

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



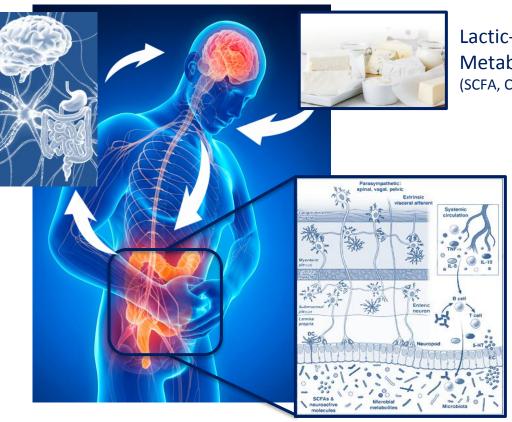
Yves LE LOIR **STLO - INRAE Institut Agro Rennes**





PROLIFIC « May your diet be your first medicine »

ENS-Central Nervous System (CNS) interactions

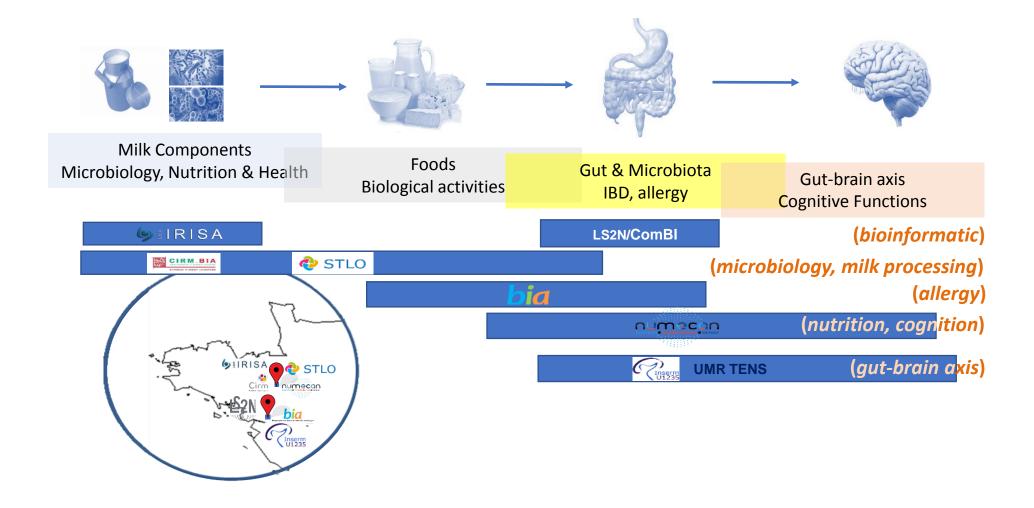


Lactic- and Propionic- Acid bacteria Metabolites of interest (SCFA, CLA, oligosaccharides, vitamins, etc.)

Food microbiota-intestinal epithelial barrier (IEB) interactions

IEB-Enteric nervous system (ENS) interactions

Scientific continuum and expertise



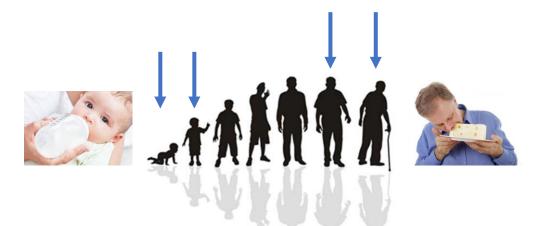


For which target populations?

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 ressources

- **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













































Questions & Answers



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



Charles LE BRAS

STLO & NuMeCan





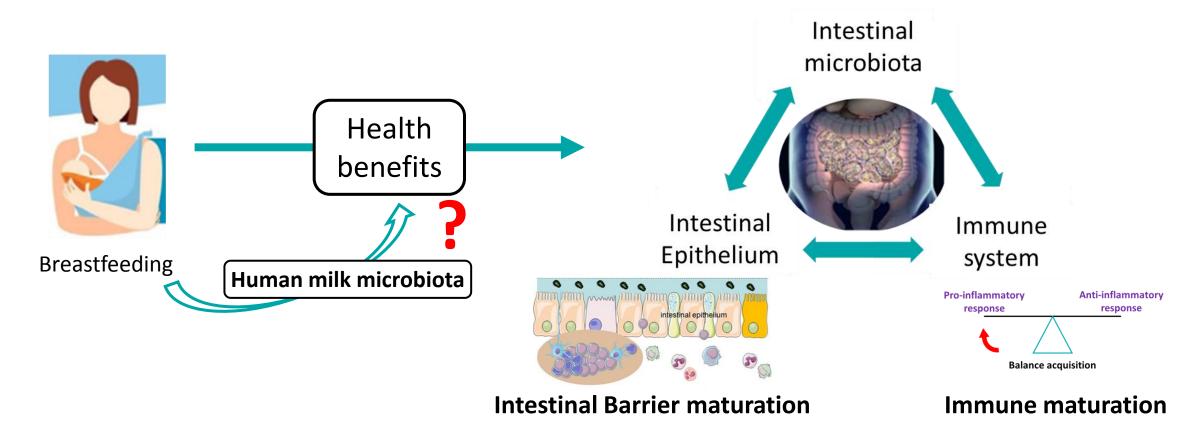




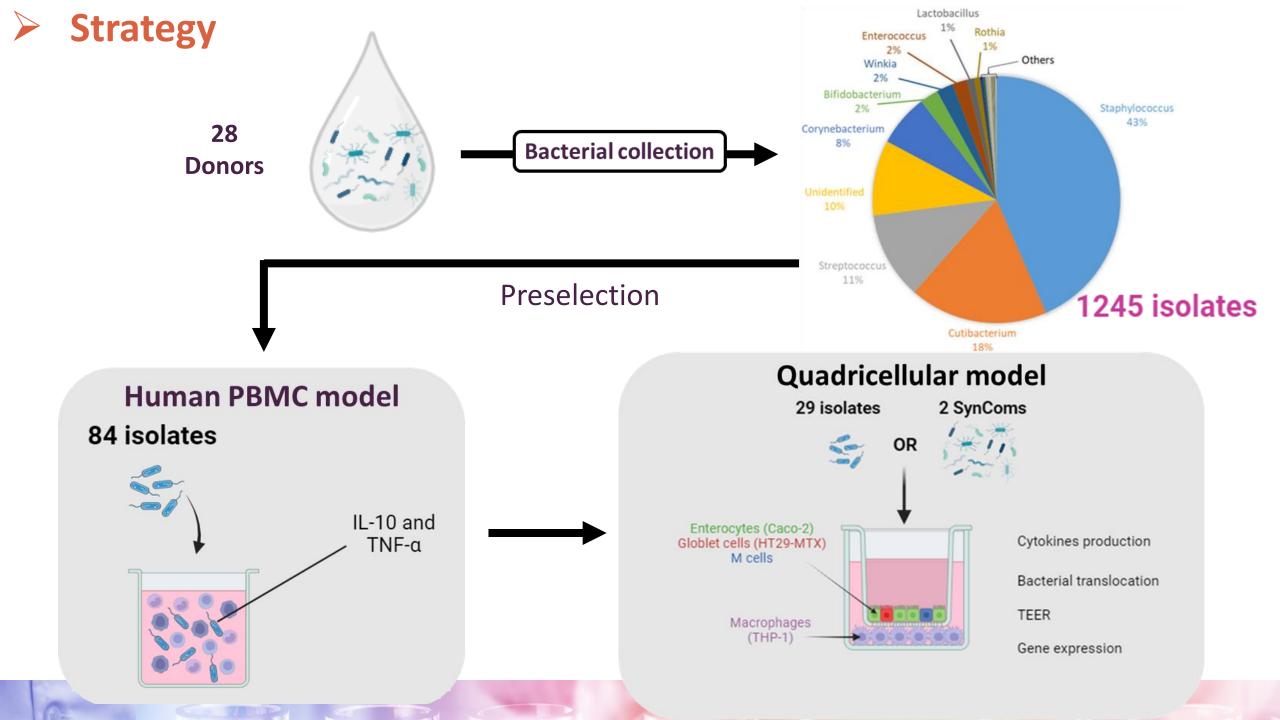


Introduction

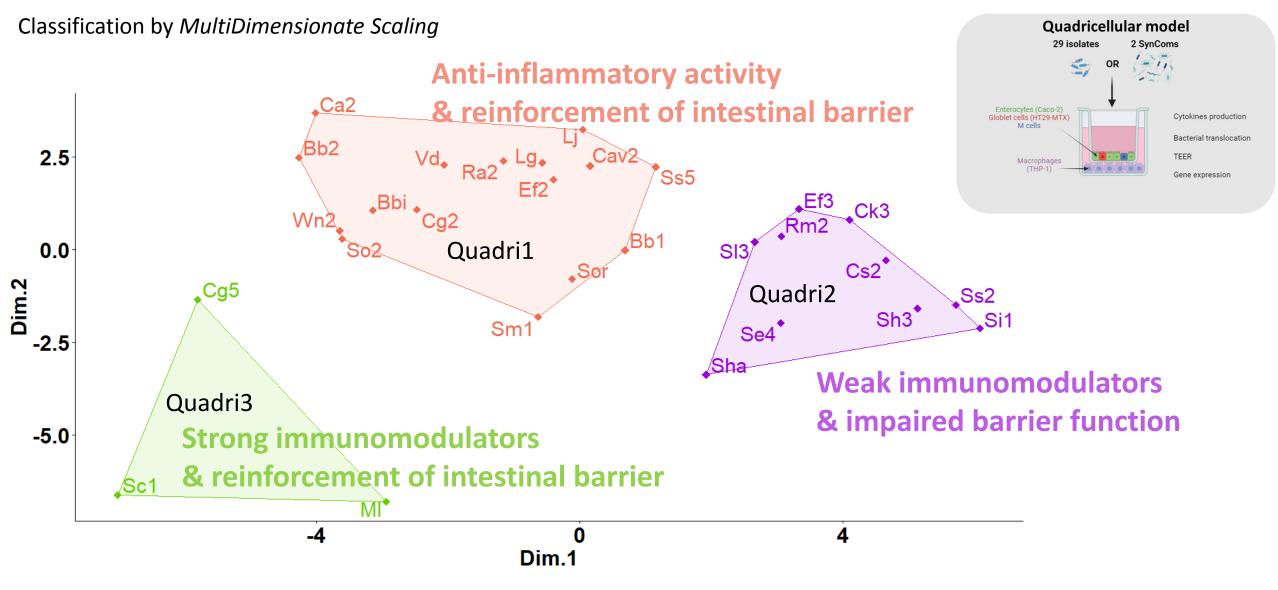
Intestinal homeostasis



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



Individual impact of HM bacteria on immune and barrier functions



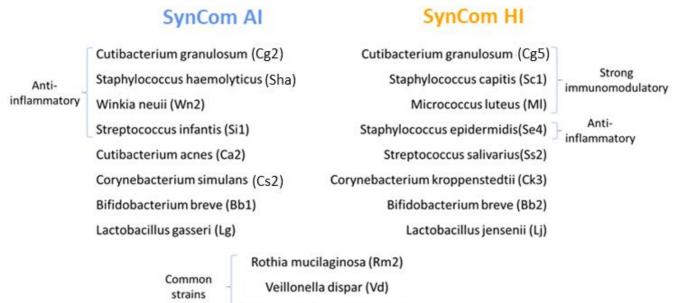
Great variability of functional profiles of HM bacteria

