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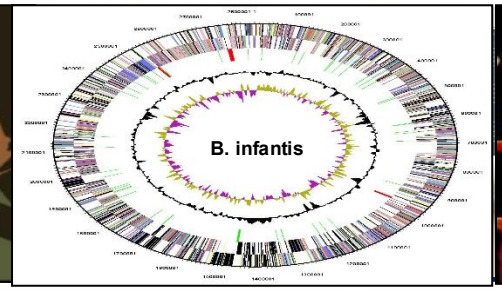
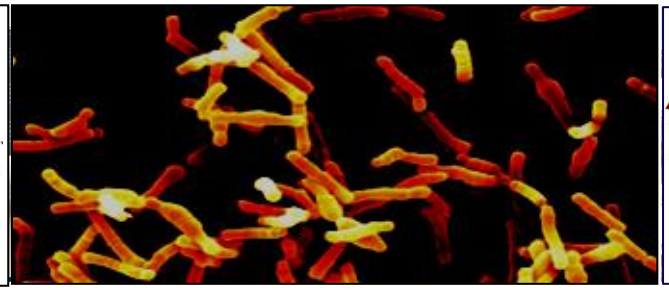
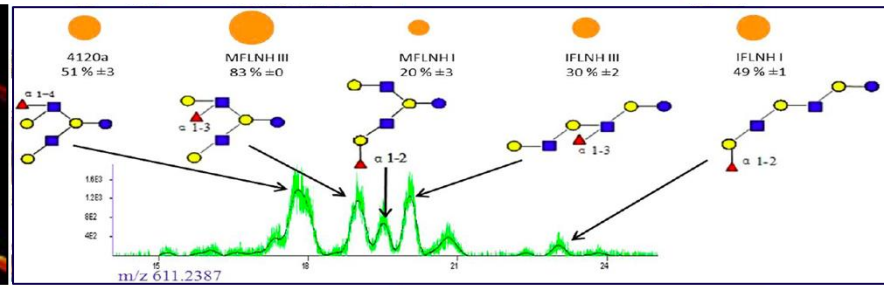
UNIVERSITY OF CALIFORNIA

Milk Builds Brains





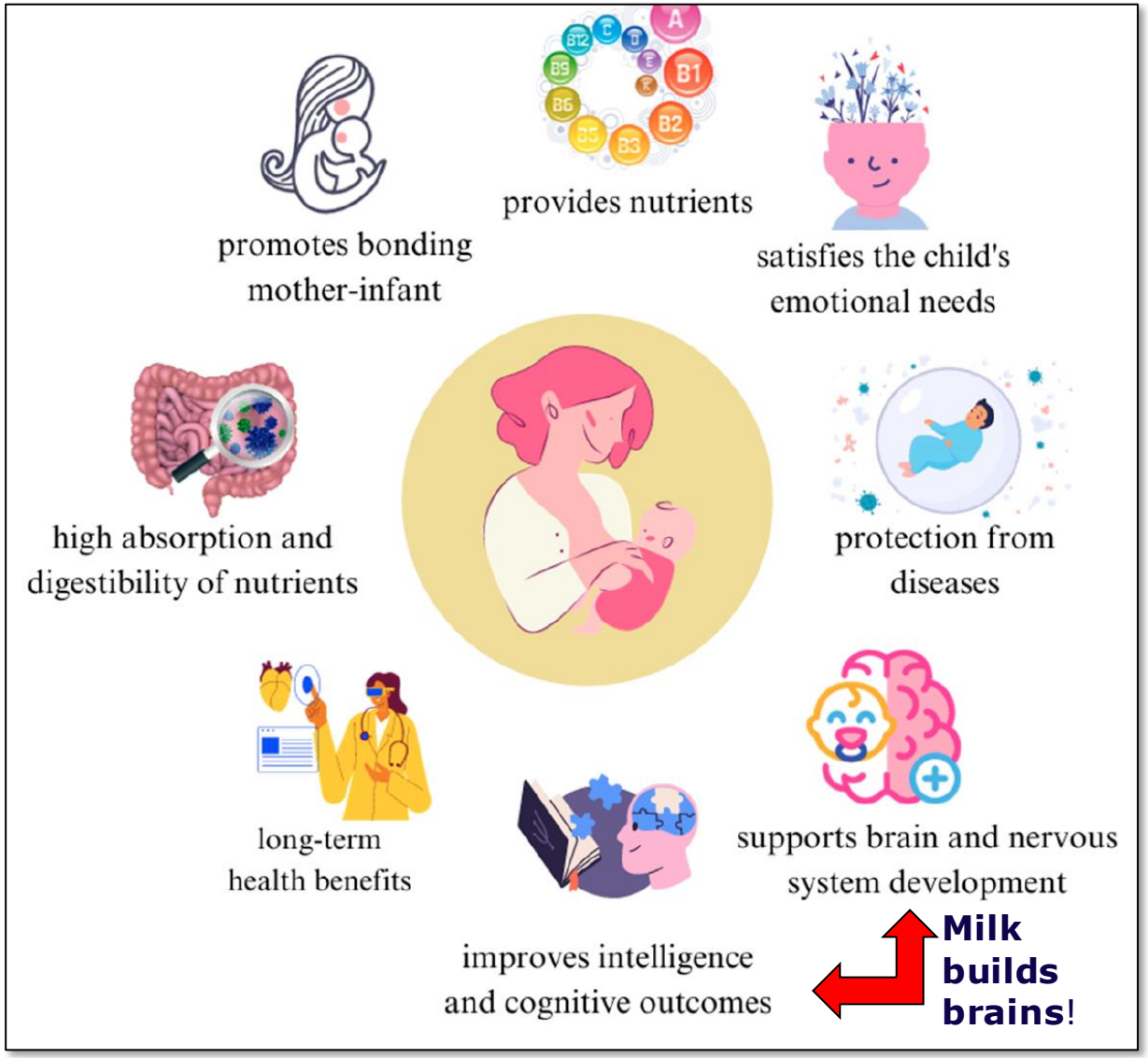


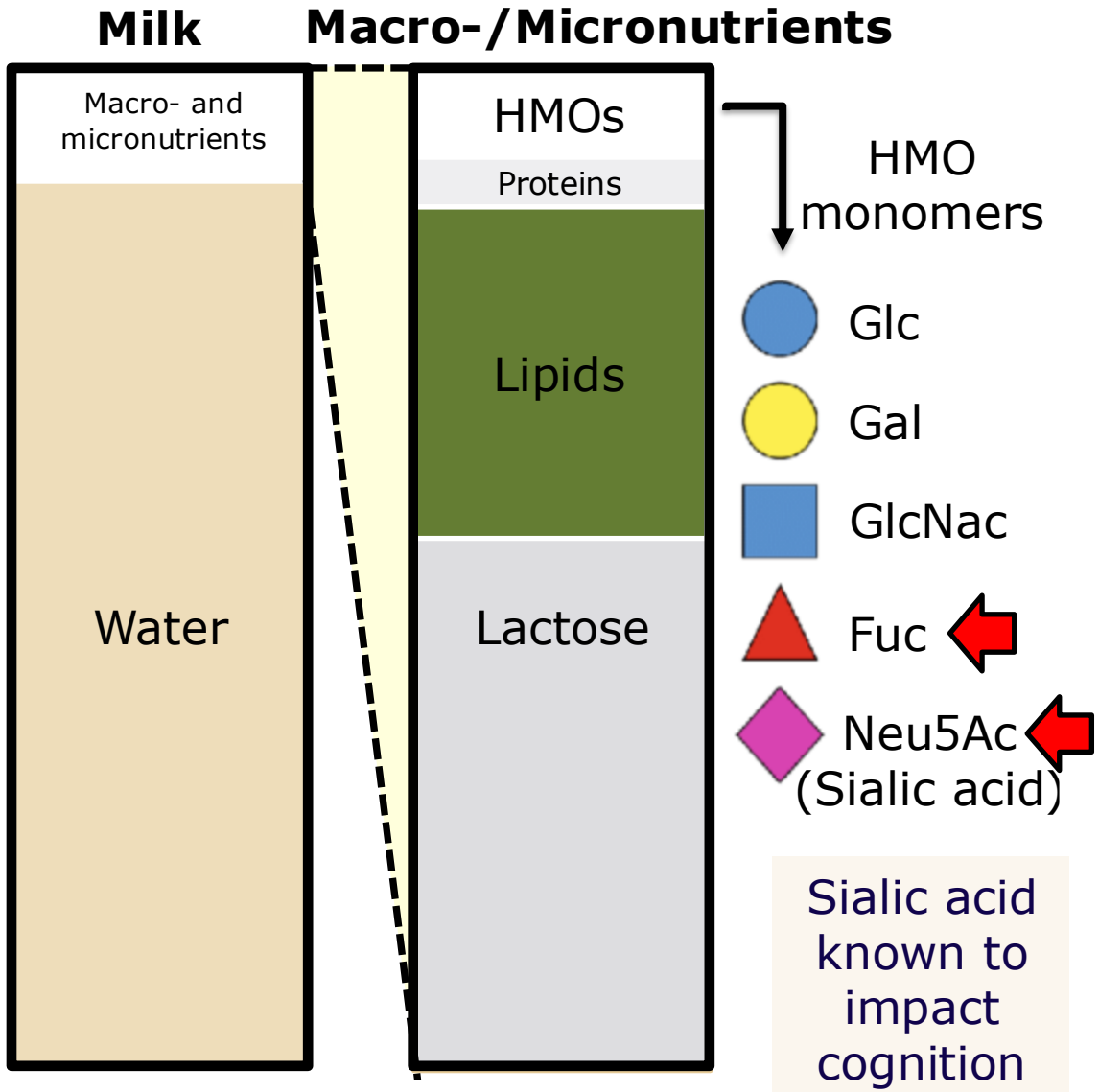
Milk is *Smart:* The Impact of Fucosylated Glycans from Milk on Cognition

David A. Mills
Distinguished Professor, UC Davis
Peter J. Shields Endowed Chair in Dairy Food Science
mills.ucdavis.edu

