

Gut-CKM Axis in Personalized Nutrition

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National Taiwan University Hospital*



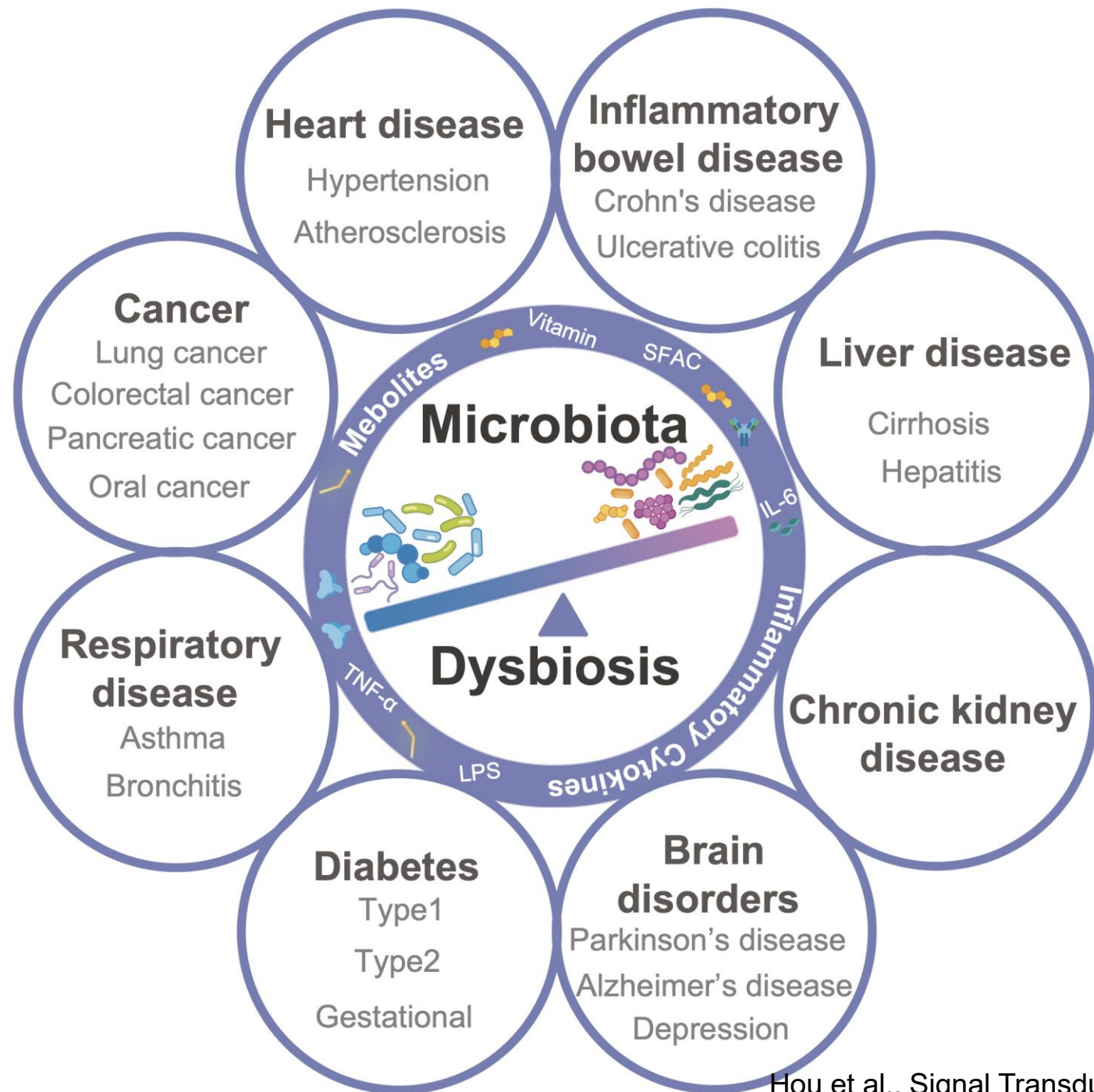


萬病之源，始於腸道

“All disease begins in the gut”
“A bad digestion is the root of all
evil”

“Death sits in the bowel”