Immune and barrier properties of the 2 SynComs

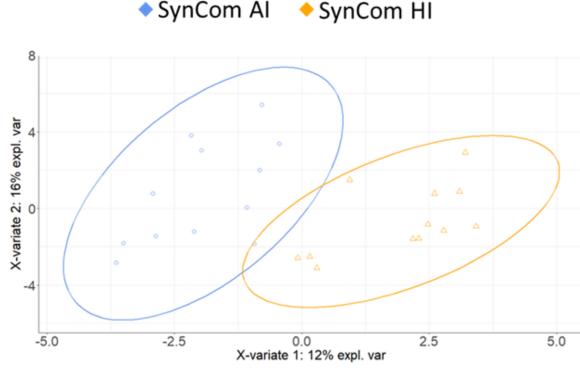
sPLS-DA analysis

Design of 2 Synthetic Communities:

- **→** Mimicking HM microbiota
- **→** With different functional properties



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



Anna LAMBERT

LS2N & TENS laboratories

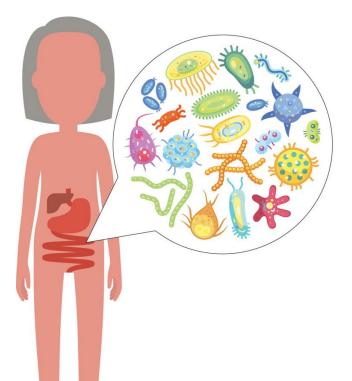








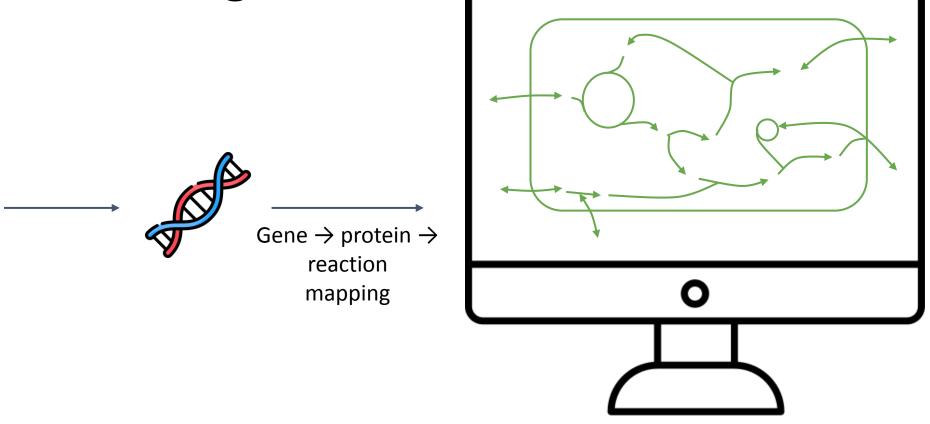
The host - microbiota ecosystem



- 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

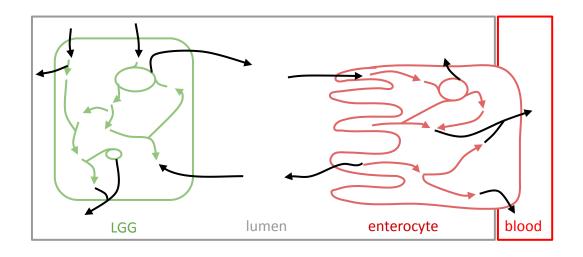
→ Explaining the influence of gut bacteria on the host using computational metabolic models

Metabolic modeling



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

Exploration of ecosystem interaction



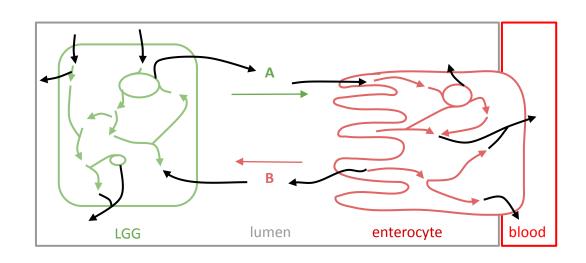
 Interaction score (competition, neutrality, mutualism)





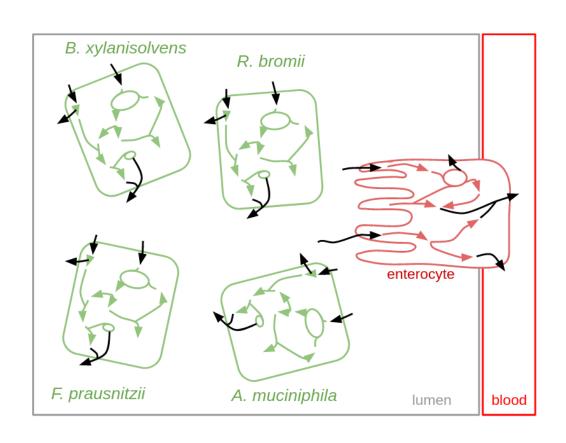


Exploration of ecosystem interaction



- 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 polyunsatured fatty acids on the intestinal barrier



Marine MANTEL

TENS & STLO laboratories



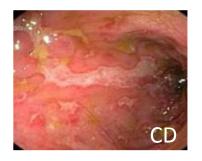


Intestinal bowel disease (IBD)



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



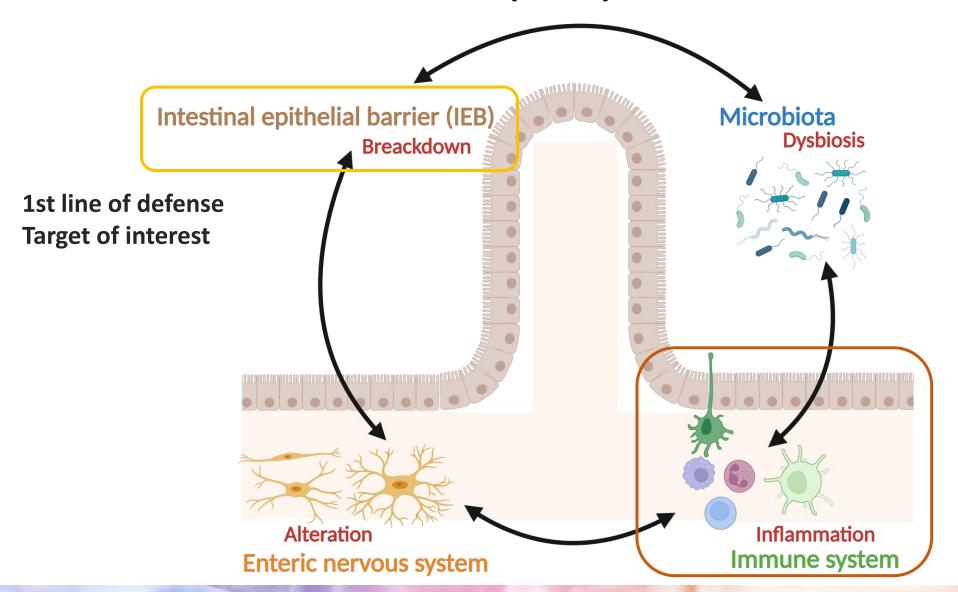




Chronic inflammation.

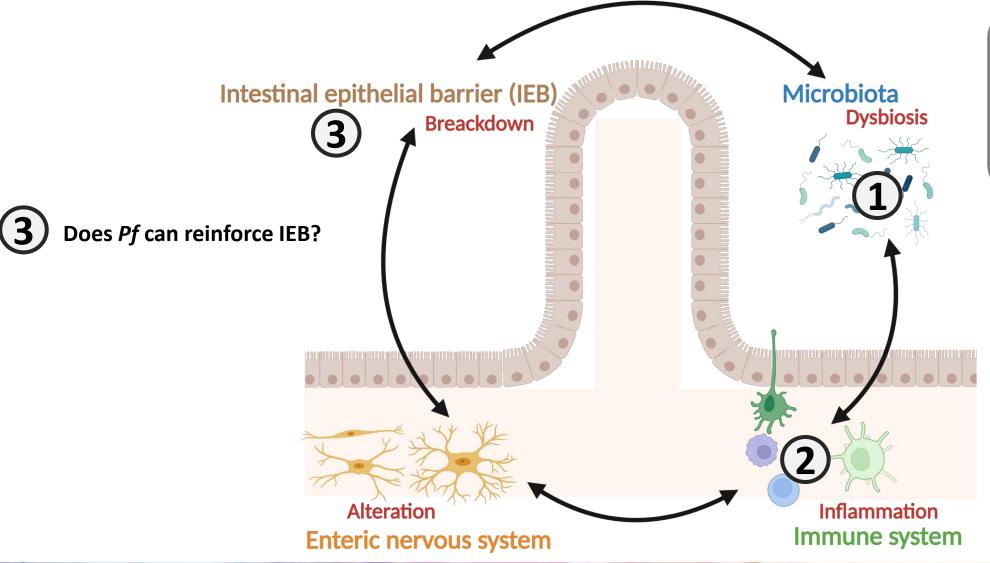
No curative treatment!

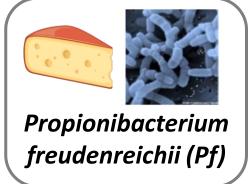
Intestinal bowel disease (IBD)



Current treatments

How to reinforce IEB?



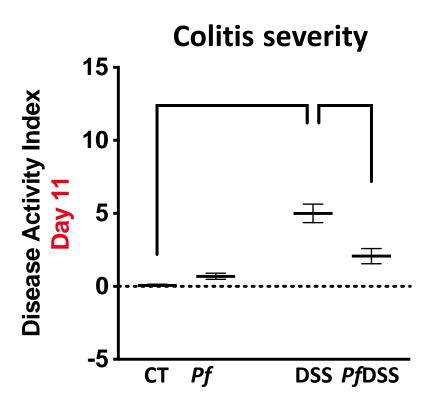


- 1 Improved gut microbiota
- 2 Anti-inflammatory

Pf supplementation

DSS-induced colitis





Pf prevents colitis severity induced by the DSS.