UC DAVIS
FOOD SCIENCE AND TECHNOLOGY

Human milk influences on neonate health

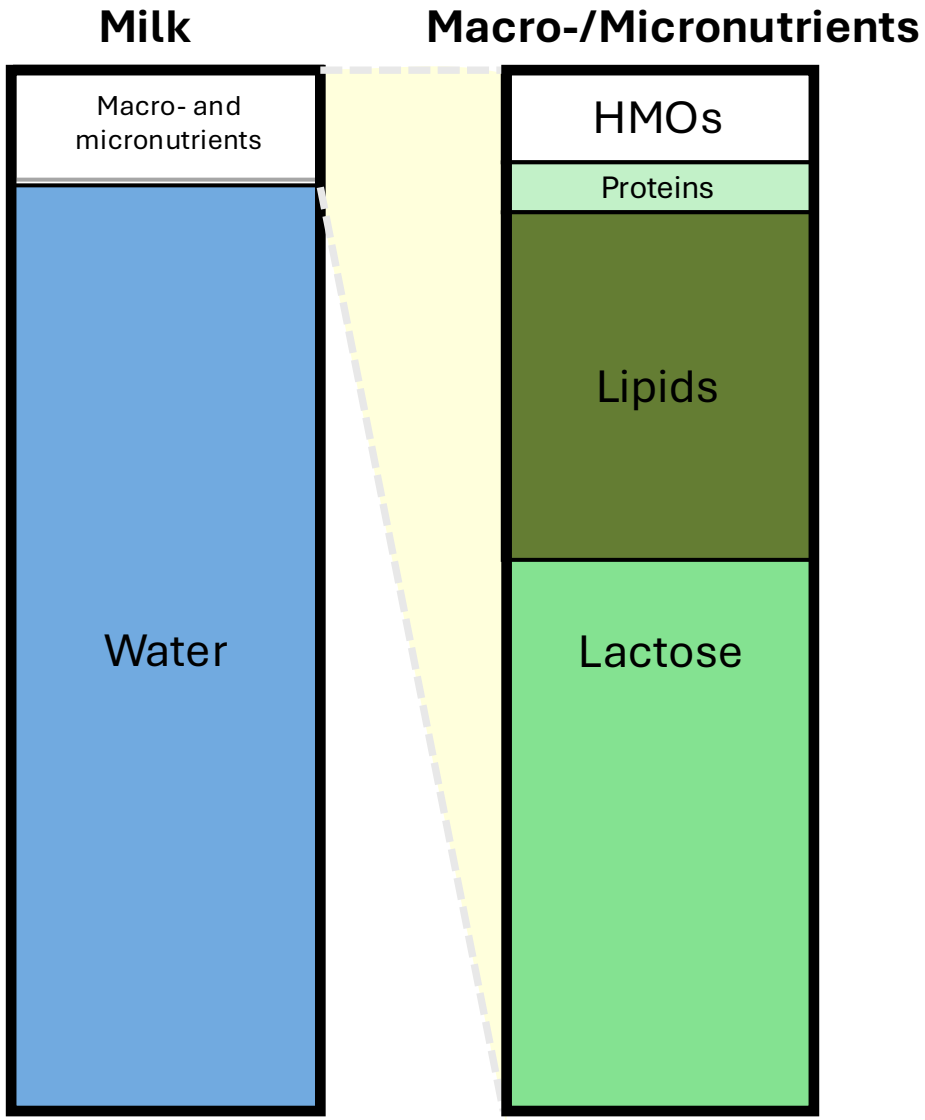




Sialic acid known to impact cognition

Nutrients 2025, 17, 1326

Human milk composition & Human milk oligosaccharides (HMOs)



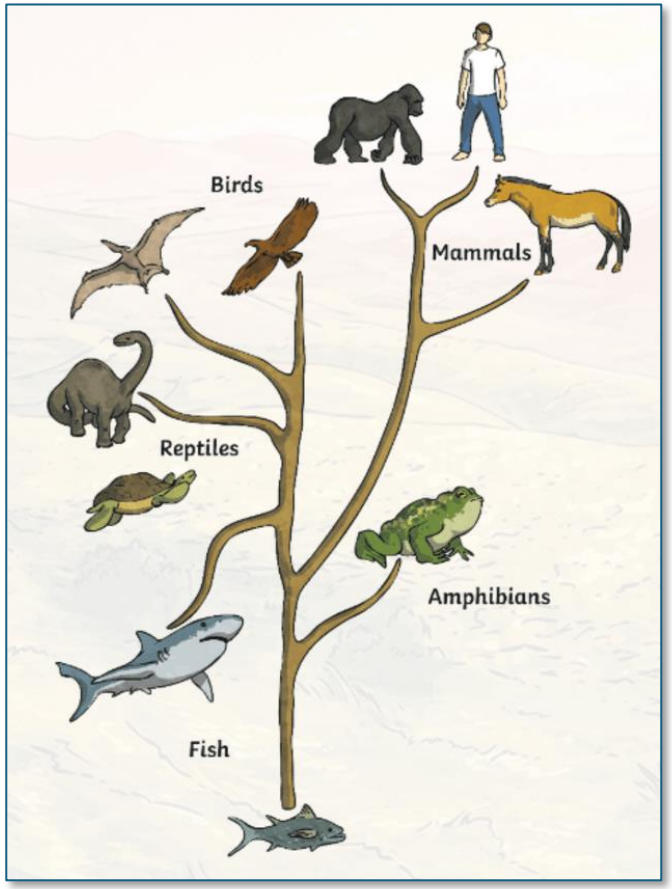
Unlike human milk, bovine milk is lacks significant fucose

Table I. Macronutrients and HMOs in mature human and bovine milk (approximate values)

	Human	Bovine
Protein (g/L)	8[a]	32[a]
Fat (g/L)	41[a]	37[a]
Lactose (g/L)	70[a]	48[a]
Oligosaccharides (g/L)	5–15[b]	0.05[c]
Number of identified oligosaccharides	100+[b,d]	~40[e]
%fucosylated	50–80%[b,d,f]	~1%[e]
%sialylated	10–20%[b,d]	~70%[e]

Newburg 2005, 2009

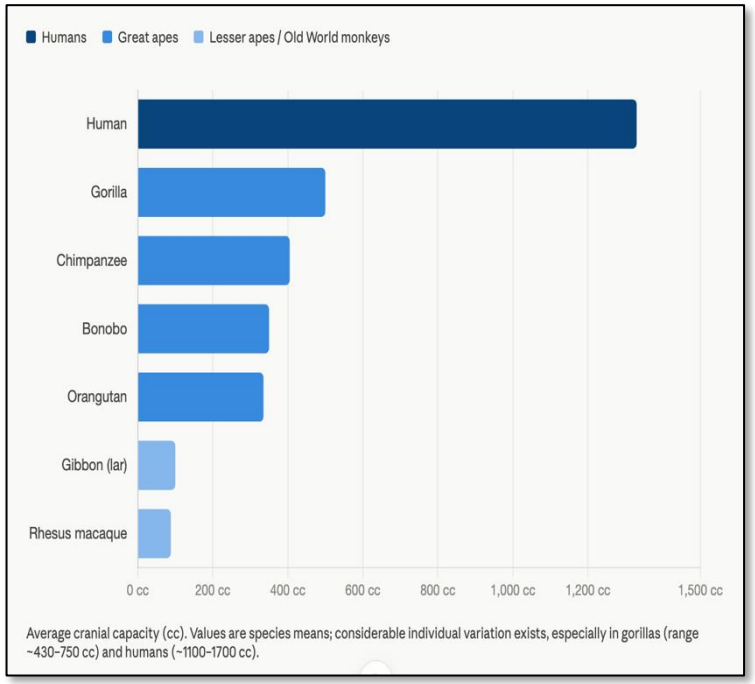
Is there a connection between fucosylated glycans and the brain?



- *Homo sapiens* have the largest amount of fucosylated milk glycans
- Nearest primates have less
- Other mammals have much less

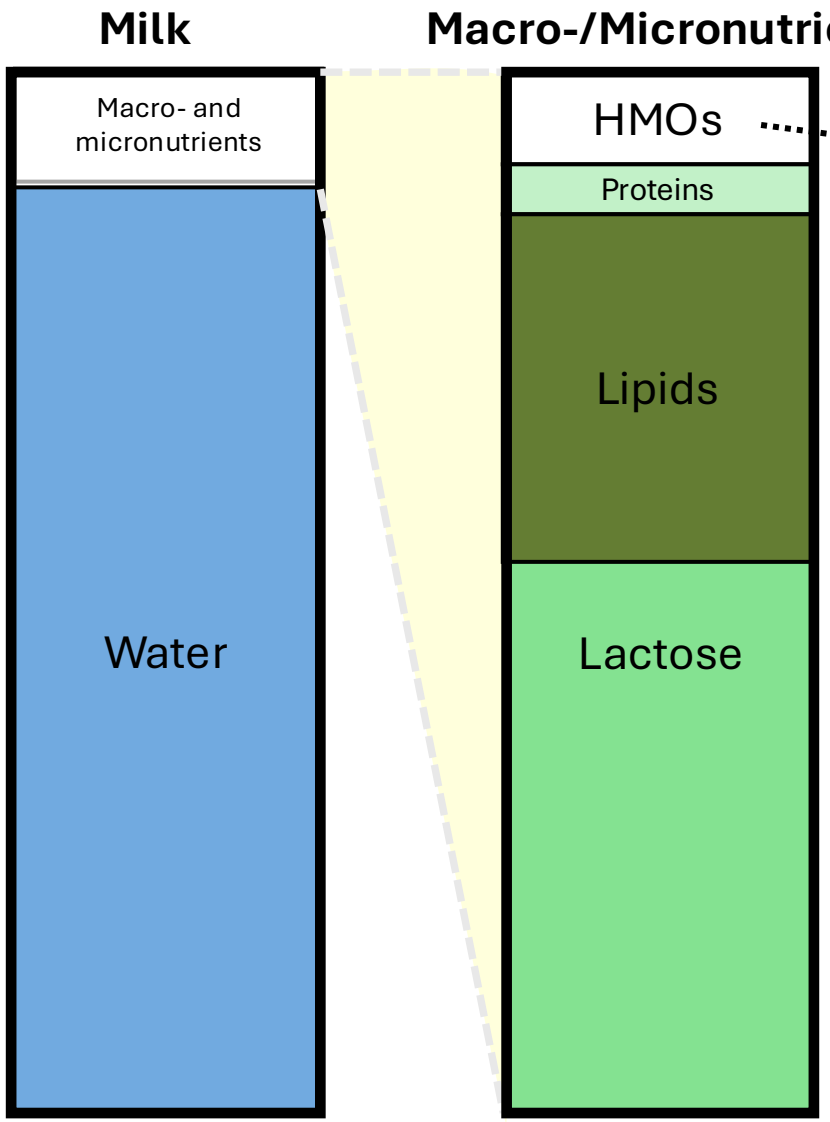
Is fucose a connection here?

Average Cranial Capacity

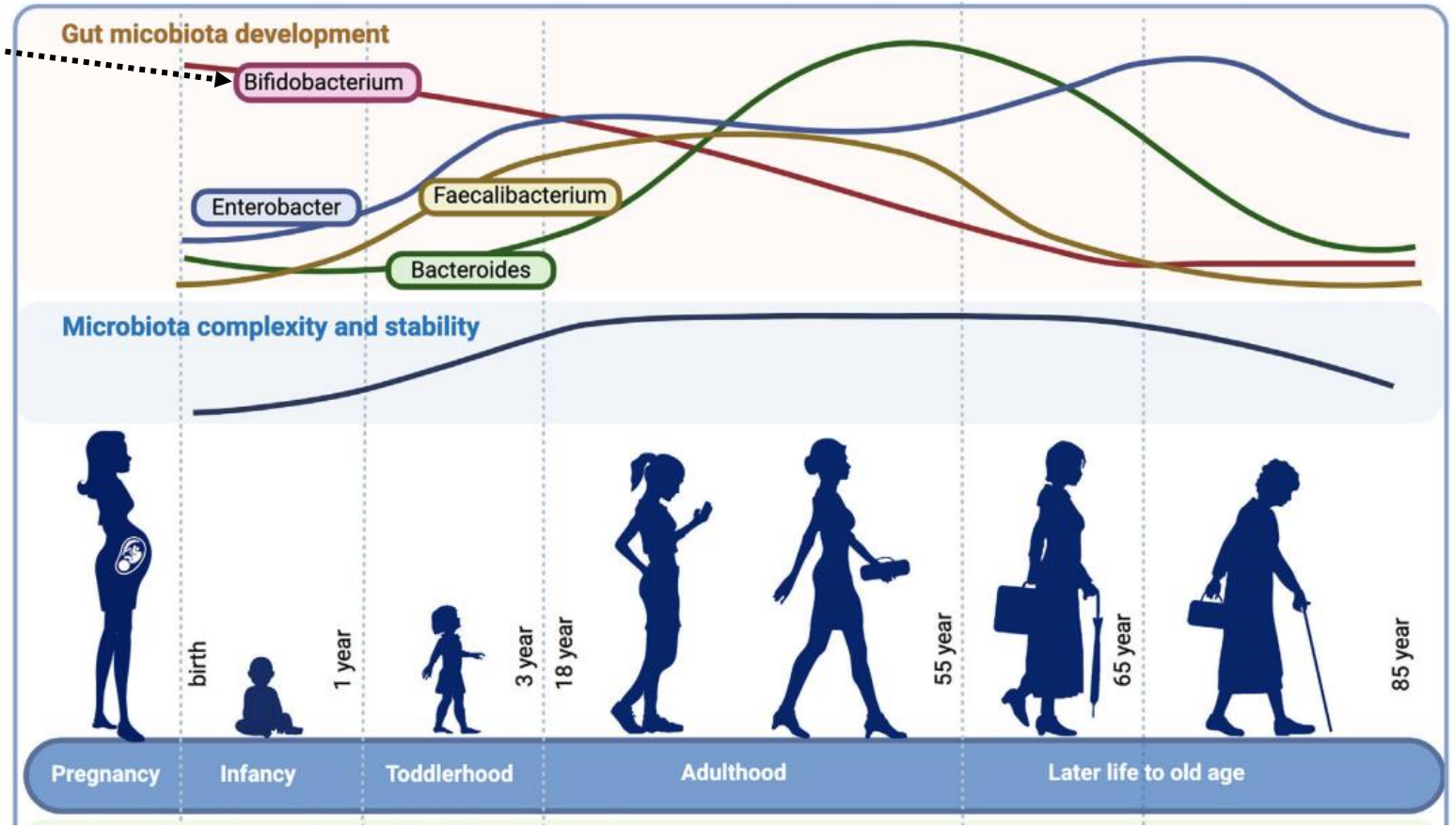


https://karger.com/fpr/article-abstract/35/1/1/142267

Human milk composition & Human milk oligosaccharides (HMOs)



Fucosylated HMOs enrich specific bifidobacteria in babies



Is a fucose-brain link mediated by bacteria?