Hippocrates, circa 400 BC



You are what you eat

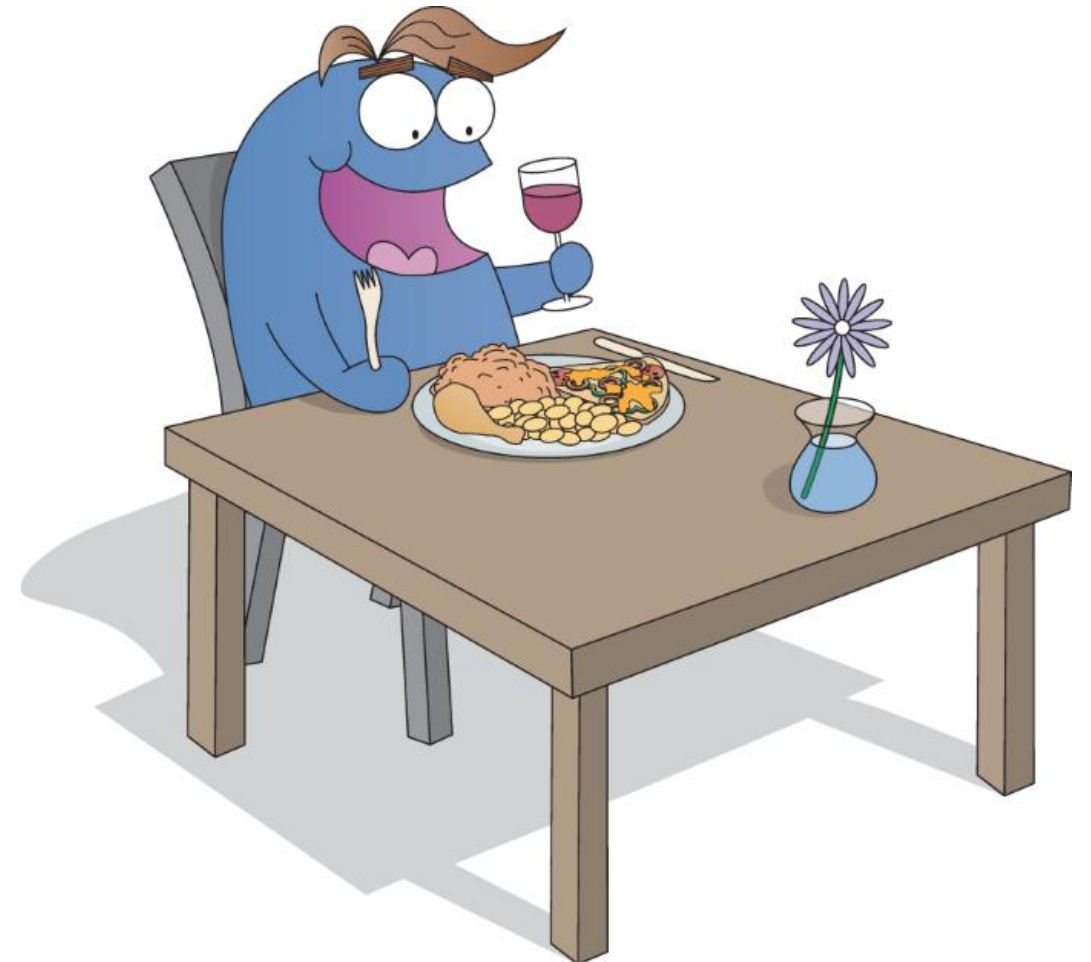
Anthelme Brillat-Savarin 1826



RESEARCH
HIGHLIGHTS

 MICROBIOME

