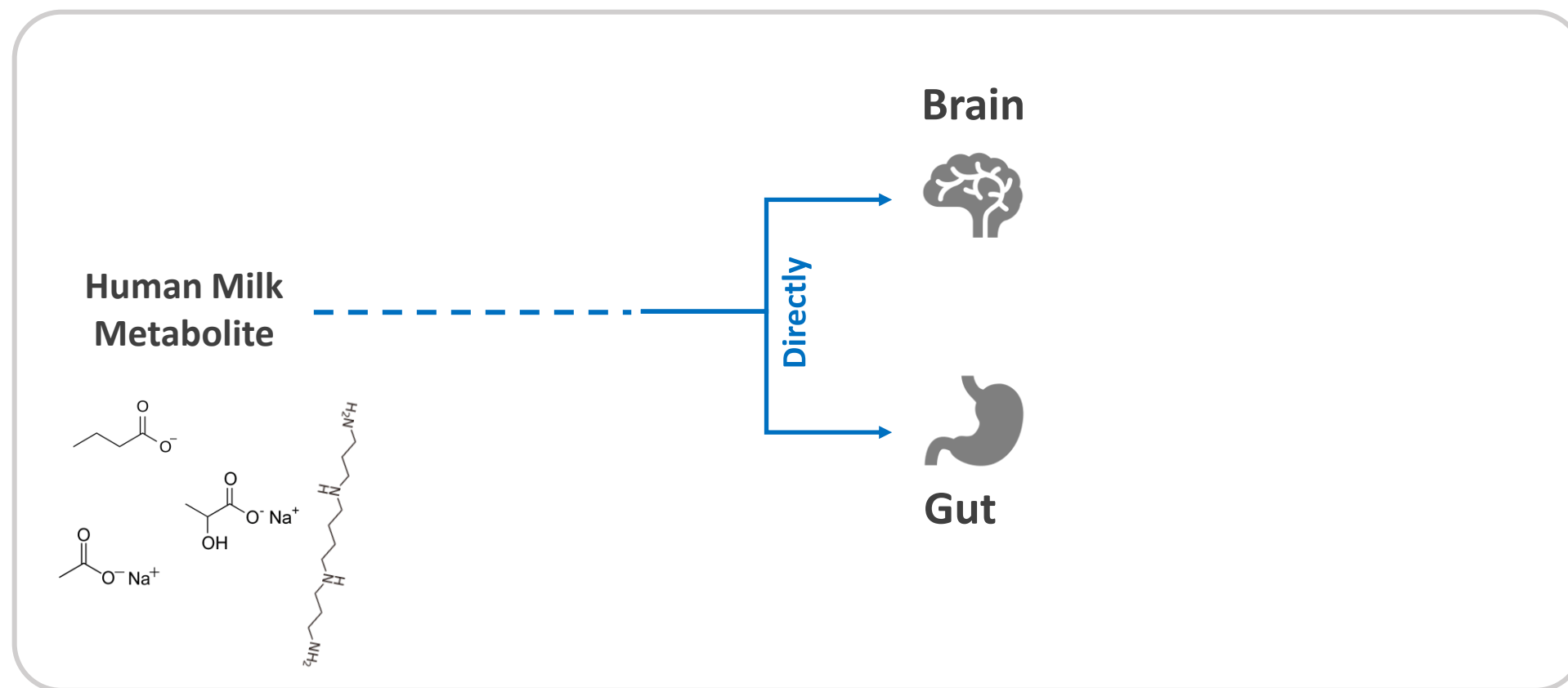
## Infant Formula



# Research questions

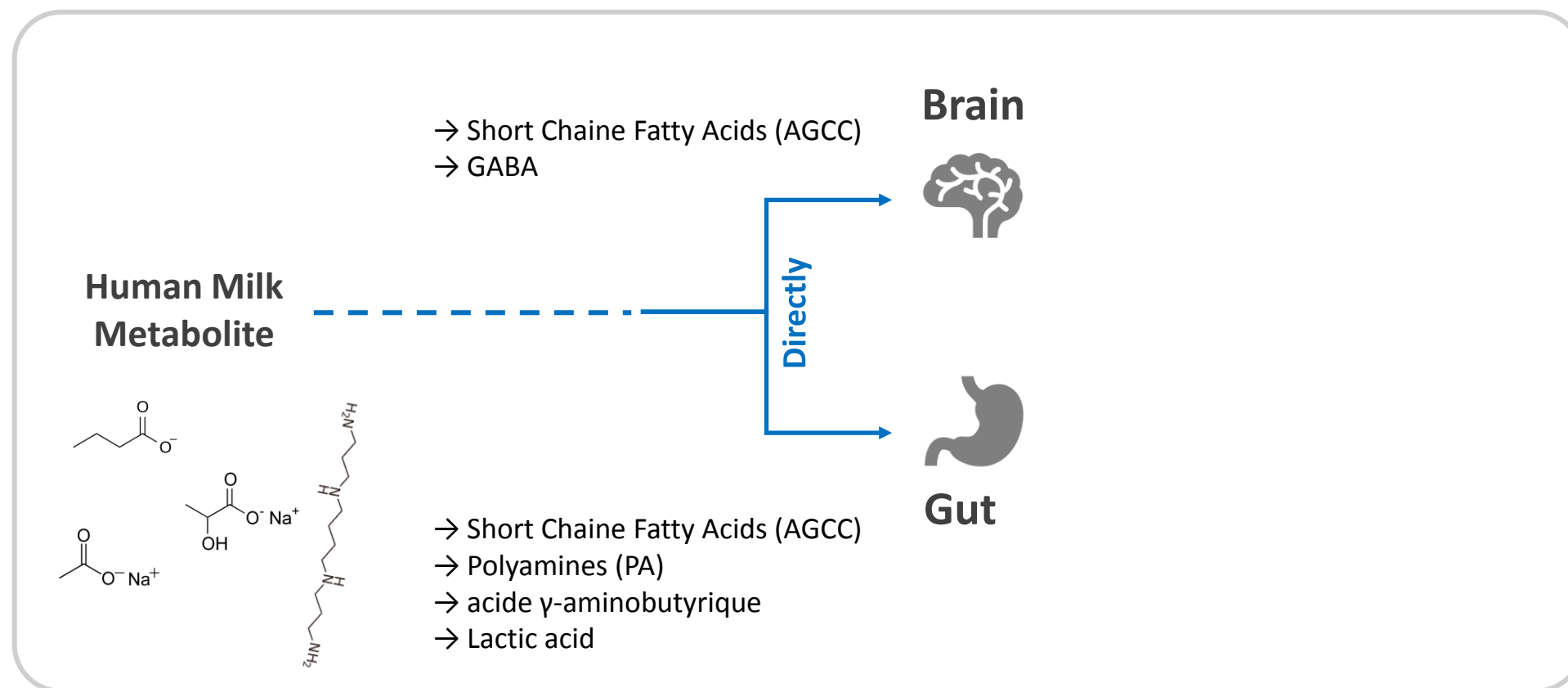


# *In vitro* study of the