Hypothesis: If dietary fucose — present in high quantities in human milk — is linked to brain health, one could envision two mechanistic routes:

Direct route

Dietary fucose is directly incorporated into a growing brain glycoconjugates towards a neuro-benefit. Same assumed route for MFGM-based sialic acid benefits.

Indirect route

Dietary fucose is fermented into specific metabolite(s) via the gut microbiome. Those metabolite(s) transit to the brain and impact brain health

Fucose and the Brain

Fucosylation is different in the brain in Alzheimer's

Alzheimer's brains are lacking normal fucosylated glycoconjugates

Received: 13 November 2022 | Revised: 3 January 2023 | Accepted: 10 January 2023

DOI: 10.1002/glia.24345

GLIA

WILEY

RESEARCH ARTICLE

The role of FUT8-catalyzed core fucosylation in Alzheimer's amyloid-β oligomer-induced activation of human microglia

Lee-Way Jin[1] | Jacopo di Lucente[1] | Ulises Ruiz Mendiola[1] | Xinyu Tang[2] | Angela M. Zivkovic[2] | Carlito B. Lebrilla[3] | Izumi Maezawa[1]

Oral fucose supplementation mitigates fucose glycan deficits in a rat model of Alzheimer's

SCIENCE ADVANCES | RESEARCH ARTICLE 2025

NEUROSCIENCE

L-Fucose is a candidate monosaccharide neuromodulator and mitigates Alzheimer's synaptic deficits

Jacopo Di Lucente[1,2], Jennyfer Tena[3], Yuanyuan Bai[3], Catelynn C. Shafer[3], Ulises Ruiz Mendiola[1,4], Elizabeth K. Neumann[3], Xi Chen[3], Carlito B. Lebrilla[3], Izumi Maezawa[1,2,4]*, Lee-Way Jin[1,2,4]*

Fucosylation, a major glycan modification, has been shown to influence neuronal and microglial mechanisms, but whether unconjugated free L-fucose can affect brain function is unknown. L-Fucose can be transported into cells and metabolized by fucokinase (FCSK) via the poorly understood salvage pathway. Using mouse hippocampal slices, we showed that L-fucose enhanced excitatory neurotransmission and long-term potentiation (LTP) through regulation of presynaptic release. Such effects required L-fucose be metabolized through the FCSK-driven salvage pathway, suggesting a metabolic-signaling mechanism. Human Alzheimer's disease (AD) and 5xFAD mouse brains showed signs of fucose hypometabolism with impaired L-fucose signaling. Such abnormalities were corrected by exogenous L-fucose, exemplified by rectification of LTP deficits in 5xFAD hippocampus. A dietary L-fucose supplement, which increased cerebral free L-fucose levels and up-regulated FCSK to drive the salvage pathway, mitigated synaptic and behavioral deficits of 5xFAD mice. Our data suggest an unrecognized neuromodulatory function of free L-fucose and reveals its therapeutic potential for AD.

Is fucose the new brain supplement?

Oral fucose supplementation is also anti-inflammatory in the brain

JBC RESEARCH ARTICLE

Exogenous L-fucose attenuates neuroinflammation induced by lipopolysaccharide

Received for publication, October 13, 2023, and in revised form, November 16, 2023 Published, Papers in Press, December 1, 2023,
https://doi.org/10.1016/j.jbc.2023.105513

Xing Xu[1], Tomohiko Fukuda[1], Jun Takai[2], Sayaka Morii[3], Yuhan Sun[1], Jianwei Liu[1], Shiho Ohno[4], Tomoya Isaji[1], Yoshiki Yamaguchi[4], Miyako Nakano[3], Takashi Moriguchi[2], and Jianguo Gu[1,*]

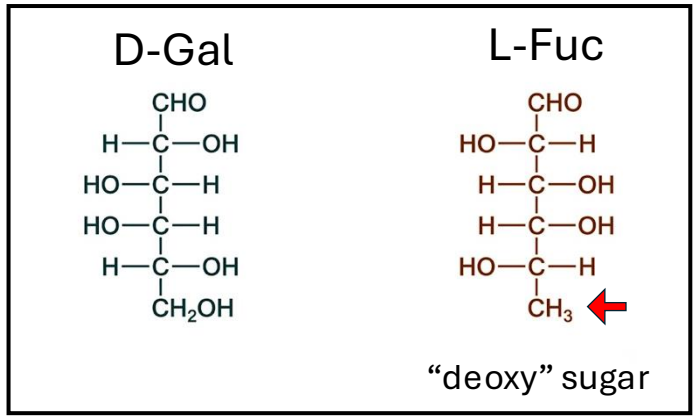
Fucose Metabolites and the Brain

Carolyn Slupsky, Ph.D.

Professor and Nutritionist

Food Science and Technology
Nutrition

Fucose metabolic pathway

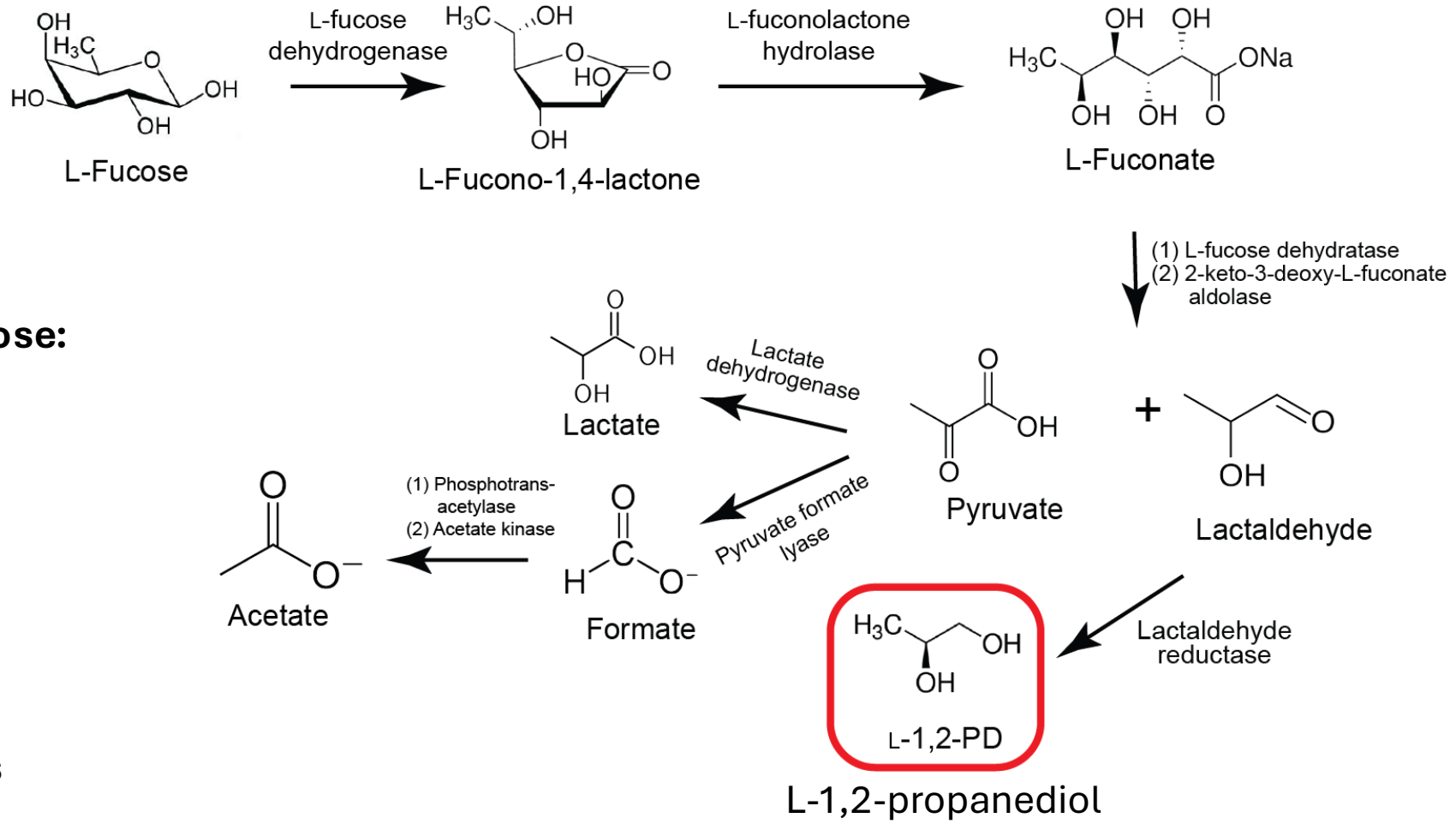


Gut microbes that can ferment fucose:

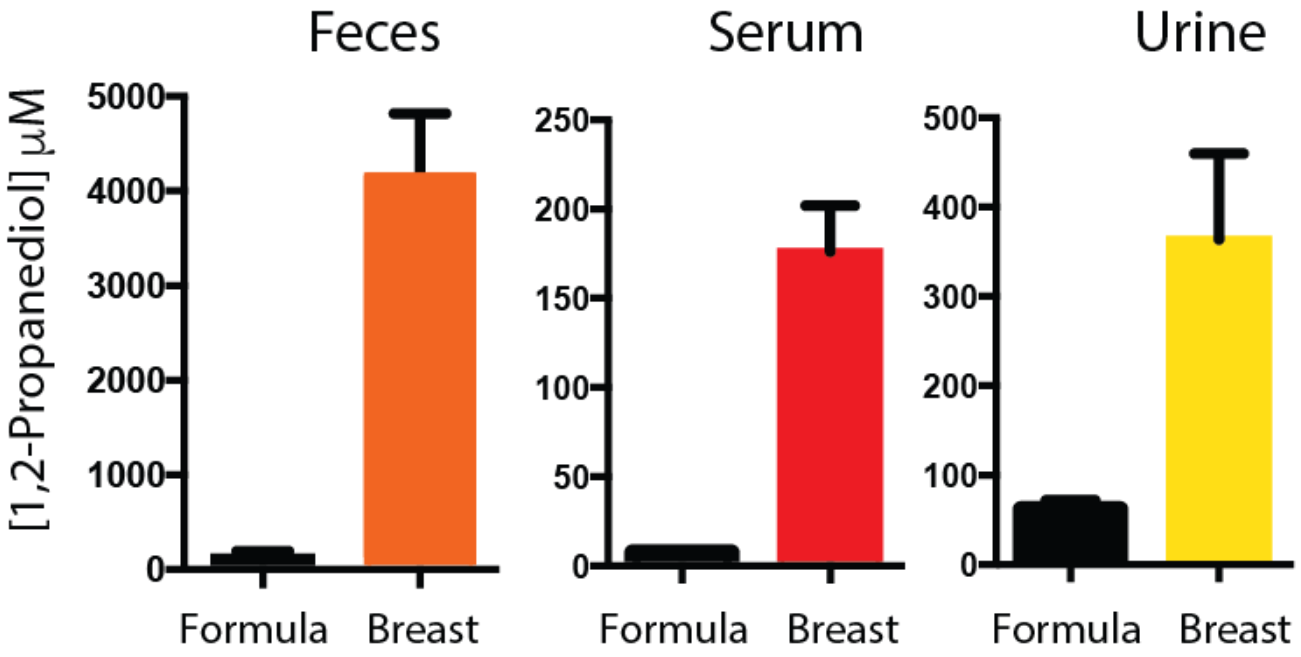
- Bifidobacterium species
- Lactobacillus species
- Clostridium species
- Roseburia species
- Blautia species
- Enterobacteriaceae species

Red = probiotics / next gen probiotics

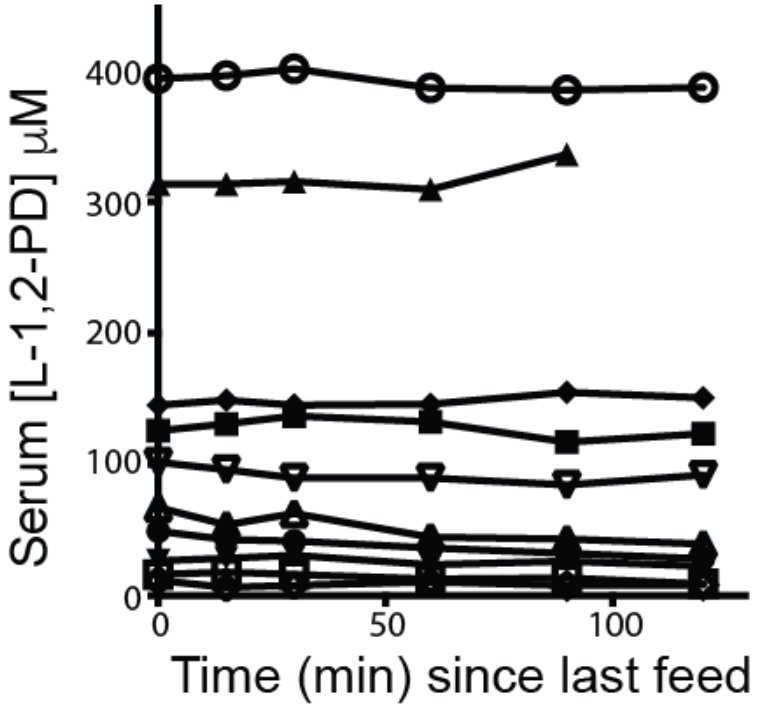
Bifidobacterium fucose metabolic pathway



Fucose metabolite L-1,2-propanediol is highly abundant in breast fed infant blood, urine, and feces



12PD persists over breastfeeding



Why would evolution have placed 12PD at such a constant high level in breast-fed babies? Does it help their brains?

Carolyn Slupsky unpublished data

Colonization of mice with bifidobacteria

Carolyn Slupsky, Ph.D.

Professor and Nutritionist

Food Science and Technology
Nutrition

David A. Mills, Ph.D.

Distinguished Professor, Peter J. Shields Chair in Dairy Food Science

Food Science and Technology

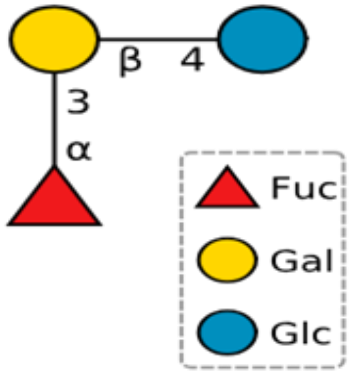
Helen Raybould

Professor Emeritus

Anatomy, Physiology & Cell Biology

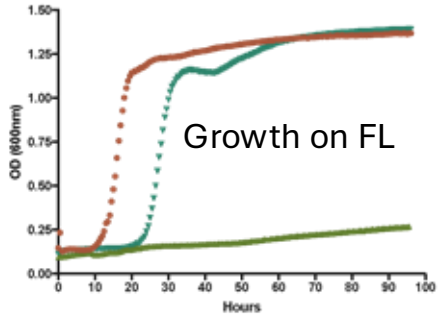
2

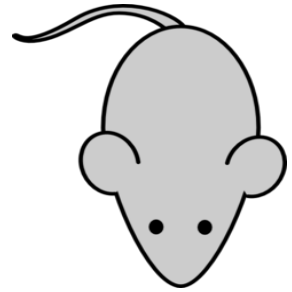
Fucosyllactose (FL)



+

Bifidobacterial strains

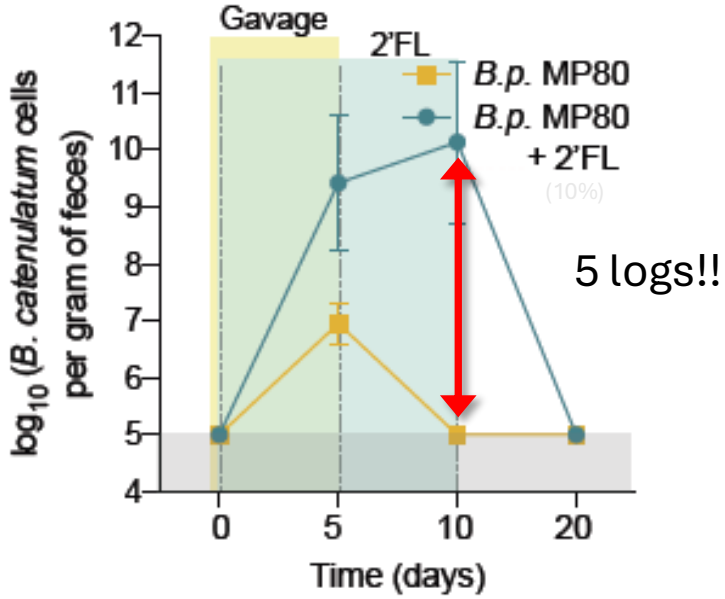




C57BL/6
WT mouse

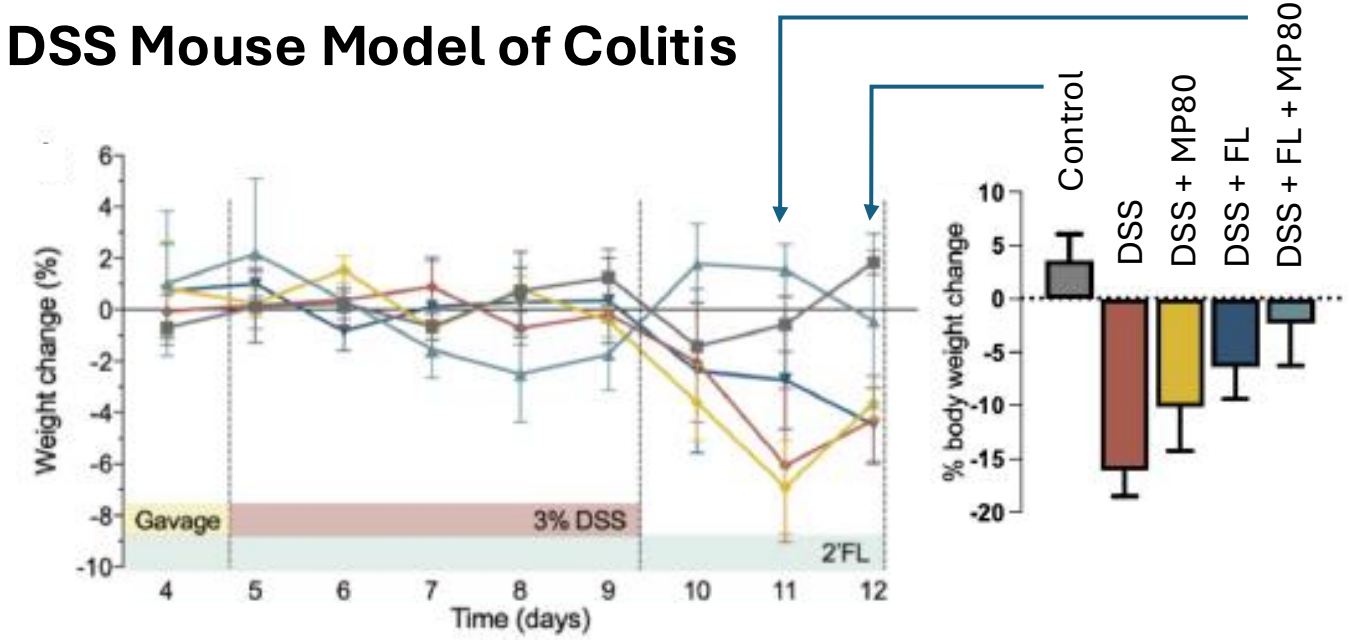
Synbiotic application enables dramatic enrichment of fucose fermenting bifidobacteria.

Does this produce 12PD and improve brain health?

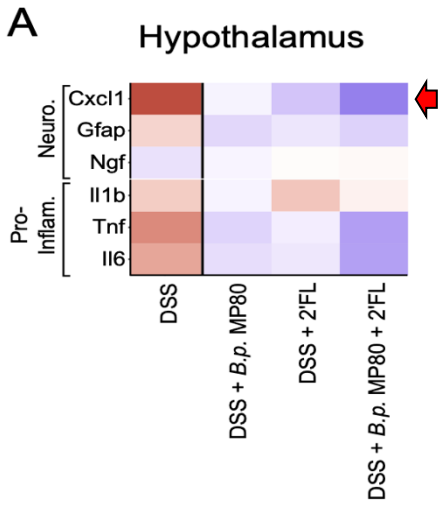


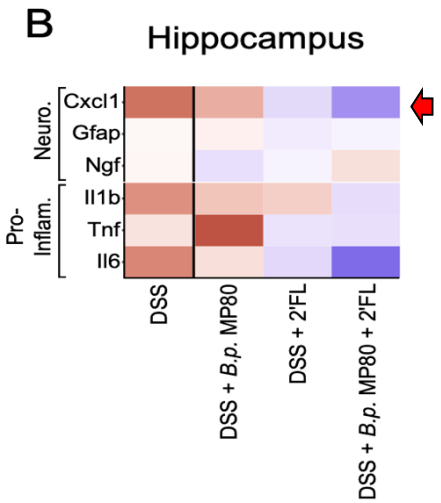
Gut Microbes 13:1986666 (2021)