Your microbiome is what you eat

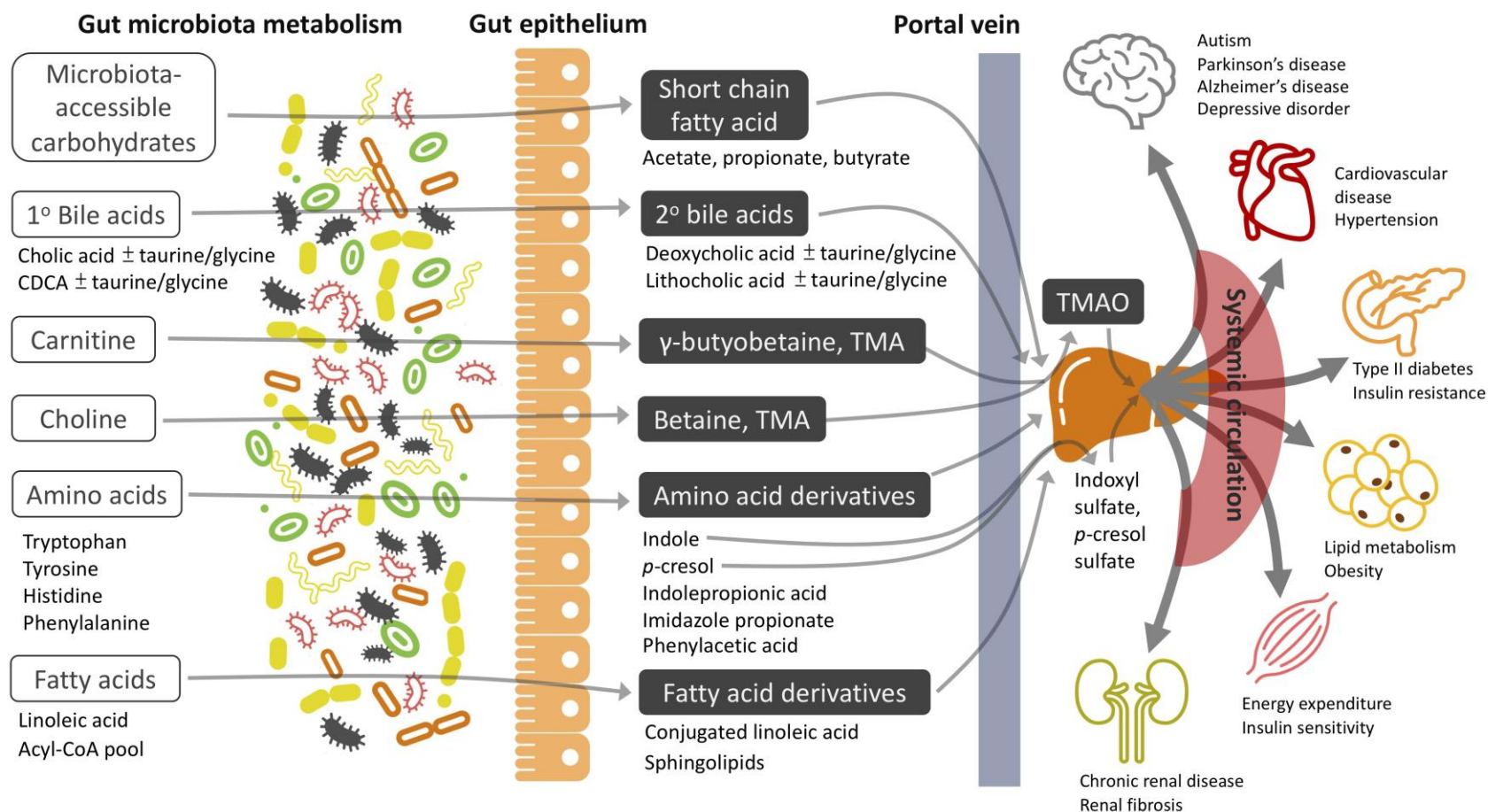


Ashley York. *Nat. Rev. Microbiol.* 2019

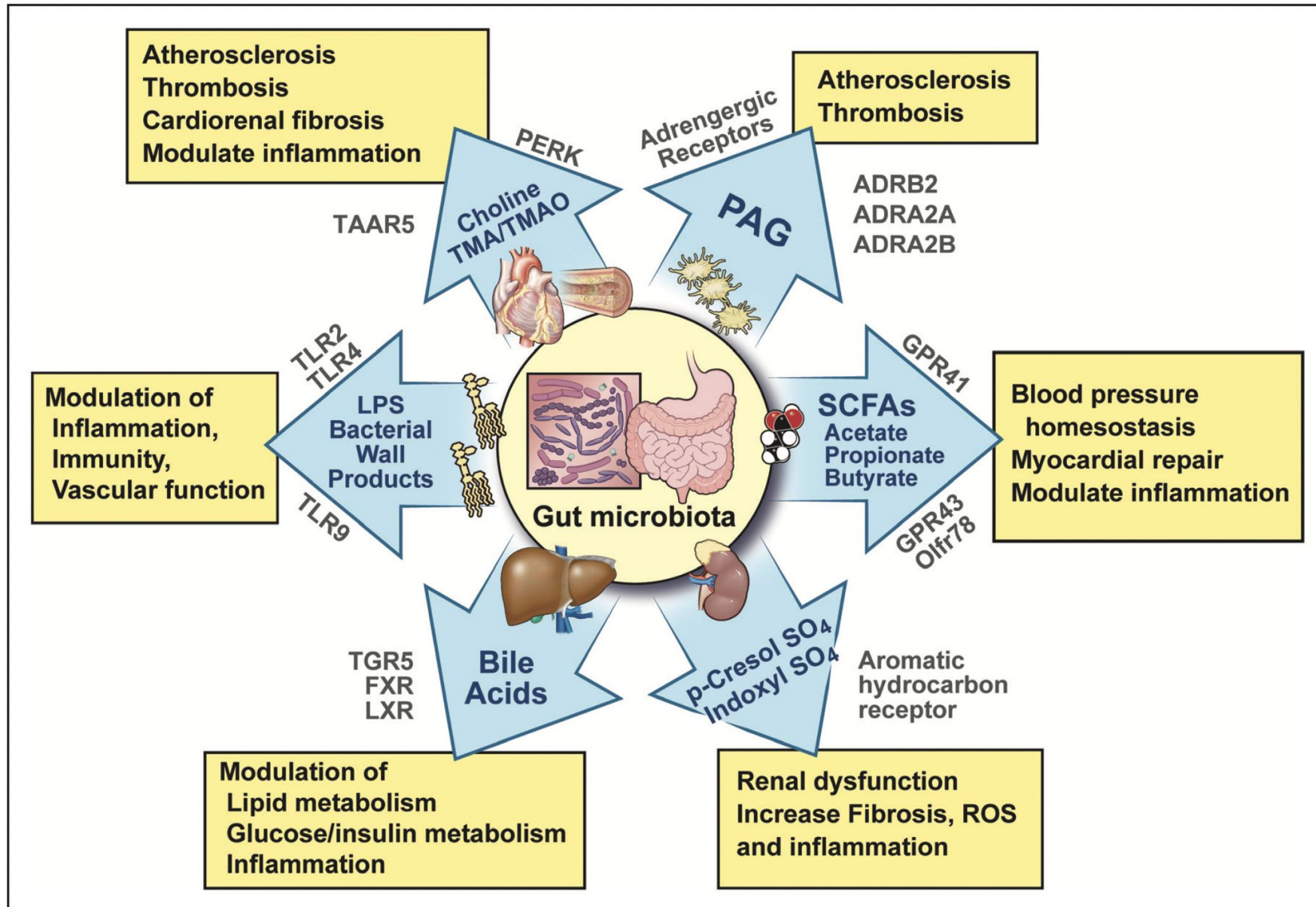
Gut microbiota eat what you eat



The Gut-Systemic Axis



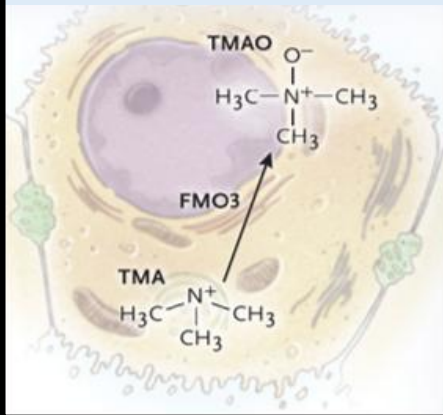
Gut Microbial Metabolites and Cardiometabolic Diseases