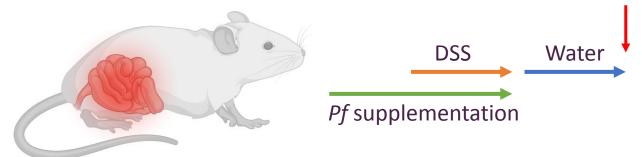
Pf supplementation

Day 11

DSS-induced colitis

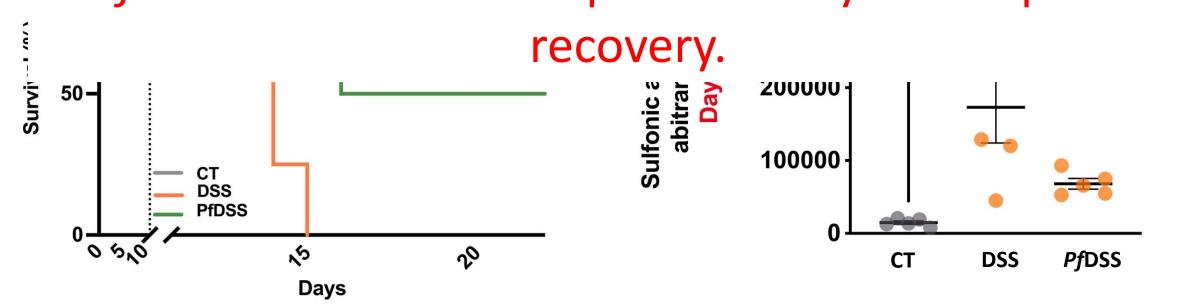


Survival

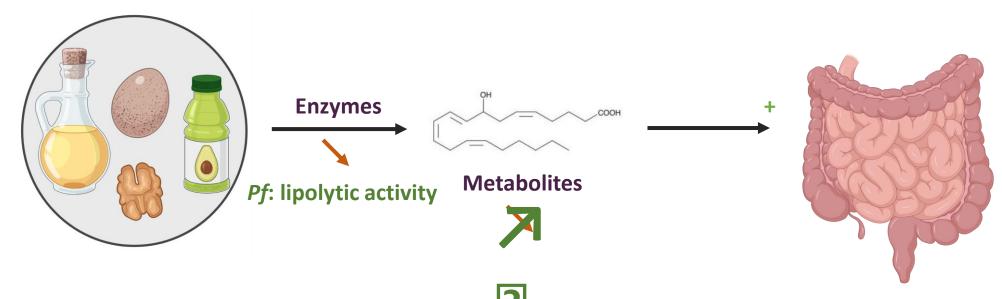


Intestinal permeability

Pf decreases intestinal permeability and improves



N-6 diet: good for the gut?

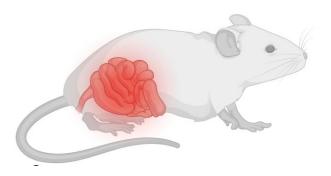


Disruption of n-6 metabolism in IBD patients.

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

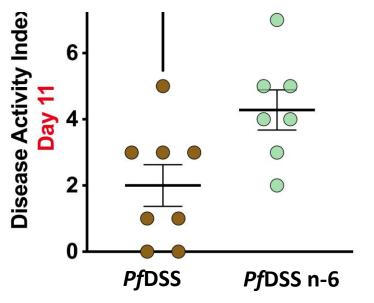
Pf supplementation N-6 enriched diet

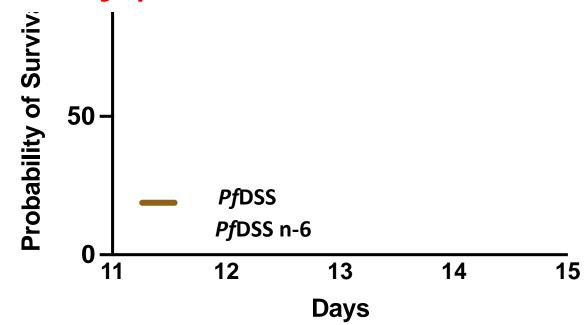
Recovery protocol



Colitis severity

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





Survival

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?



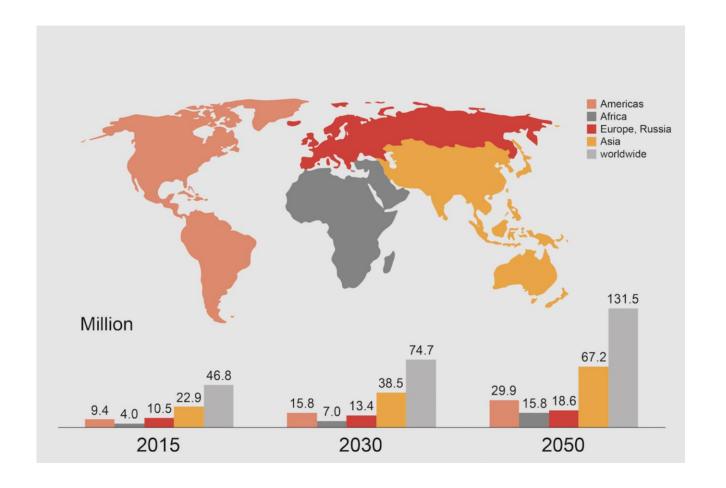
Rodrigue BROSSAUD

TENS & STLO laboratories



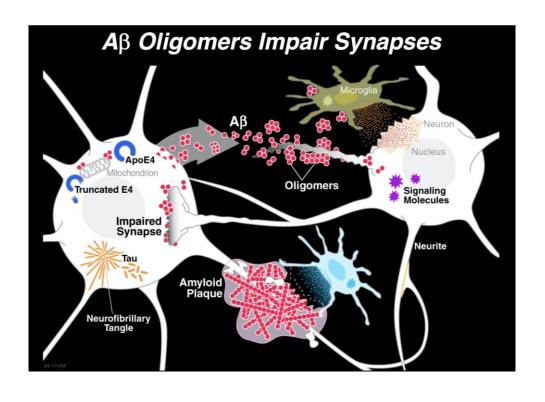


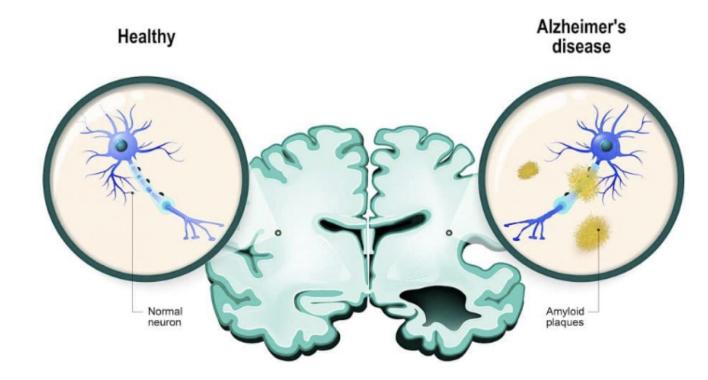
Alzheimer's disease: epidemiology and symptoms





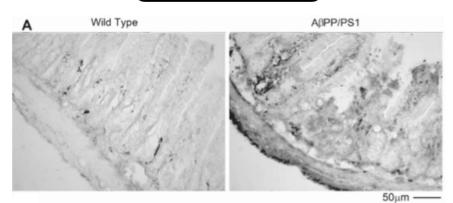
Alzheimer's disease: Amyloïd-ß toxicity



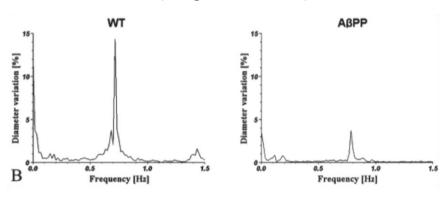


Alzheimer's disease : A gut-brain disease ?

Animal models

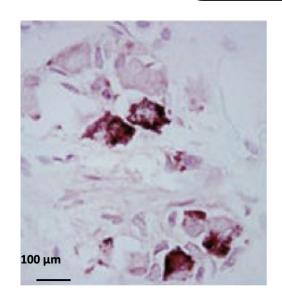


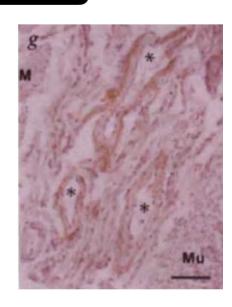
Intestinal amyloïd aggregates (Puig et al., 2015)



 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?

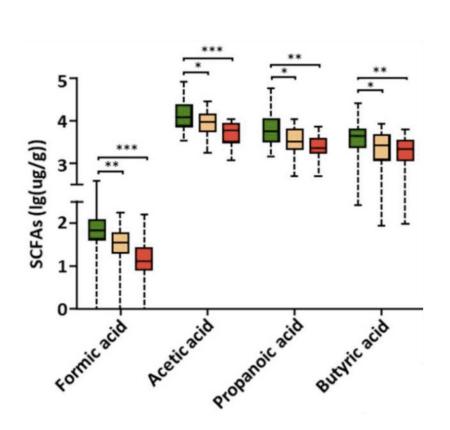
	Diagnosis with	in 0–2 years	;		Diagnosis within 2–10 years			
	UK		France		UK		France	
	OR (corrected 95% CI)	Corrected p value	OR (corrected 95% CI)	Corrected p value	OR (corrected 95% CI)	Corrected p value	OR (corrected 95% CI)	Correcte p value
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Anxiety, 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

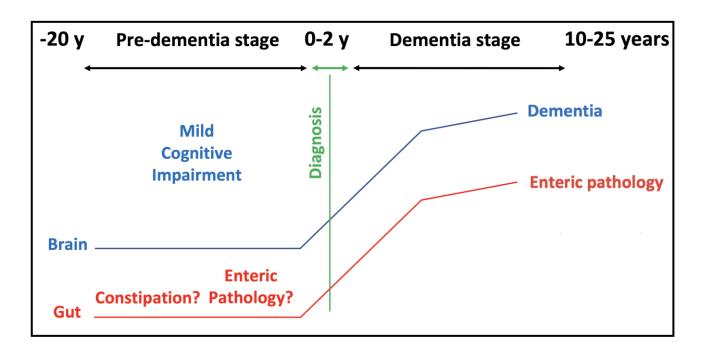
- Early GI disorders in AD patients (Nedelec et al., 2022)
- Early GI disorders

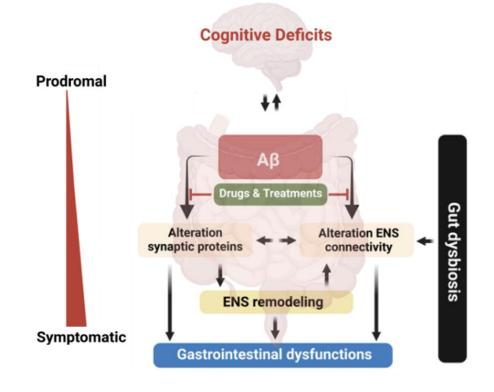
 ↑ the risk of developing severe AD (Nakase et al., 2022)