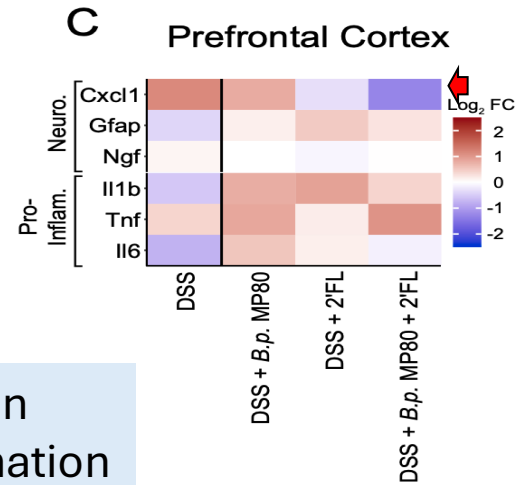
Attenuated neuroinflammation after treatment with *B. pseudocatenulatum* MP80 and 2'FL



Proinflammatory cytokine Cxcl1 is reduced





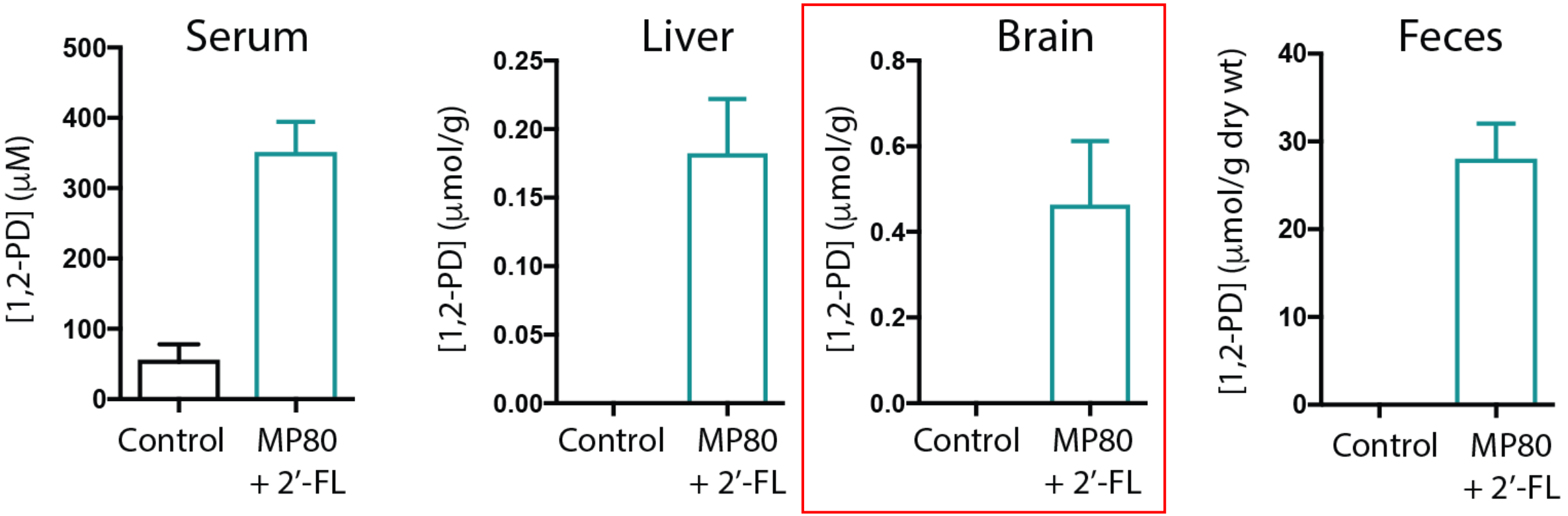


Synbiotic application improved neuroinflammation

Gut Microbes 13:1986666 (2021)

Bifidobacterium colonized mice provided 2'FL produce systemic 1,2-PD

12PD crossed blood brain barrier at a high level



Larke et al Microbiome 2023.

DIRECT Impact of 1,2-PD on the rat brain *in vitro*

Erkin Şeker, Ph.D.
Professor
Electrical and Computer Engineering
University of California

Goshi *et al. Journal of Neuroinflammation* (2020) 17:155
https://doi.org/10.1186/s12974-020-01819-z

Journal of Neuroinflammation

RESEARCH Open Access

A primary neural cell culture model to study neuron, astrocyte, and microglia interactions in neuroinflammation

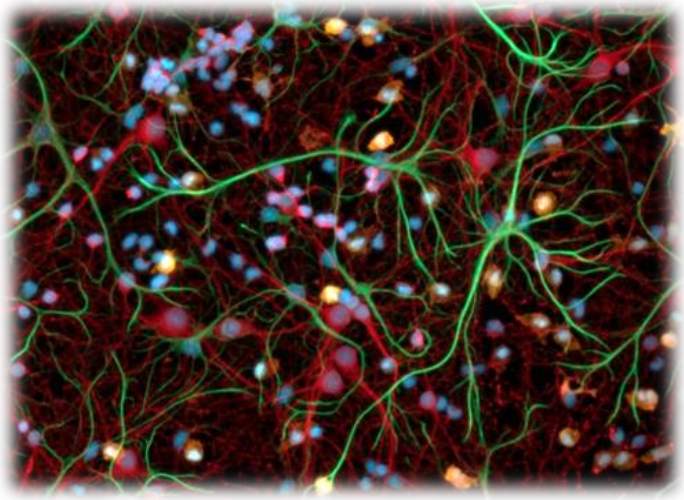
Noah Goshi[1], Rhianna K. Morgan[2], Pamela J. Lein[2] and Erkin Seker[3*]

Cortical cell tri-cultures from Rat

Three major cell types associated with neuroinflammation:

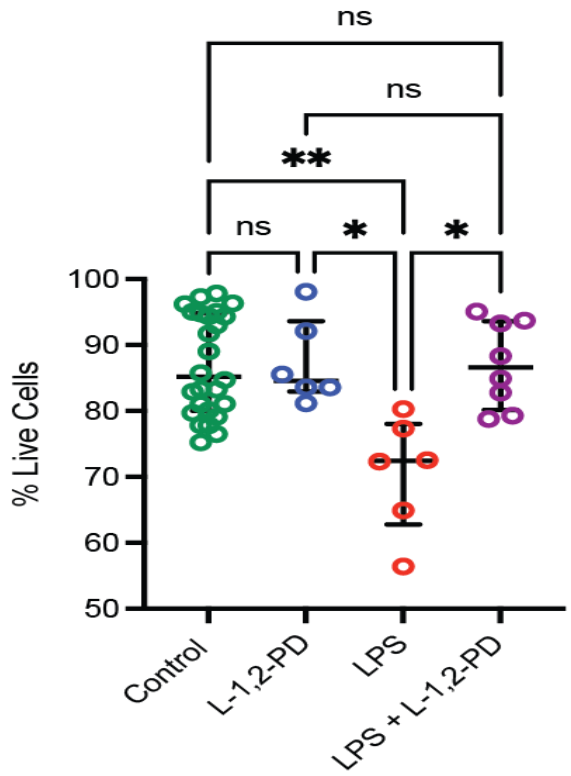
Neurons (tubulin-βIII)
Sstrocyte (GFAP)
Microglia (Iba1)

Nuclei (DAPI)



The tri-culture more faithfully mimics in vivo neuroinflammatory responses than standard mono- and co-cultures

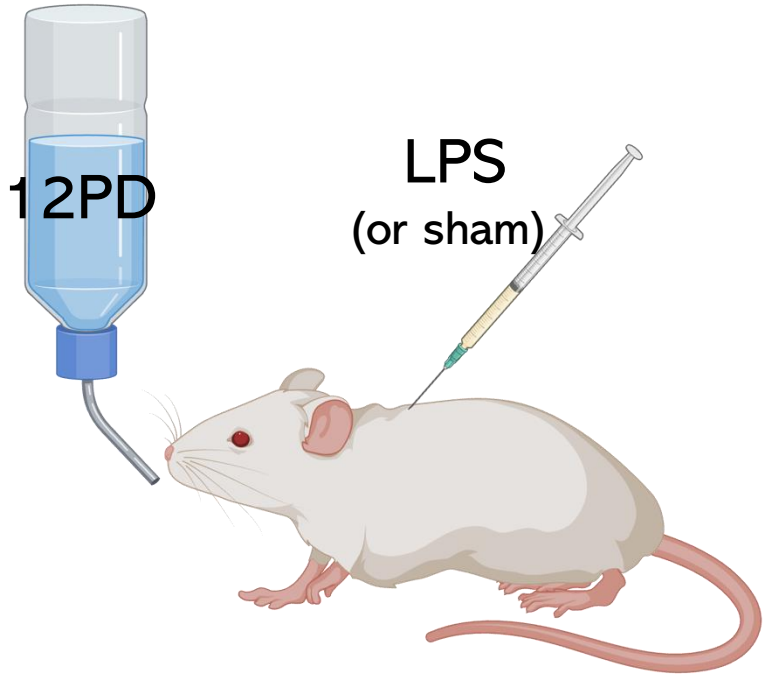
12PD protected neural tri-culture from LPS-driven cell death



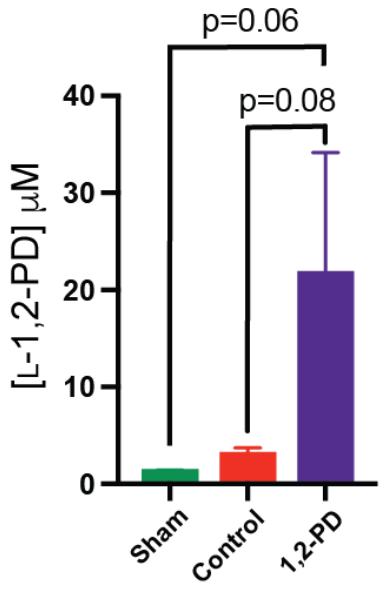
→ **Maybe 12PD protects brains from inflammation!**

U.S. Patent Application 63/712,087

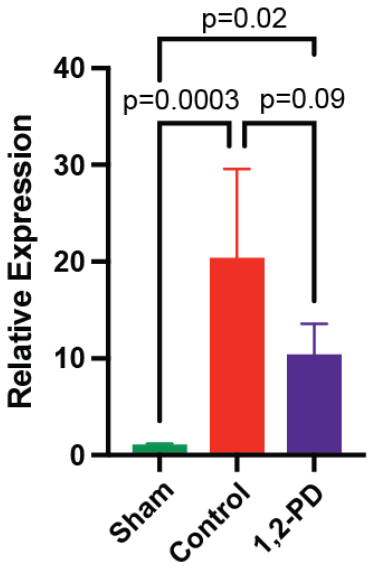
Oral delivery of 1,2 PD *appears* to impact LPS-induced neuro-inflammation in a rat model



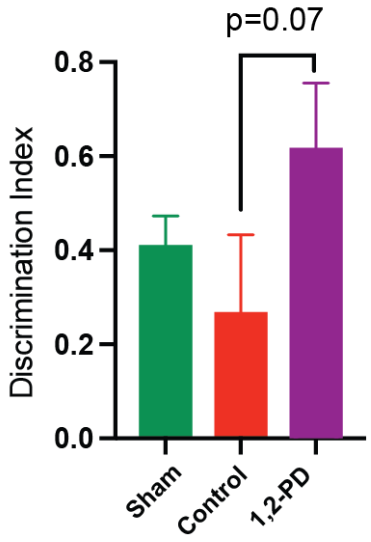
Serum concentrations of 1,2-PD



Proinflammatory Cyctokine CXCL1



Short term memory test



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Nutrition

Ameer Taha, Ph.D.