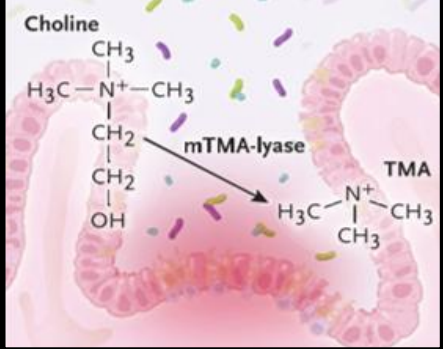
L-Carnitine



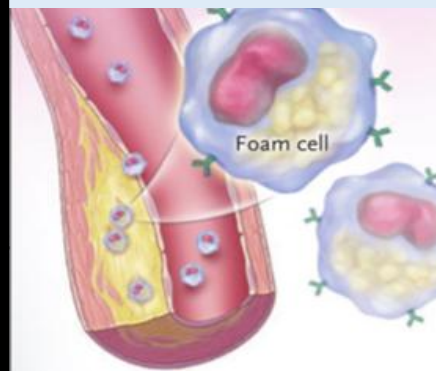
TMA→TMAO



L-carnitine→TMA by gut microbiota



Atherosclerosis



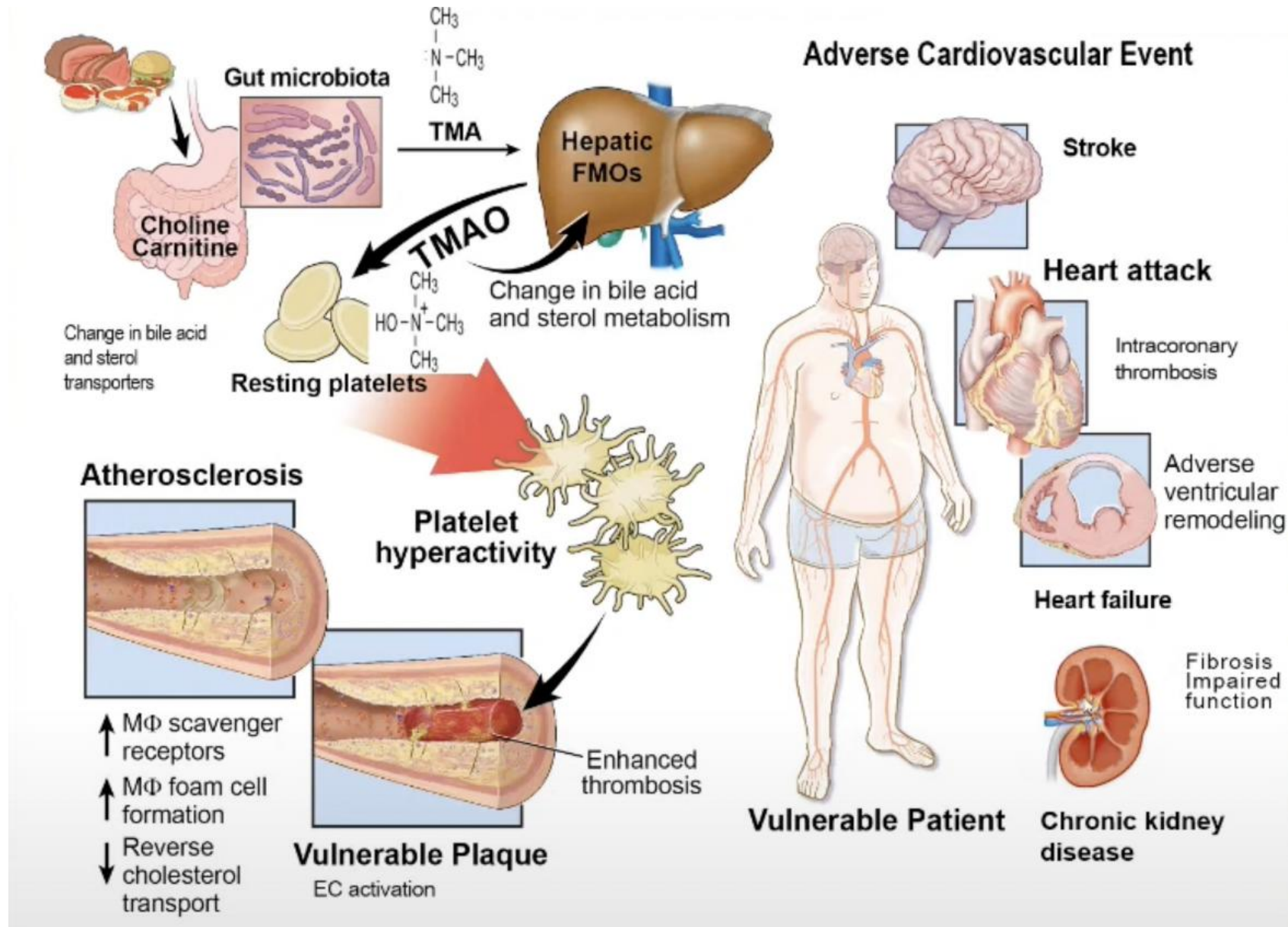
Thrombosis potential



Heart attack
Stroke
Heart Failure



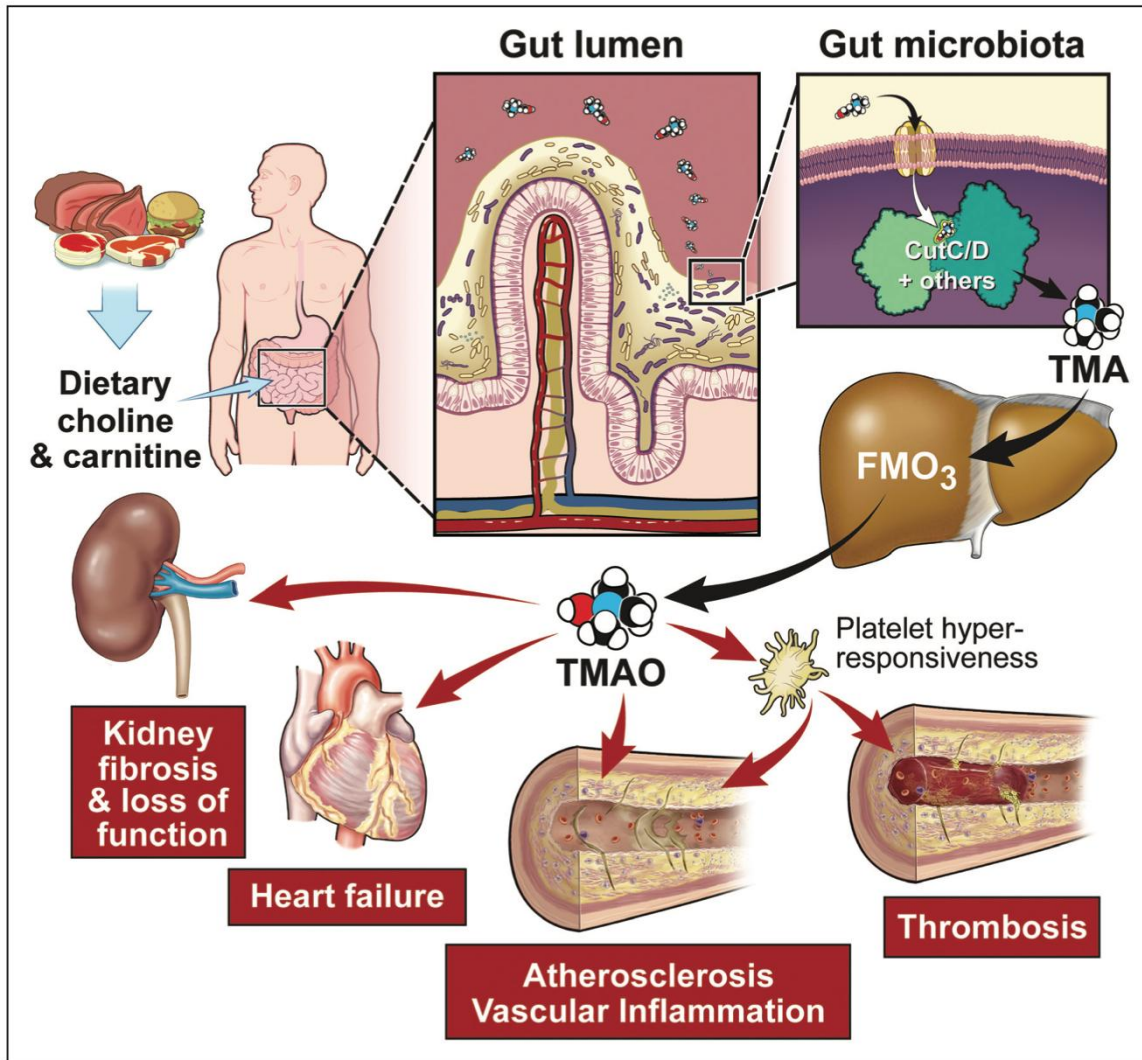
TMAO: a well-studied pathophysiological molecular from gut microbiota



Z Wang (2011) [*Nature*](#)
R Koeth (2013) [*Nature Medicine*](#)
W Tang (2013) [*New Engl J Med*](#)
B Bennett (2013) [*Cell Metab*](#)
Z Wang (2014) [*Eur Heart J*](#)
WHW Tang (2014) [*JACC*](#)
WH Tang (2015) [*J Card Fail*](#)
WHW Tang (2015) [*Circ Res*](#)
Z Wang (2015) [*Cell*](#)
W Zhu (2016) [*Cell*](#)
V Senthong (2016) [*JACC*](#)
W Tang (2016) [*Clin. Chem.*](#)
X Li (2017) [*Eur Heart J*](#)
W Zhu (2018) [*J Hamatol Thromb*](#)
A Roberts (2018) [*Nature Med*](#)
S Skye (2018) [*Circ Research*](#)
X Li (2019) [*J Clin Invest Insight*](#)
R Koeth (2019) [*J Clin Invest*](#)
X Li (2019) [*Eur Heart J*](#)
Z Wang (2019) [*Eur Heart J*](#)
N Gupta (2020) [*ATVB*](#)
C Organ (2020) [*JAHA*](#)
Zhang W (2021) [*Sci Rep*](#)