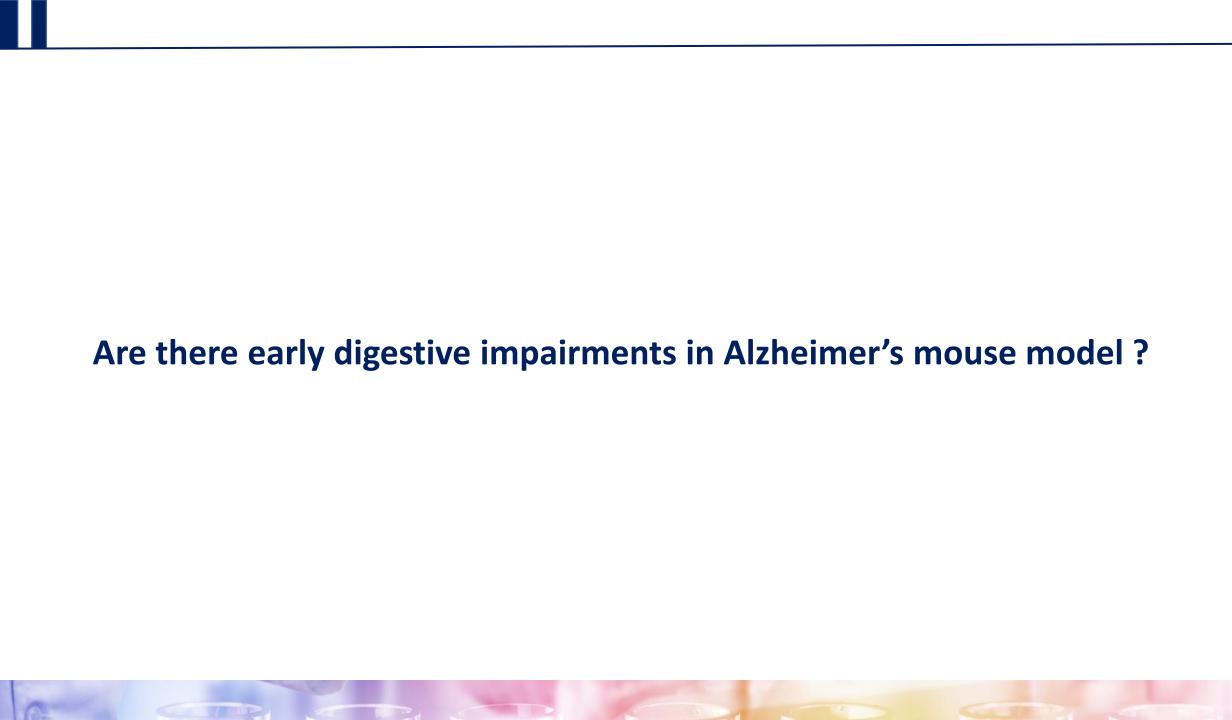
HC aMCI

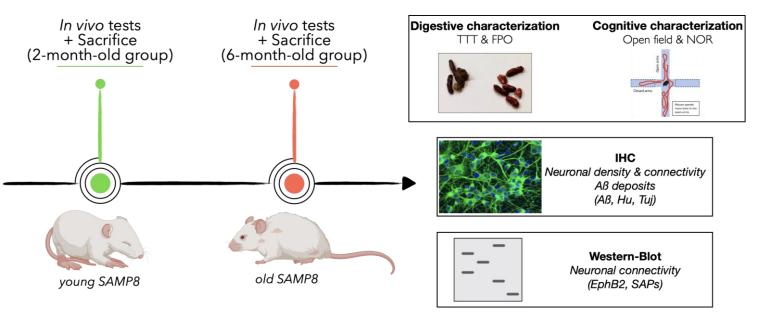
- Dysbiosis of intestinal microbiota in AD patients (Liu et al., 2019)
- Alteration in the composition of metabolites in AD patients (Wu et al., 2021)

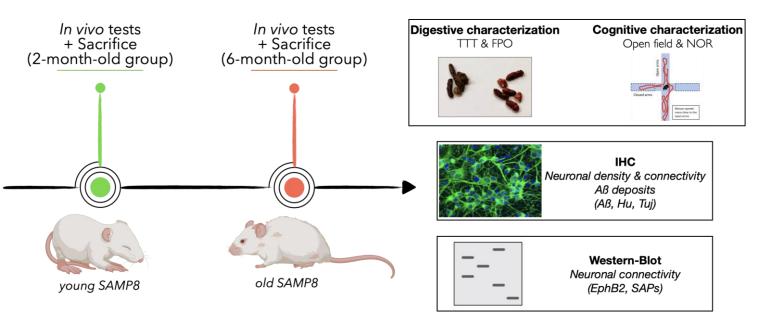




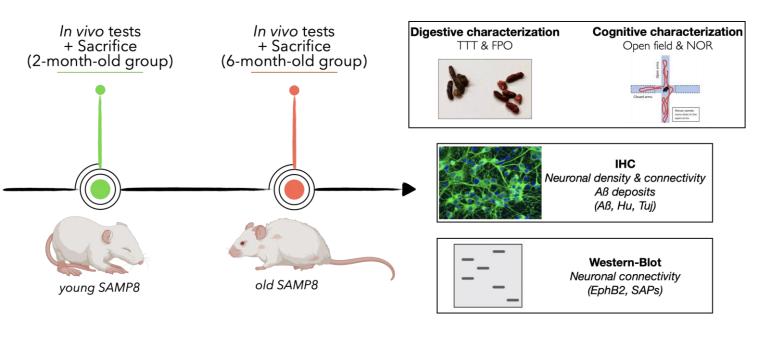
What are the beneficial effects of bacterial metabolites on cognitive and digestive functions in Alzheimer's disease ?





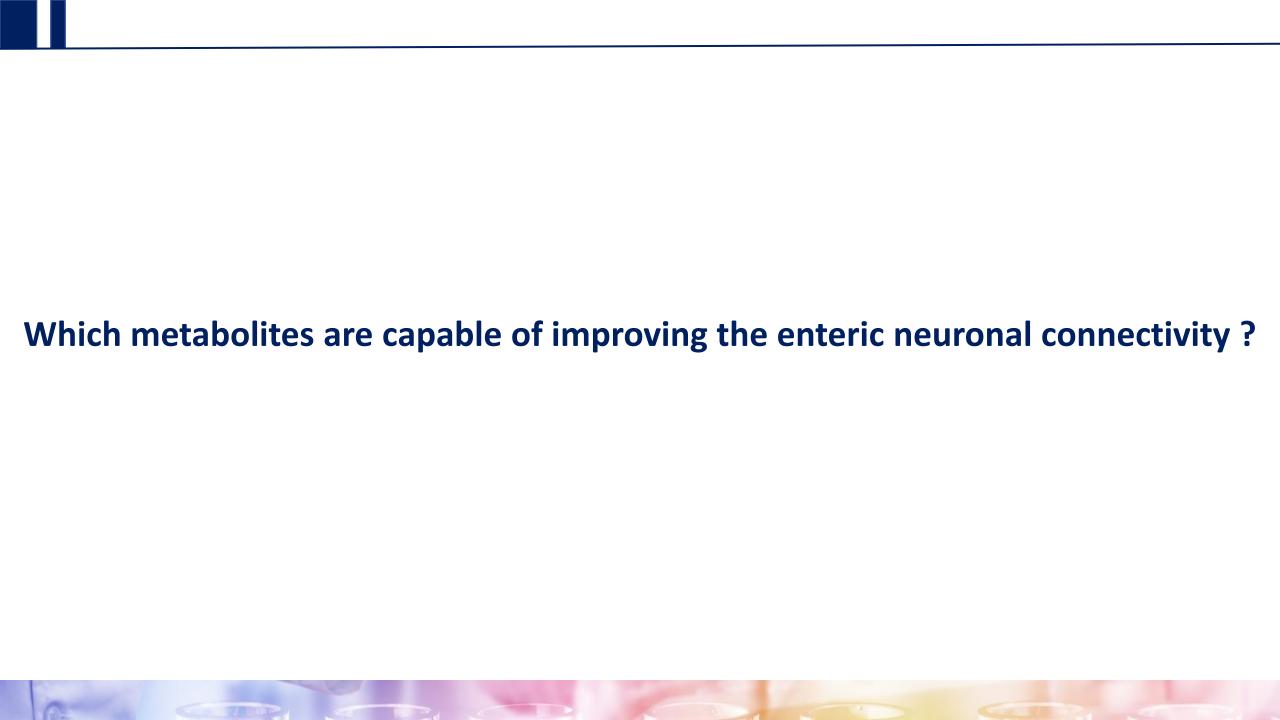


- Constipation and alterations in transit velocity as early as 2 months of age (in vivo)
- Memory impaiments only appear only from the age of 6 months (in vivo)
- Amyloïd-ß deposits in the gut at 2 months of age and only from the age of 6 months in the brain (ex vivo)
- Synaptic alterations in the ENS at 2 months of age, while they appear in the brain at the age of 6 months (in vitro)

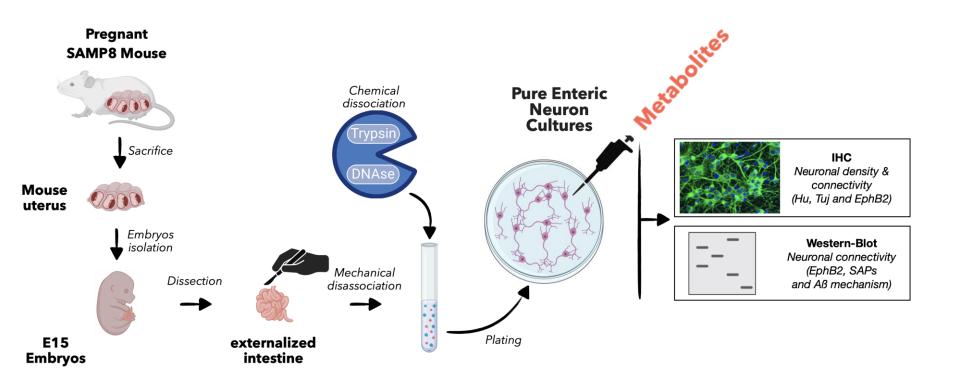


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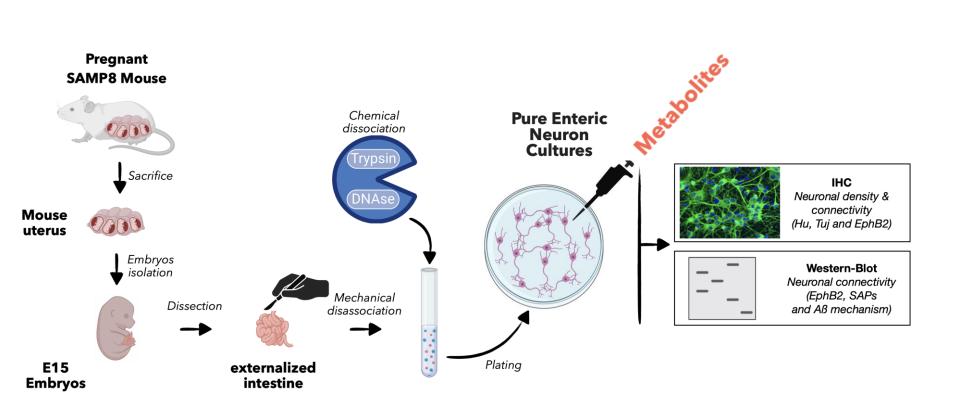
There are early digestive impairments in SAMP8 mouse



Which metabolites are capable of improving the enteric neuronal connectivity?