Professor

Food Science and Technology

(530) 752-7096 | ataha@ucdavis.edu |
Google Scholar | ResearchGate

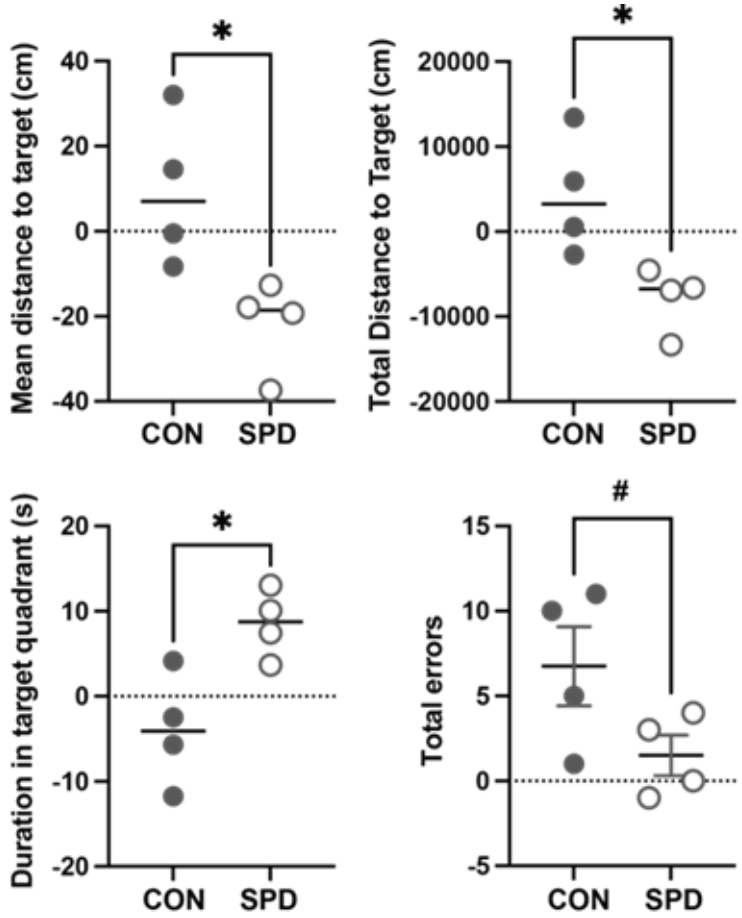
U.S. Patent Application 63/712,087

Oral 1,2PD dramatically improves cognition in healthy rats

12PD

Tests spatial learning, reference memory, and cognitive flexibility

Barnes maze outcomes



Additional testing indicates oral 12PD appears to lower anxiety in healthy rats via open field testing

U.S. Patent Application: 64/052,752

Hypothesis: If dietary fucose — present in high quantities in human milk — is linked to brain health, one could envision two mechanistic routes:

✓ **Direct route**

Dietary fucose is directly incorporated into a growing brain glycoconjugates towards a neuro-benefit. Same assumed route for MFGM-based sialic acid benefits.

✓ **Indirect route**

Dietary fucose is fermented into specific metabolite(s) via the gut microbiome. Those metabolite(s) transit to the brain and impact brain health

Ok, how do we improve brain health with this knowledge?

Can this be translated?

Translation can readily occur via both direct and indirect routes

Direct supplementation of 1,2PD

As a Drug

Ongoing research evaluating precise mechanism and dosage

As a Postbiotic product

→ Can move quickly into food products

Julia Finestone
Lactobacillus

Barbara Gachet
Bifidobacterium

Dylan Haynes
Yeast

Examining food grade, fucose fermenting, strains

Active Projects with UCD Milk Group

Translation of this can readily occur via both direct and indirect routes

Indirect supplementation by increasing fucose in our diets

HMO supplementation
or
HMO + bifidobacterial synbiotics

$$$$

Find fucose-rich foods and get people to eat lots of them

Problem → Very few foods have significant fucose!

What few foods have lots of fucose in them?

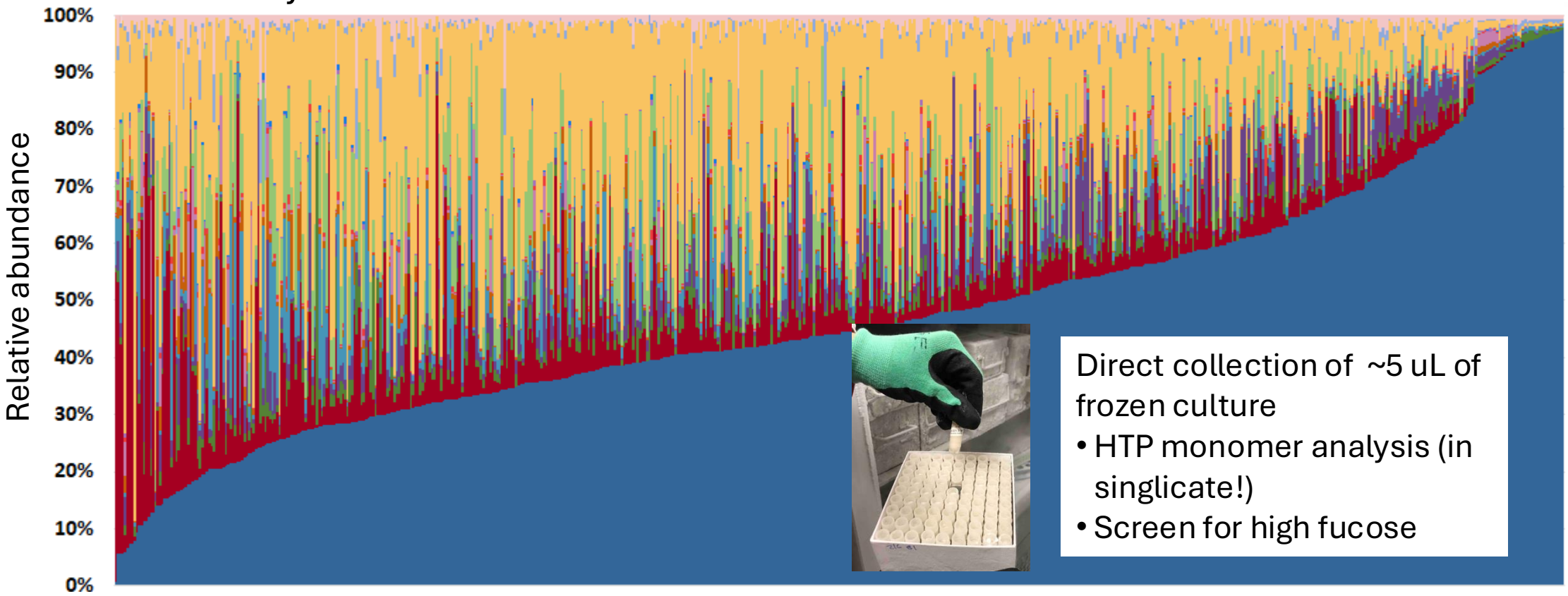
→ Human Milk

→ Brown algae (multicellular algae)

Unfortunately fucoidan fucose isn't significantly fermented in the human gut likely due to fucose sulfation

Select fungi have fucose in their cell walls!

Screened yeast in the UCD Phaff Yeast Culture Collection → IDed numerous candidates



Direct collection of ~5 uL of frozen culture

- HTP monomer analysis (in singlicate!)
- Screen for high fucose

Kyria Boundy-Mills

Matt Amicucci

one·bio

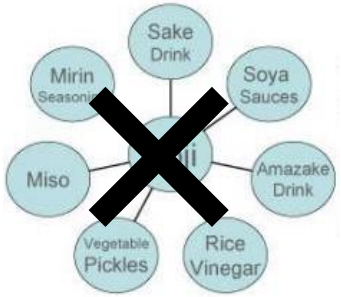
We need a scalable fucose fiber in order to provide abundant daily levels of dietary fucose

Idea → Target mycoprotein fungal strains

- Food grade
- Currently being scaled for alt protein use

Fusarium venenatum

Neurospora crassa



Aspergillus oryzeae

✕ = no fucose in cell wall

More food fermentation fungi

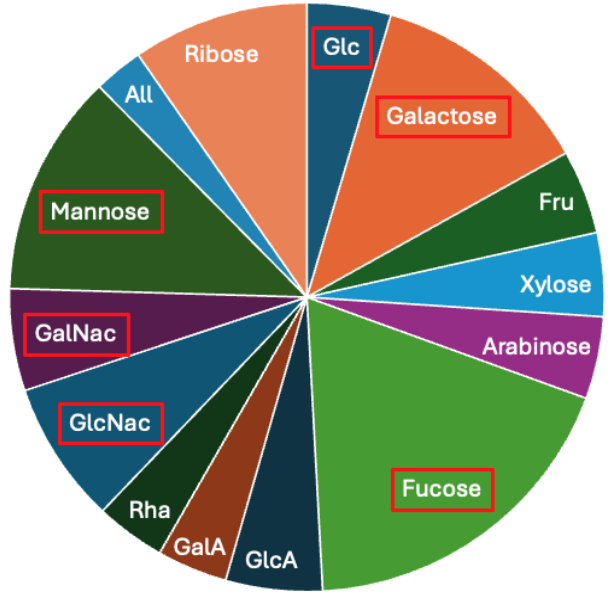
- ***Penicillium* sp.**: Blue cheese, white surface of sausage etc.
- ***Neurospora intermedia***: A fungus used in the fermentation of red oncom
- ***Rhizopus oryzae***: A fungus used in the fermentation of tempeh

Blue Cheese

Oncom

Tempeh

R. oryzae cell wall monomers



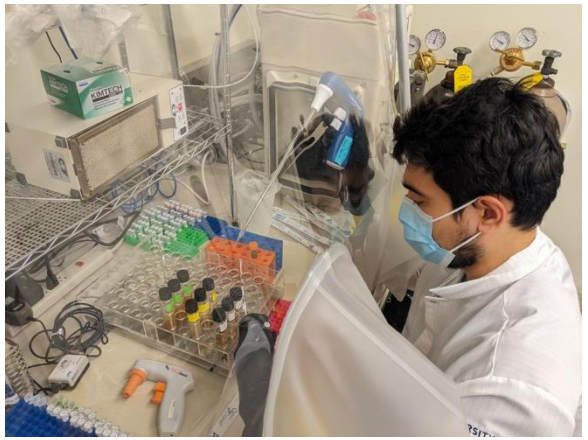
Variation among 14 strains
→ 7-19% fucose,
→ 0.5-5% rhamnose