metabolites



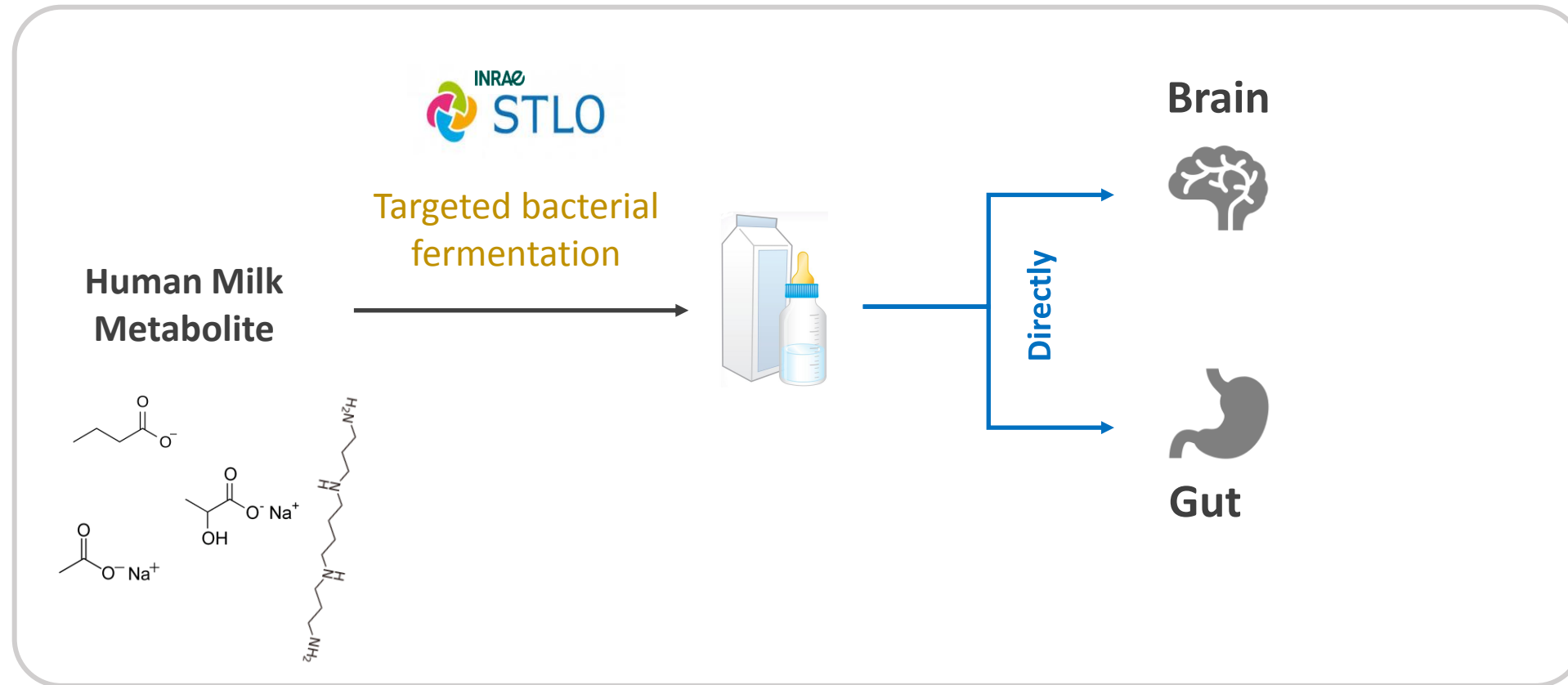
*in vitro* : cellular models of intestinal epithelium and central neurons (screening of relevant metabolites)