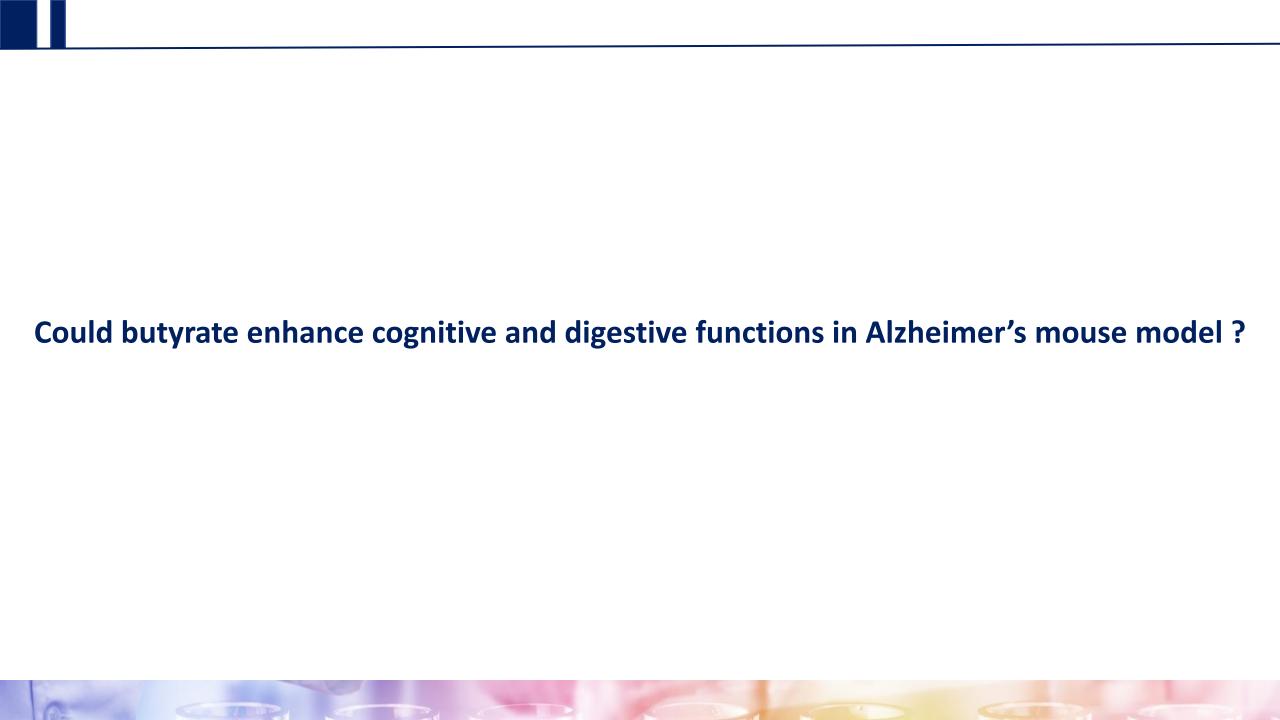


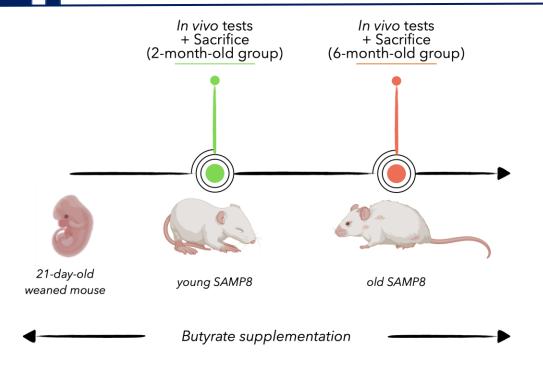
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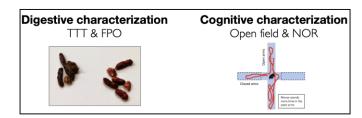


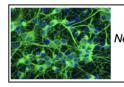
METABOLITE	BENEFICIAL EFFECTS?				
Acétate	NO				
Propionate	NO				
Butyrate	YES				
Lactate	NO				
GABA	NO				
Spermine	NO				
Spermidine	NO				
Kynurénine	NO				
Vitamine B9	NO				
Vitamine B12	NO				

Butyrate treatment improves the enteric neuronal connectivity in vitro





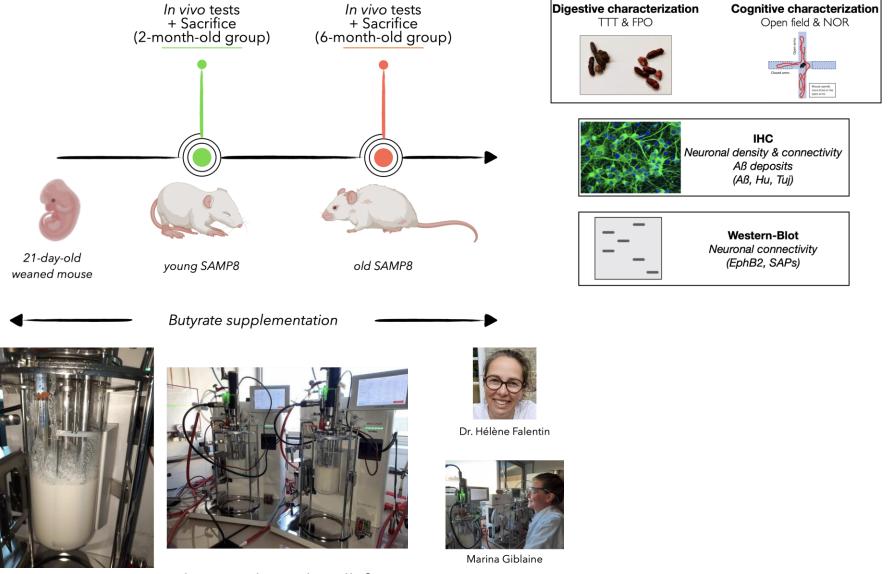




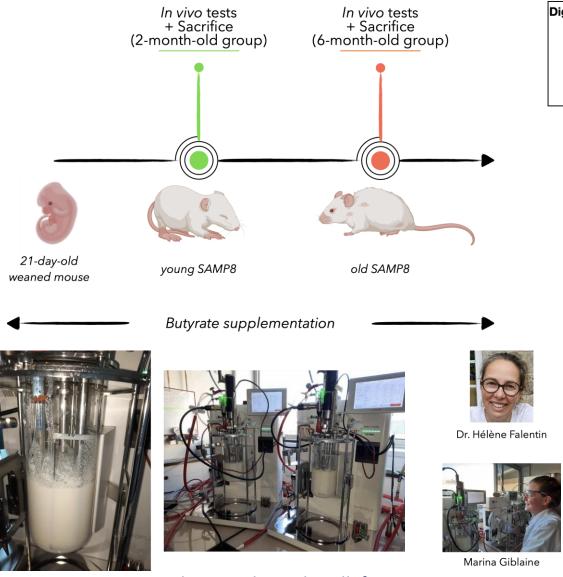
IHC Neuronal density & connectivity Aß deposits (Aß, Hu, Tuj)



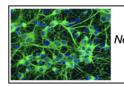
Western-Blot Neuronal connectivity (EphB2, SAPs)



Butyrate production through milk fermentation using a bacterial consortium







IHC Neuronal density & connectivity Aß deposits (Aß, Hu, Tuj)



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Work in progress ...

Butyrate production through milk fermentation using a bacterial consortium



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



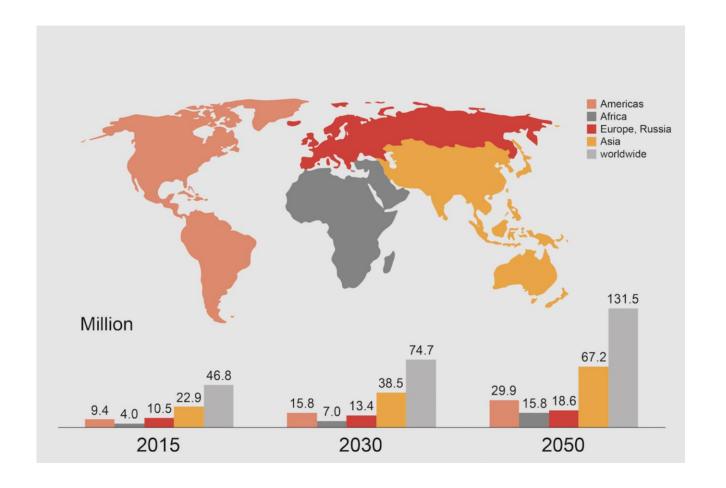
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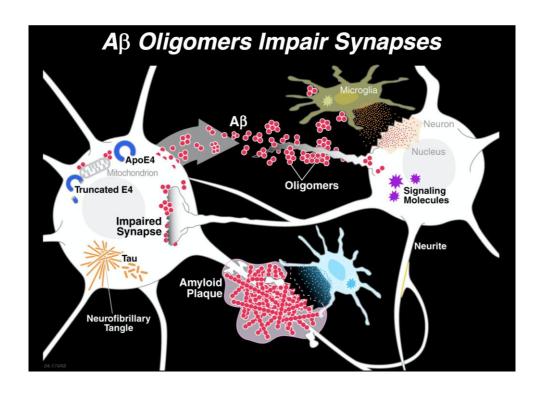


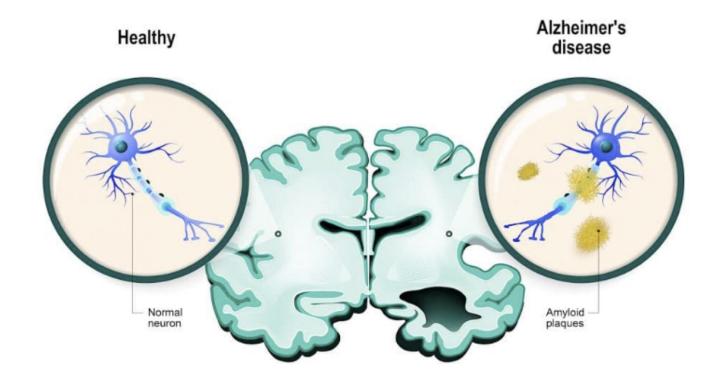
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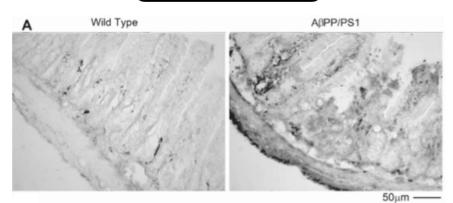
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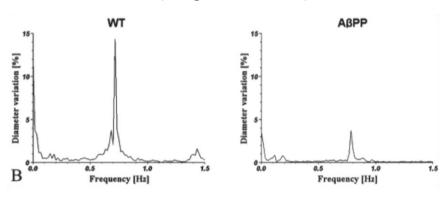


Alzheimer's disease : A gut-brain disease ?