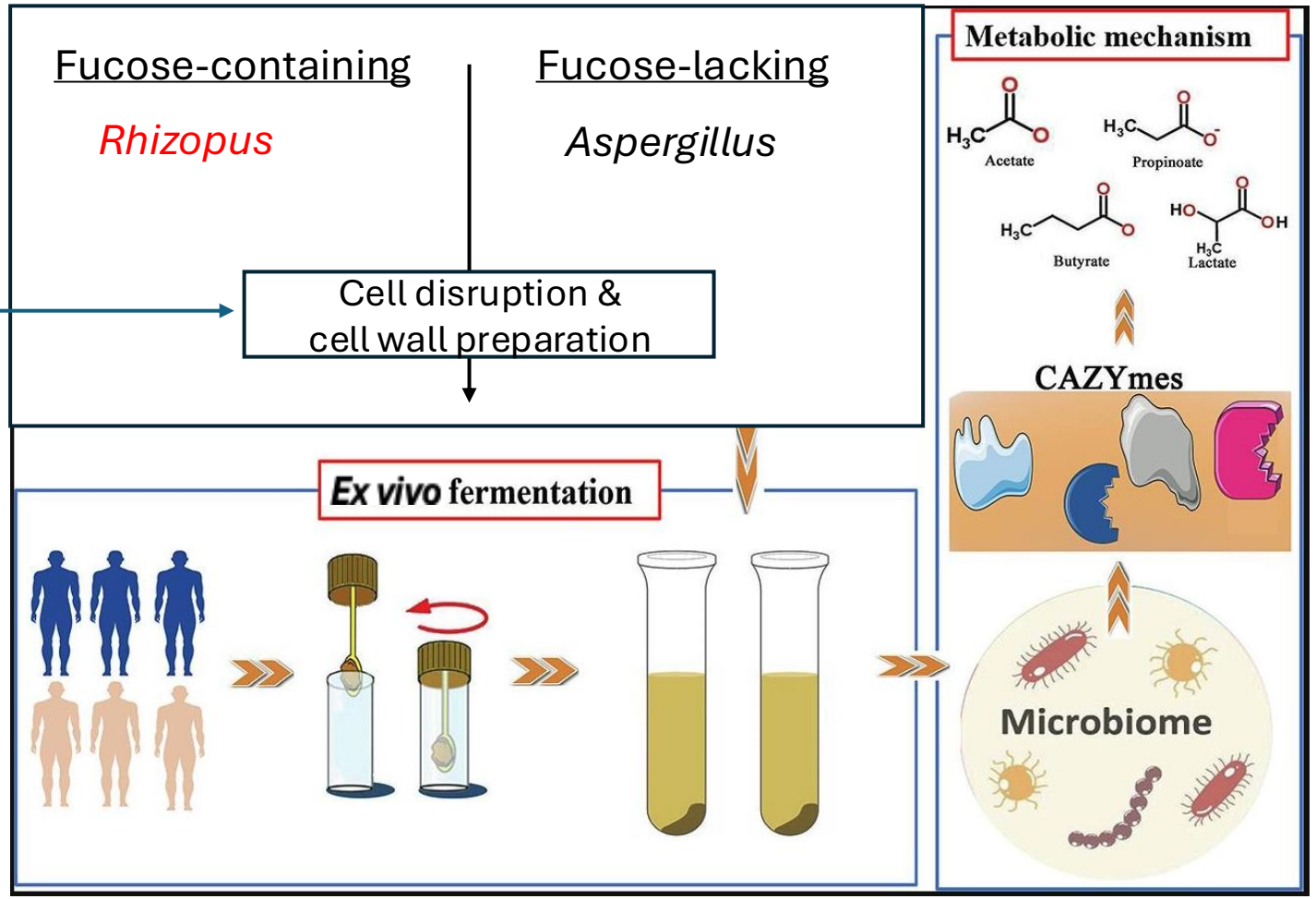
Do *Rhizopus* cell walls promote 12PD in *ex vivo* fecal fermentations

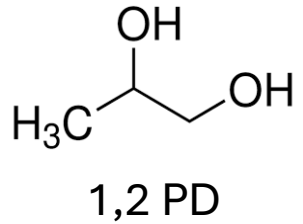
Juliana Maria Leite Nobrega de Moura Bell, Ph.D.

Associate Professor

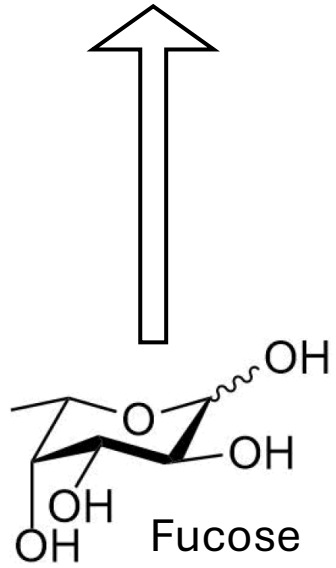
Food Science and Technology
Biological and Agricultural Engineering







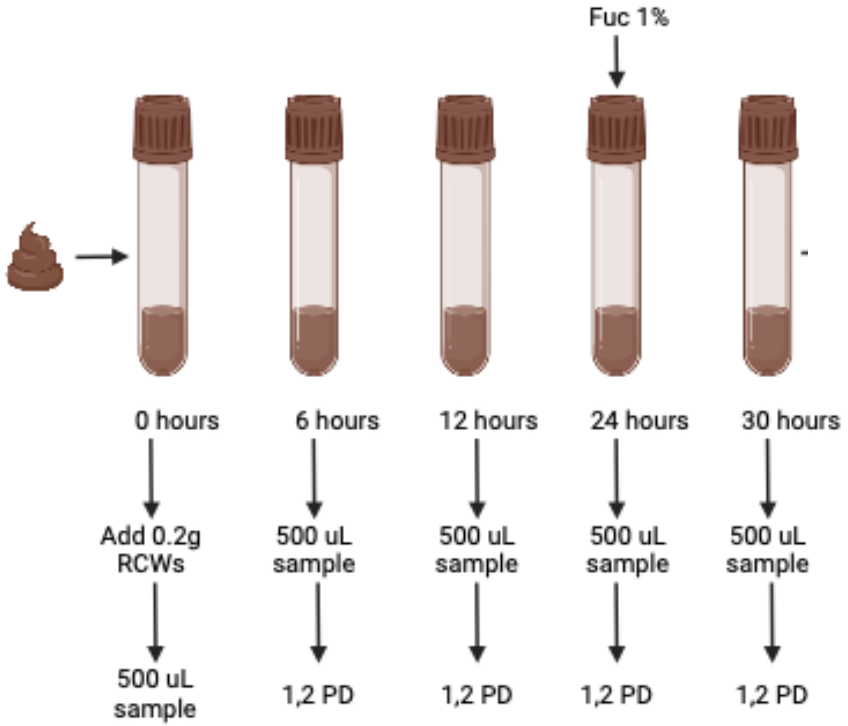
1,2 PD



Fucose

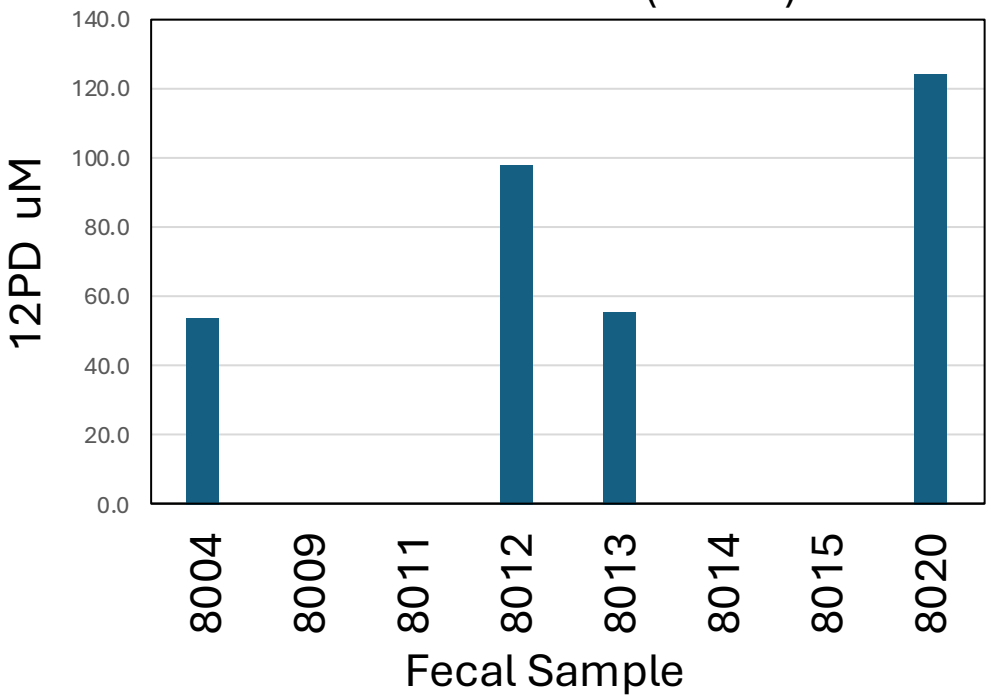
Fecal fermentation of *Rhizopus oryzae* cell walls

Note, cell walls were crudely prepared (i.e. this is not processed fiber)



Spiked 1% fucose after the 24 hr sample was taken

Production of 12PD from 24 hr *R. oryzae* Fecal Fermentation (24 hrs)



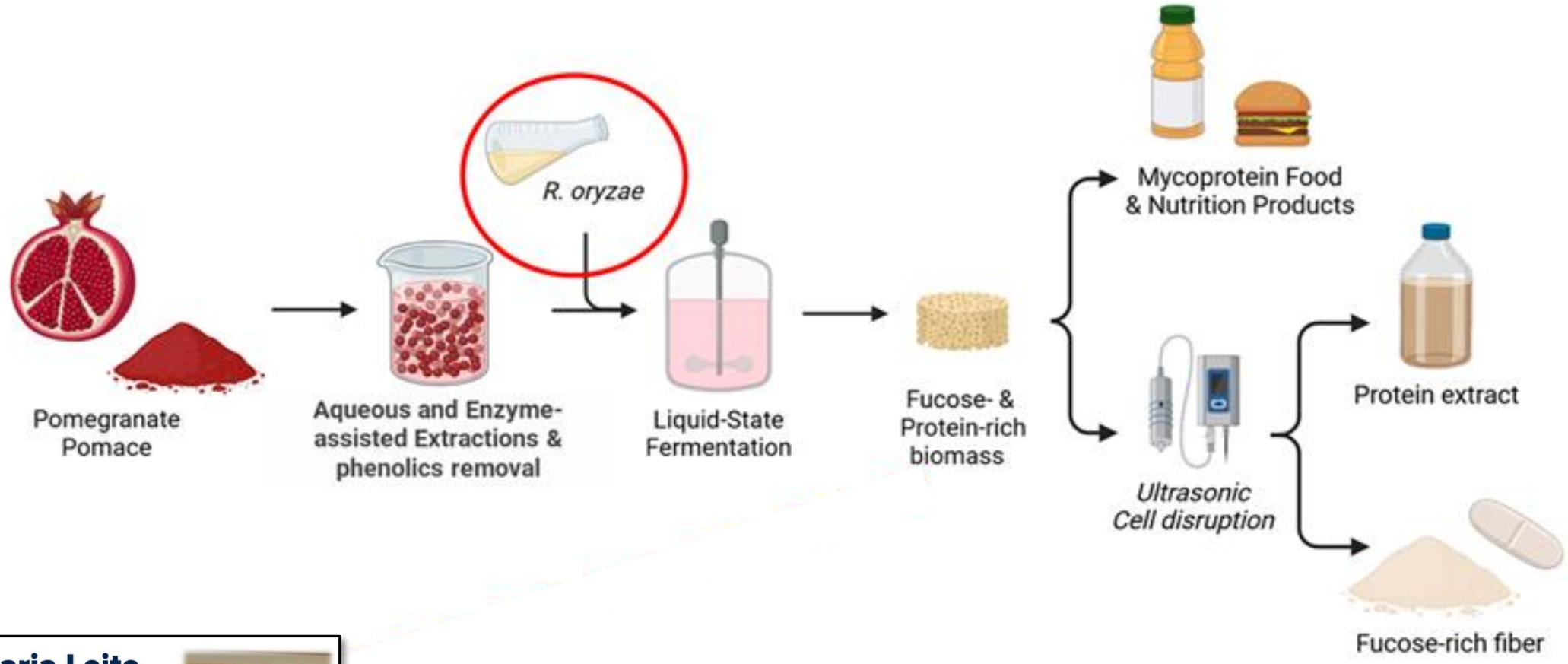
Dr. Romina Diaz

Johanna Keigler

- 12PD is produced by 50% of human fecal fermentations
- 100% responded to monomer fucose addition (not shown)

These results suggests *Rhizopus* cell wall food processing may increase 12PD production in more of the population.

Can we grow *Rhizopus* sp. on agricultural waste streams for downstream product opportunities



Juliana Maria Leite Nobrega de Moura Bell, Ph.D.