# In vitro study of the metabolites

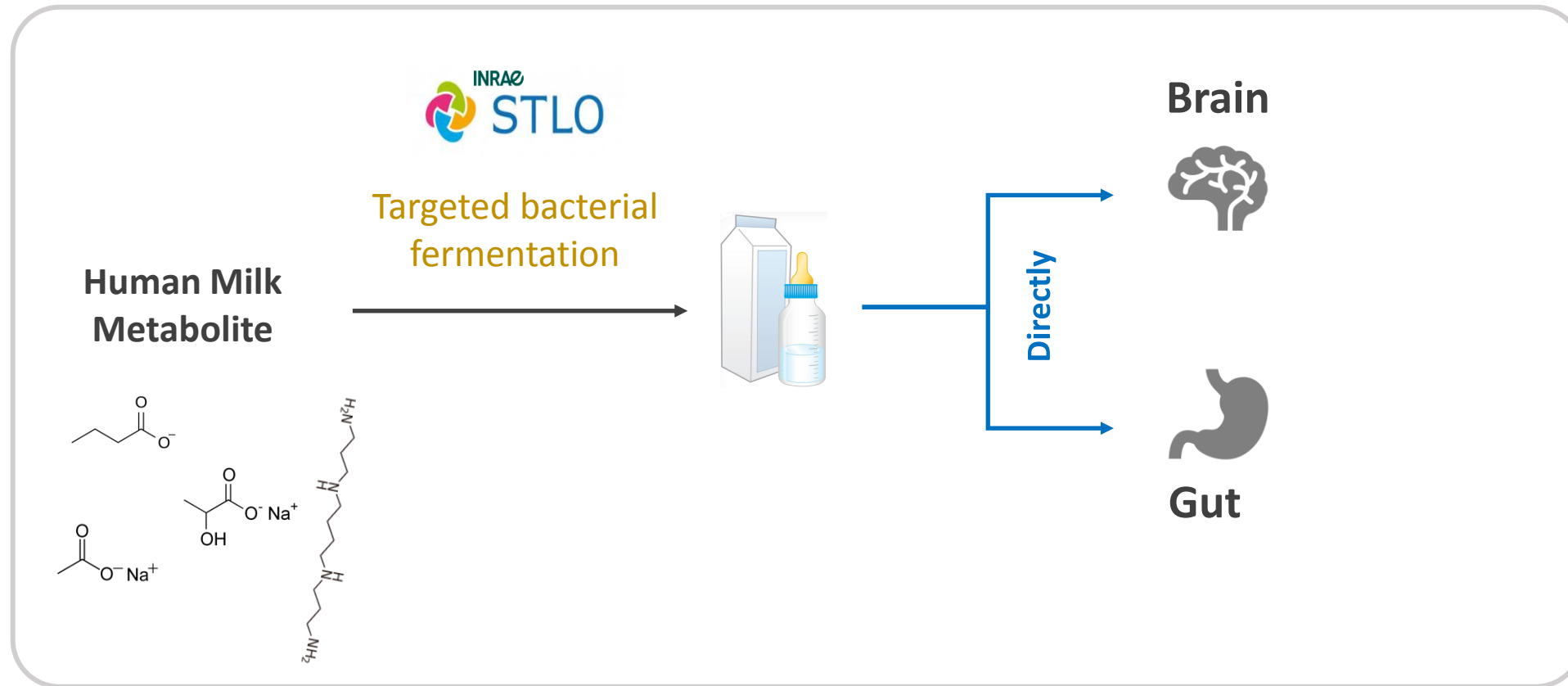


**in vitro : cellular models of intestinal epithelium and central neurons** (screening of relevant metabolites)

# *In vivo* study of metabolites produced by targeted bacterial fermentation

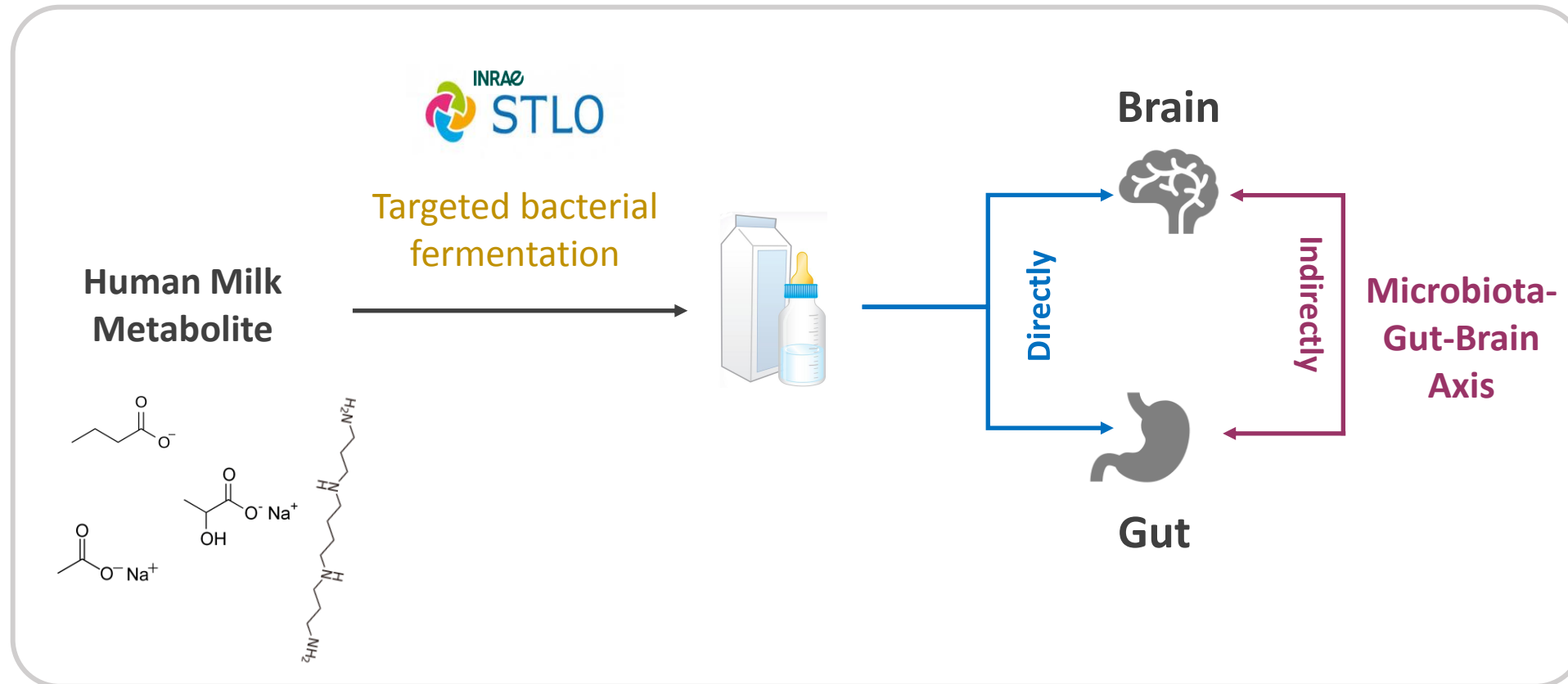


# *In vivo* study of metabolites produced by targeted bacterial fermentation



*in vivo* : piglet ; the Yucatan mini-pig (preclinical model)

# *In vivo* study of metabolites produced by targeted bacterial fermentation



*in vivo* : piglet ; the Yucatan mini-pig (preclinical model)

Thank you for your  
attention



# Questions & Answers





# Thank you for attending our session

Need more information? Contact:

- Hervé LE DEIT : [herve.le-deit@ouest-valorisation.fr](mailto:herve.le-deit@ouest-valorisation.fr)
- Candice LAMOUREUX : [candice.lamoureux@ouest-valorisation.fr](mailto:candice.lamoureux@ouest-valorisation.fr)
- Clair-Yves BOQUIEN : [clair-yves.boquien@univ-nantes.fr](mailto:clair-yves.boquien@univ-nantes.fr)
- Pierre-Etienne SADO : [pierre-etienne.sado@univ-nantes.fr](mailto:pierre-etienne.sado@univ-nantes.fr)