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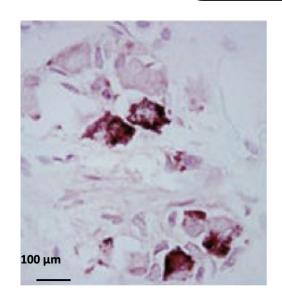


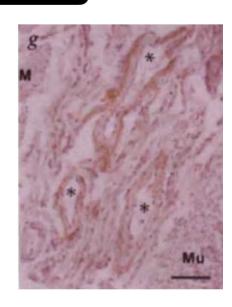
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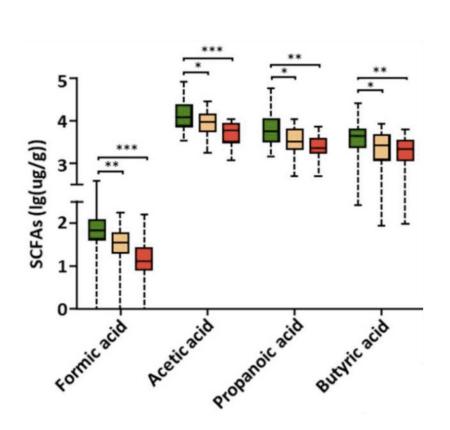
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Malaise and fatigue, R53	1·36 (1·17-1·58)	<0.0001	1-78 (1-59-2-0)	<0.0001	1·23 (1·08-1·39)	<0.0001	1·59 (1·36-1·86)	<0.0001
Syncope and collapse, R55	1·95 (1·53-2·48)	<0.0001	2·49 (1·68-3·69)	<0.0001	1·23 (1·01-1·5)	0-034	1·57 (1·06-2·34)	0.007
Abnormal 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

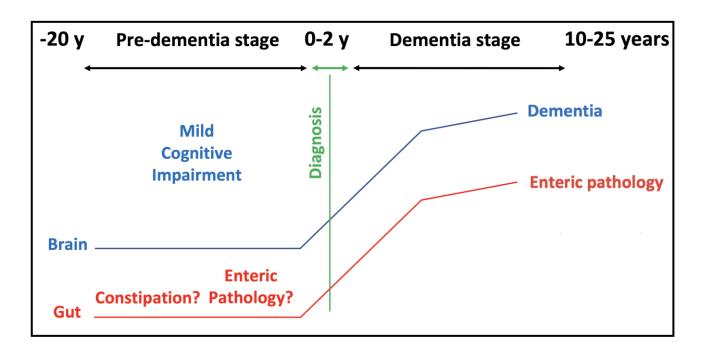
- Early GI disorders in AD patients (Nedelec et al., 2022)
- Early GI disorders

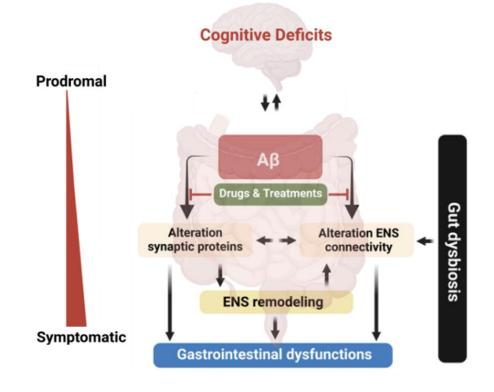
 ↑ the risk of developing severe AD (Nakase et al., 2022)



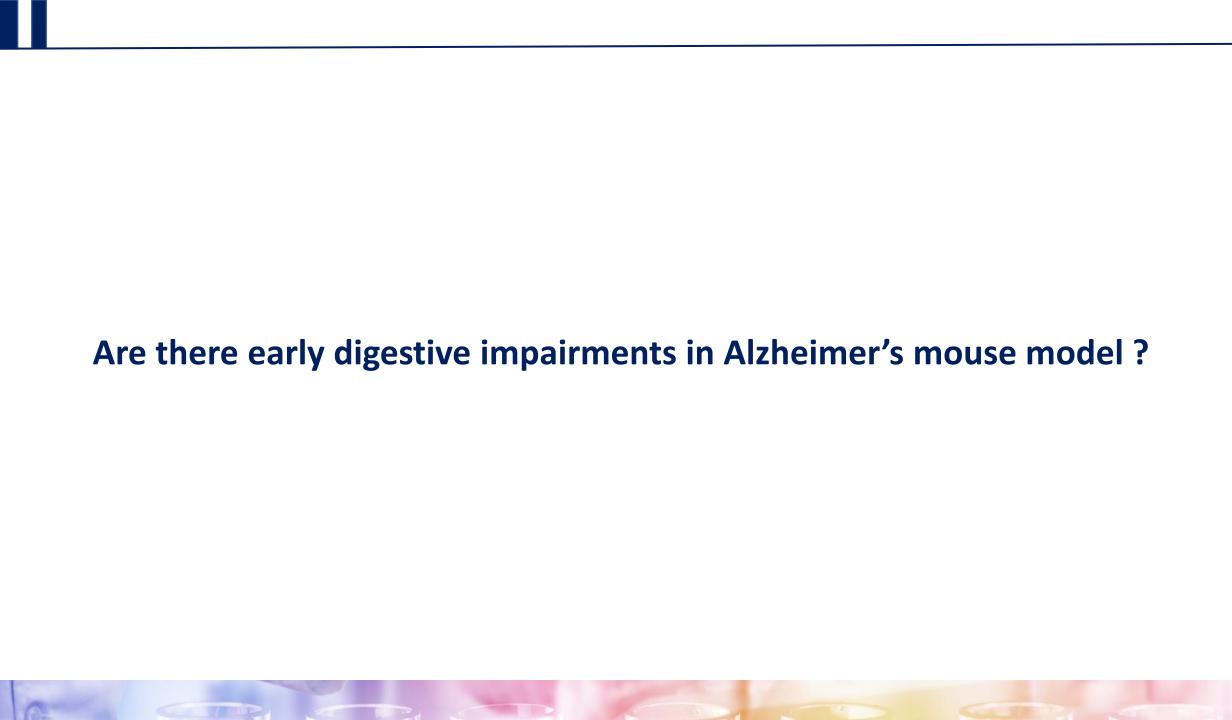
HC aMCI

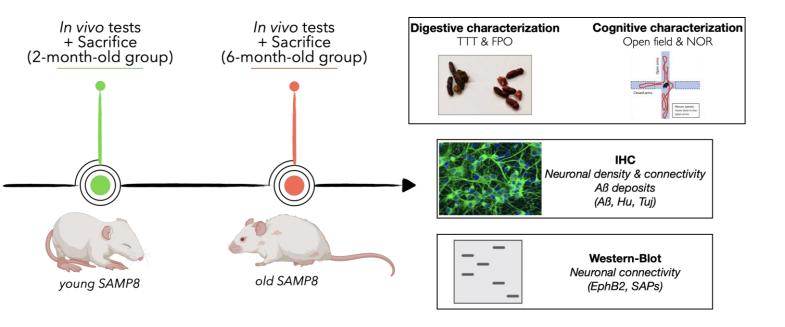
- Dysbiosis of intestinal microbiota in AD patients (Liu et al., 2019)
- Alteration in the composition of metabolites in AD patients (Wu et al., 2021)

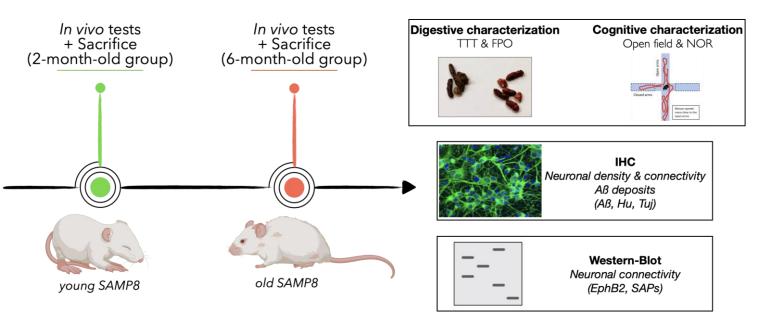




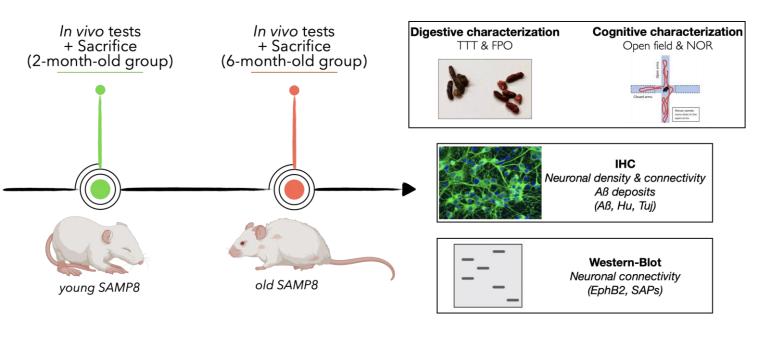
What are the beneficial effects of bacterial metabolites on cognitive and digestive functions in Alzheimer's disease ?





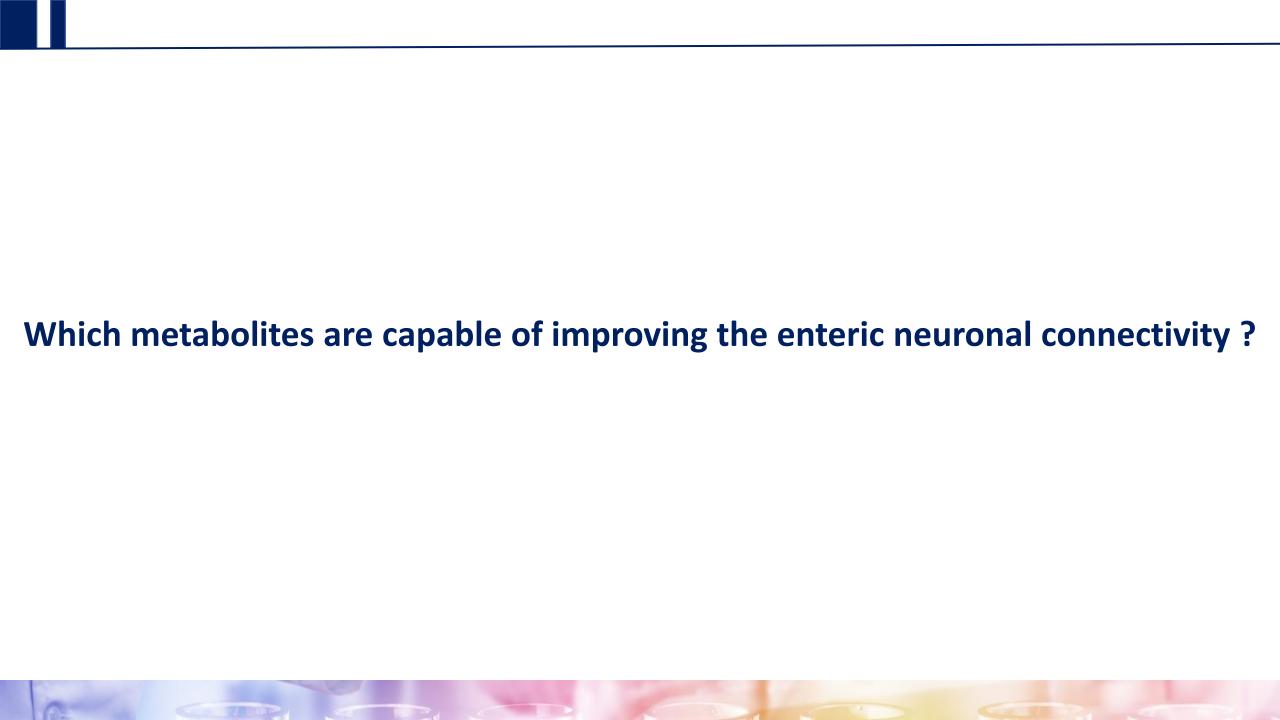


- Constipation and alterations in transit velocity as early as 2 months of age (in vivo)
- Memory impaiments only appear only from the age of 6 months (in vivo)
- Amyloïd-ß deposits in the gut at 2 months of age and only from the age of 6 months in the brain (ex vivo)
- Synaptic alterations in the ENS at 2 months of age, while they appear in the brain at the age of 6 months (in vitro)