Associate Professor

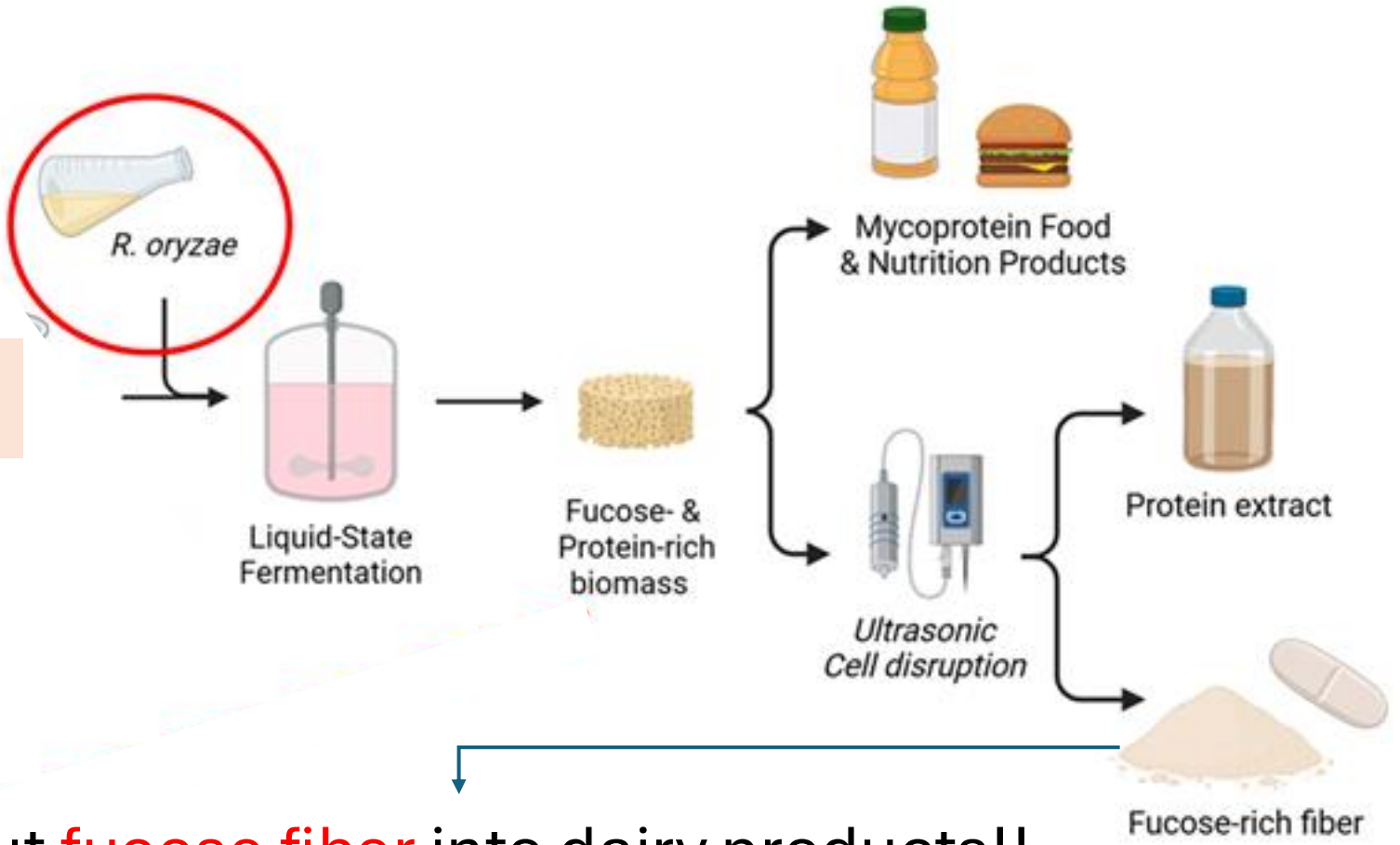
Food Science and Technology
Biological and Agricultural Engineering

Ongoing project funded by Resnick Agricultural Innovation Research Fund

the Wonderful company™

Can we grow *Rhizopus* sp. on dairy waste streams for downstream product opportunities

Use whey streams?



Put fucose fiber into dairy products!!

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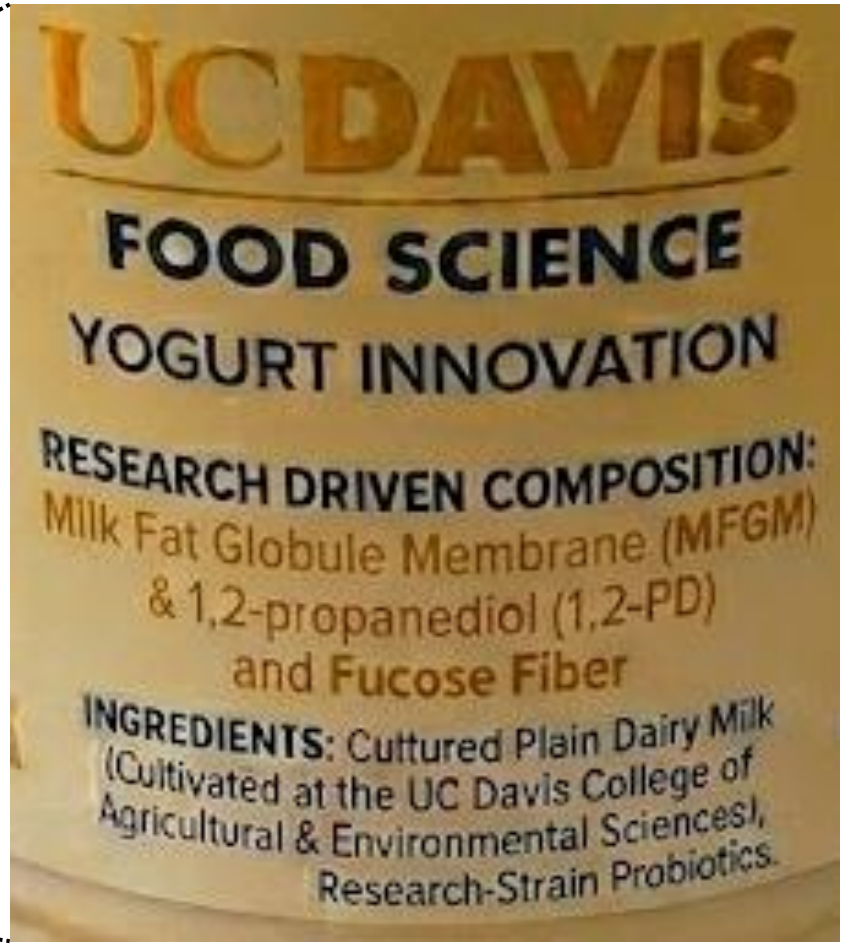
UCDAVIS
FOOD SCIENCE AND TECHNOLOGY

Can we create a brain heathy yogurt?



Aggregate UC Davis research on MGFM, 12PD and fucose fiber into dairy products!!!

Summary

- Dietary fucose is linked to repair of cognition decline directly (as fucose) and indirectly via the metabolite 1,2 propanediol
- Evidence indicates 1,2 propanediol traffics systemically, is anti-inflammatory and neuroprotective, and improves cognition!
- Food grade, fucose-containing, fungi can be scaled and delivered as fiber to *possibly* improve cognition
- If you fund **research networks** you can solve bigger problems and foster bigger opportunities

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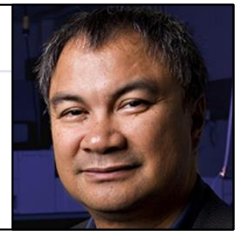

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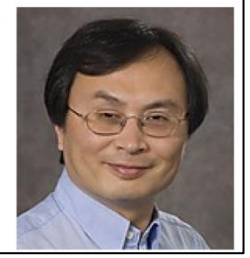
Faculty Profile

Tags

Genes and Molecules



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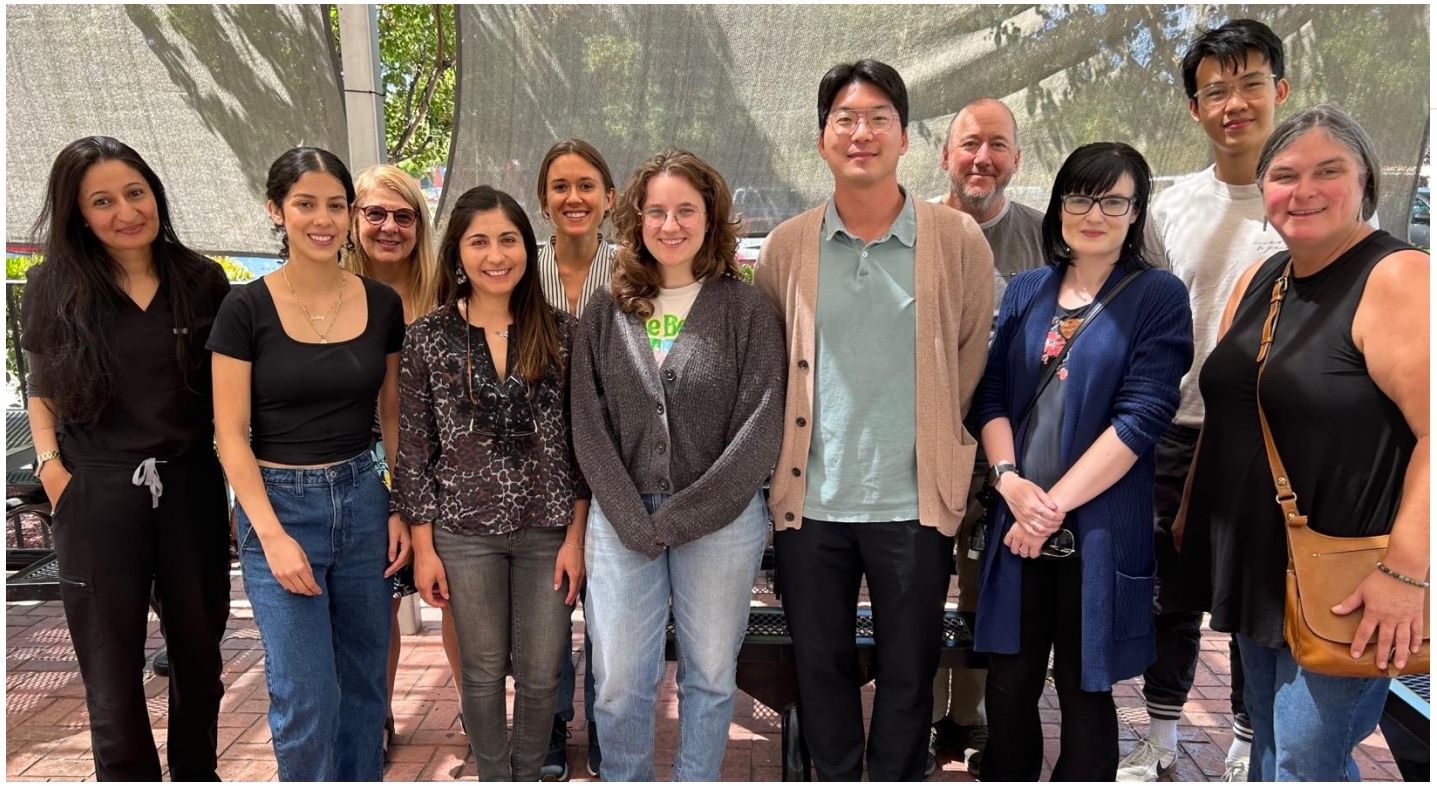
Mills Lab Acknowledgements



Current & former students working on glycans:

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Funding Acknowledgements for Dairy & Fiber Projects

National Center for Complementary and Integrative Health

National Institute of Diabetes and Digestive and Kidney Diseases

arla foods ingredients
powering nutrition together Arla

Resnick Agricultural Innovation Research Fund