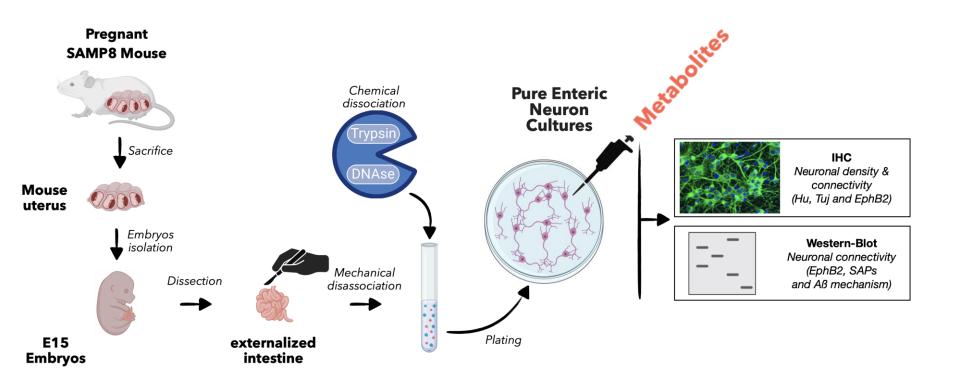


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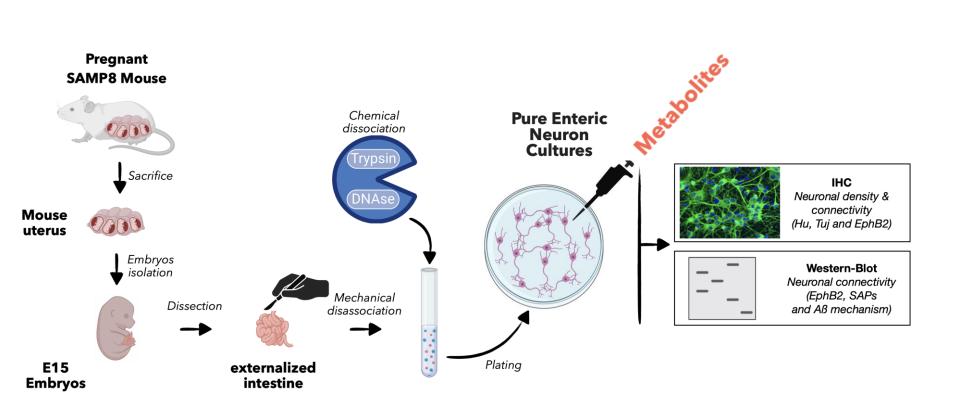
There are early digestive impairments in SAMP8 mouse



Which metabolites are capable of improving the enteric neuronal connectivity?

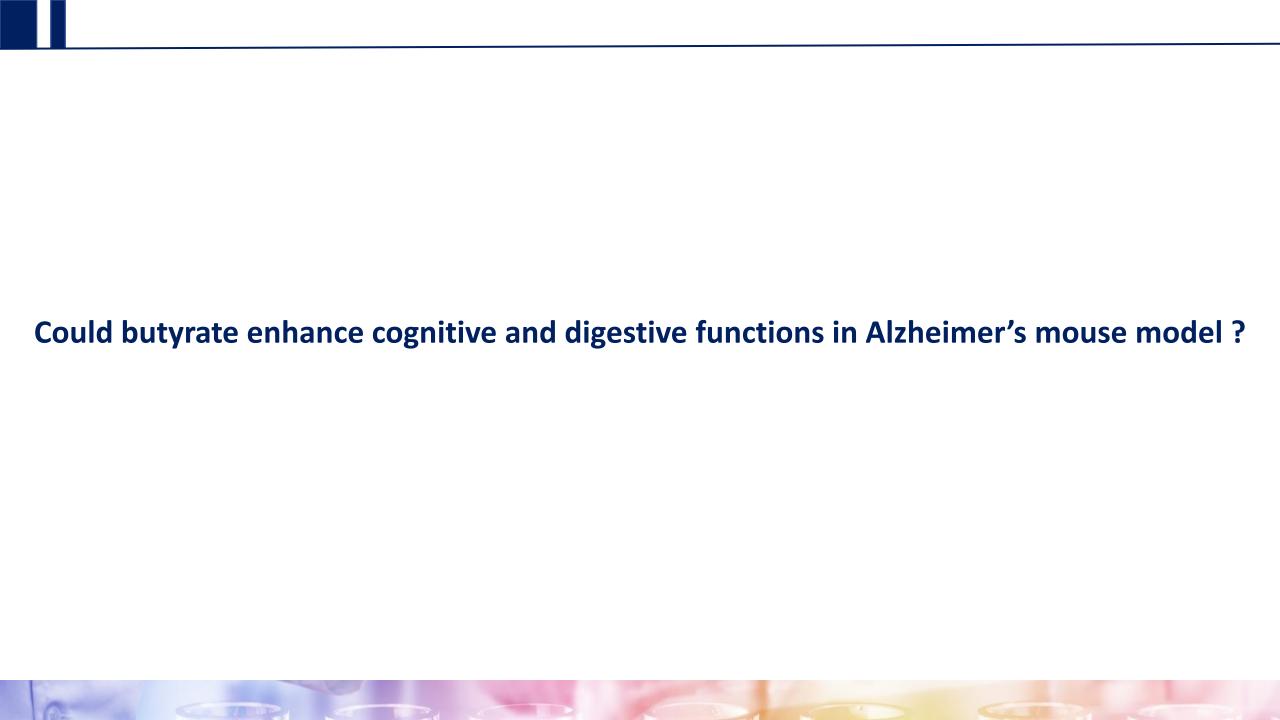


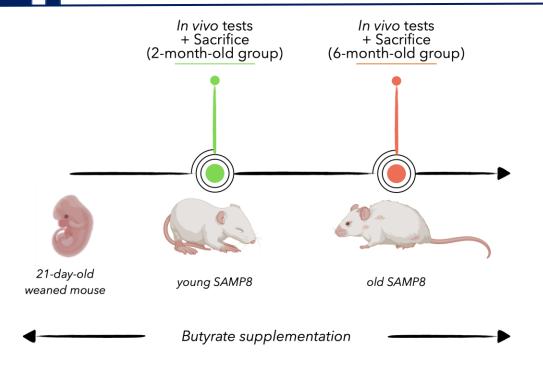
Which metabolites are capable of improving the enteric neuronal connectivity?

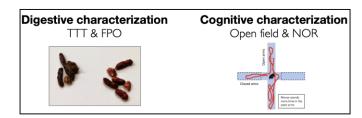


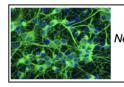
METABOLITE	BENEFICIAL EFFECTS?				
Acétate	NO				
Propionate	NO				
Butyrate	YES				
Lactate	NO				
GABA	NO				
Spermine	NO				
Spermidine	NO				
Kynurénine	NO				
Vitamine B9	NO				
Vitamine B12	NO				

Butyrate treatment improves the enteric neuronal connectivity in vitro





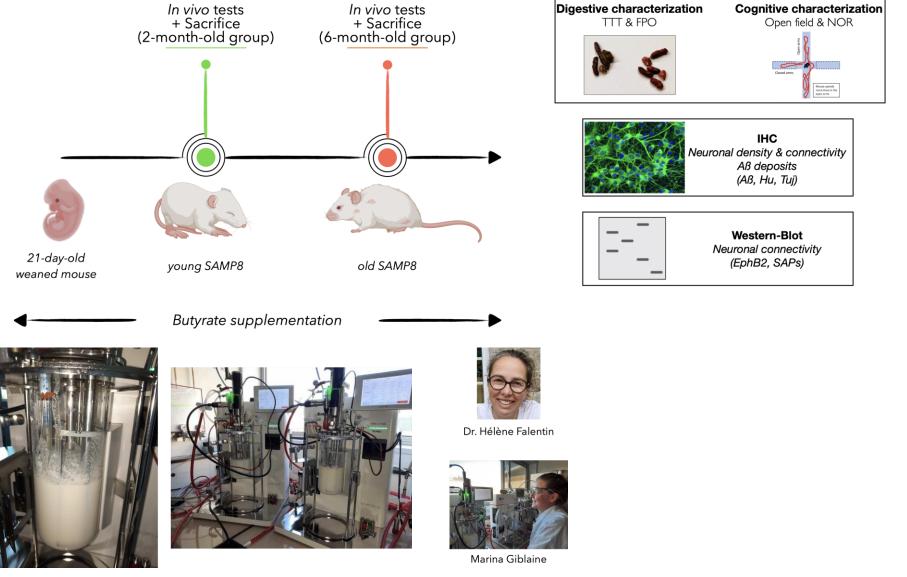




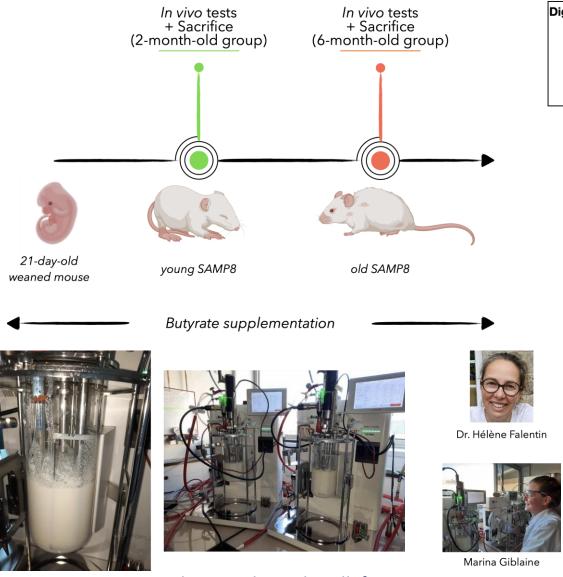
IHC Neuronal density & connectivity Aß deposits (Aß, Hu, Tuj)



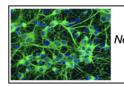
Western-Blot Neuronal connectivity (EphB2, SAPs)



Dairy product enriched with butyrate







IHC Neuronal density & connectivity Aß deposits (Aß, Hu, Tuj)



Western-Blot Neuronal connectivity (EphB2, SAPs)



Work in progress ...

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

Sarah BLANCHET Directed by Sophie BLAT and by Sergine **EVEN**























Human milk

→ Optimal post-natal nutrition for the newborn.



Human milk



Infant Formula





Infant Formula

Meet the nutritional needs of the newborn by:

Macronutrients: Proteins, Carbohydrates, Lipids

Micronutrients: Minerals, vitamins



Human milk

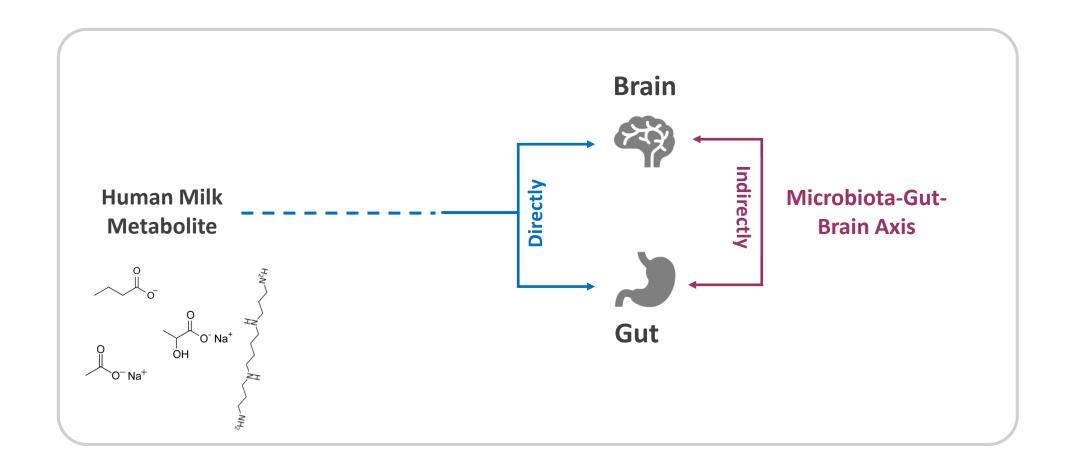
Human Milk Metabolite



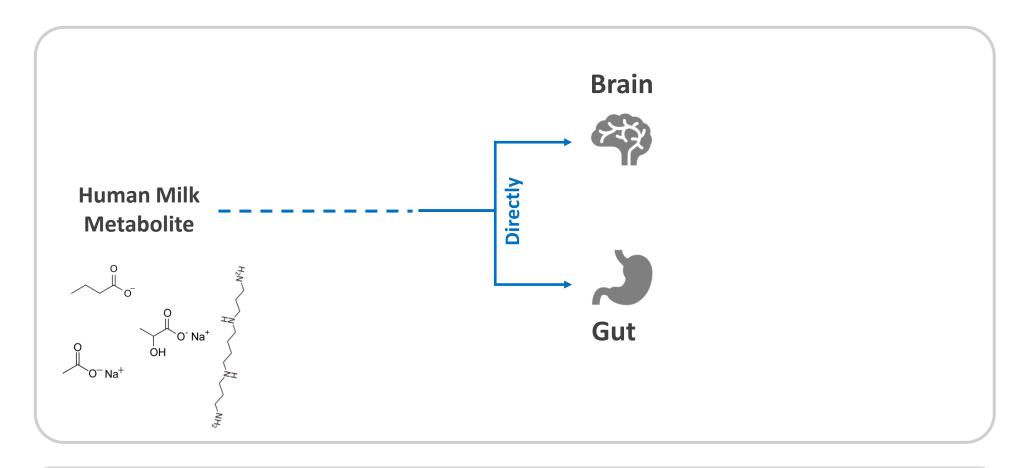


Infant Formula

Research questions



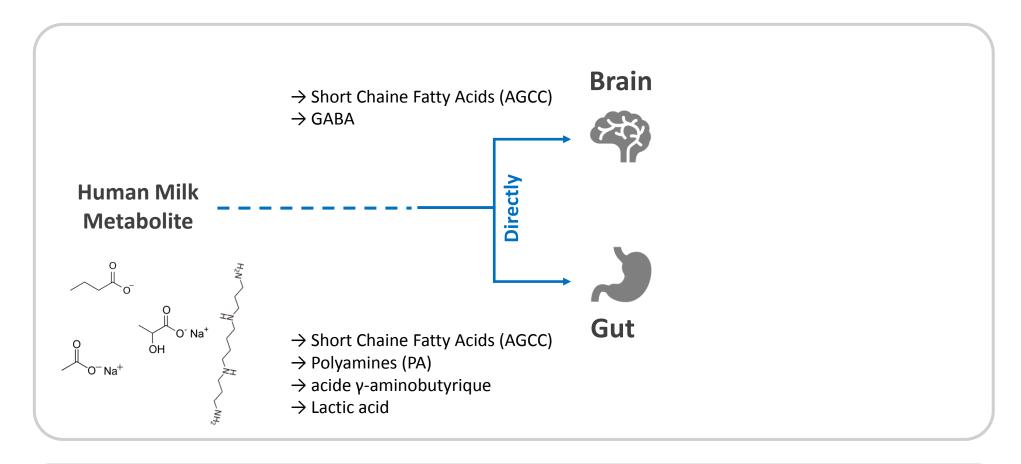
In vitro study of the metabolites





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

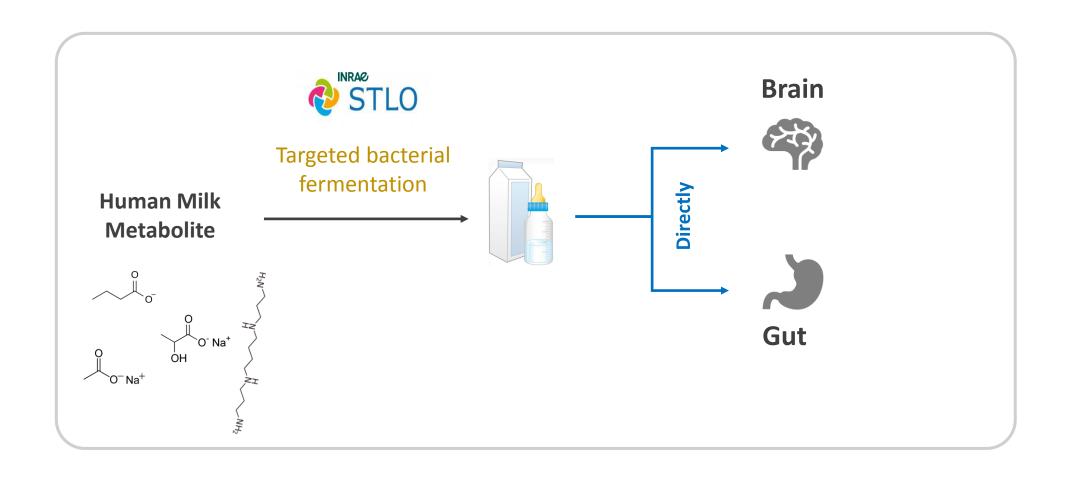
In vitro study of the metabolites



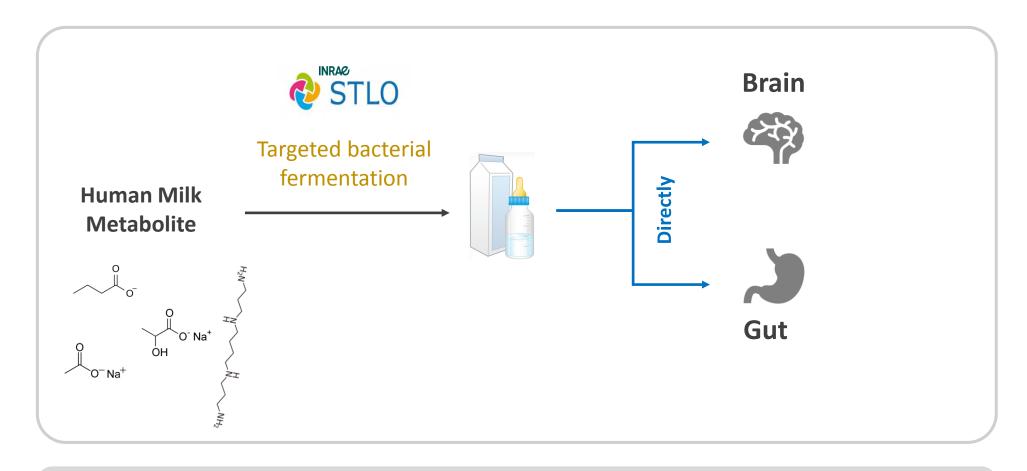


in vitro : cellular models of intestinal epithelium and central neurons (screening of relevant metabolites)

In vivo study of metabolites produced by targeted bacterial fermentation



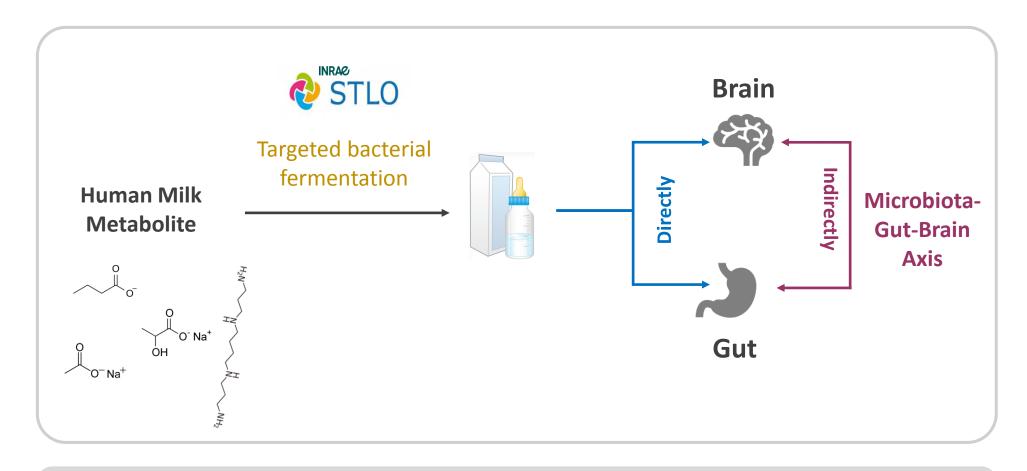
In vivo study of metabolites produced by targeted bacterial fermentation





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:

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