TMAO may serve as a therapeutic target for CKM Syndrome

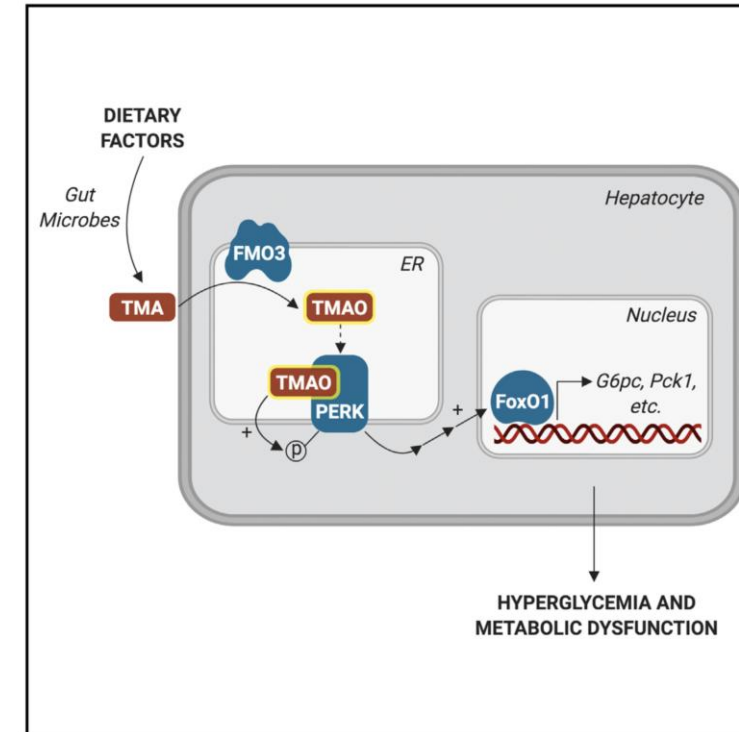
Short Article



Cell Metabolism

Trimethylamine N-Oxide Binds and Activates PERK to Promote Metabolic Dysfunction

Graphical Abstract



Authors

Sifan Chen, Ayana Henderson,
Michael C. Petriello, ...,
Federico E. Rey, Andrew J. Morris,
Sudha B. Biddinger

Correspondence

sudha.biddinger@childrens.harvard.edu

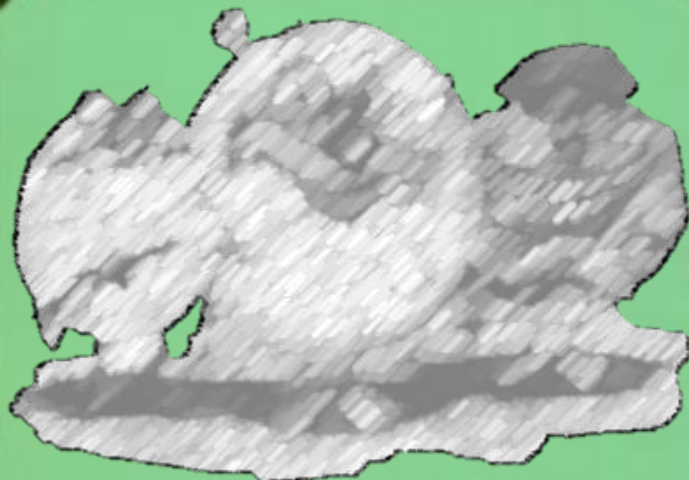
In Brief

The gut-derived metabolite trimethylamine N-oxide (TMAO) is increased by insulin resistance. Chen et al. identify the endoplasmic reticulum stress kinase PERK as a receptor for TMAO: TMAO binds PERK, selectively activates the PERK arm of the unfolded protein response, and promotes hyperglycemia. The nutraceutical 3,3'-diindolylmethane reverses these effects, suggesting that the TMAO-PERK pathway could be targeted to ameliorate metabolic disorders.

Microbes



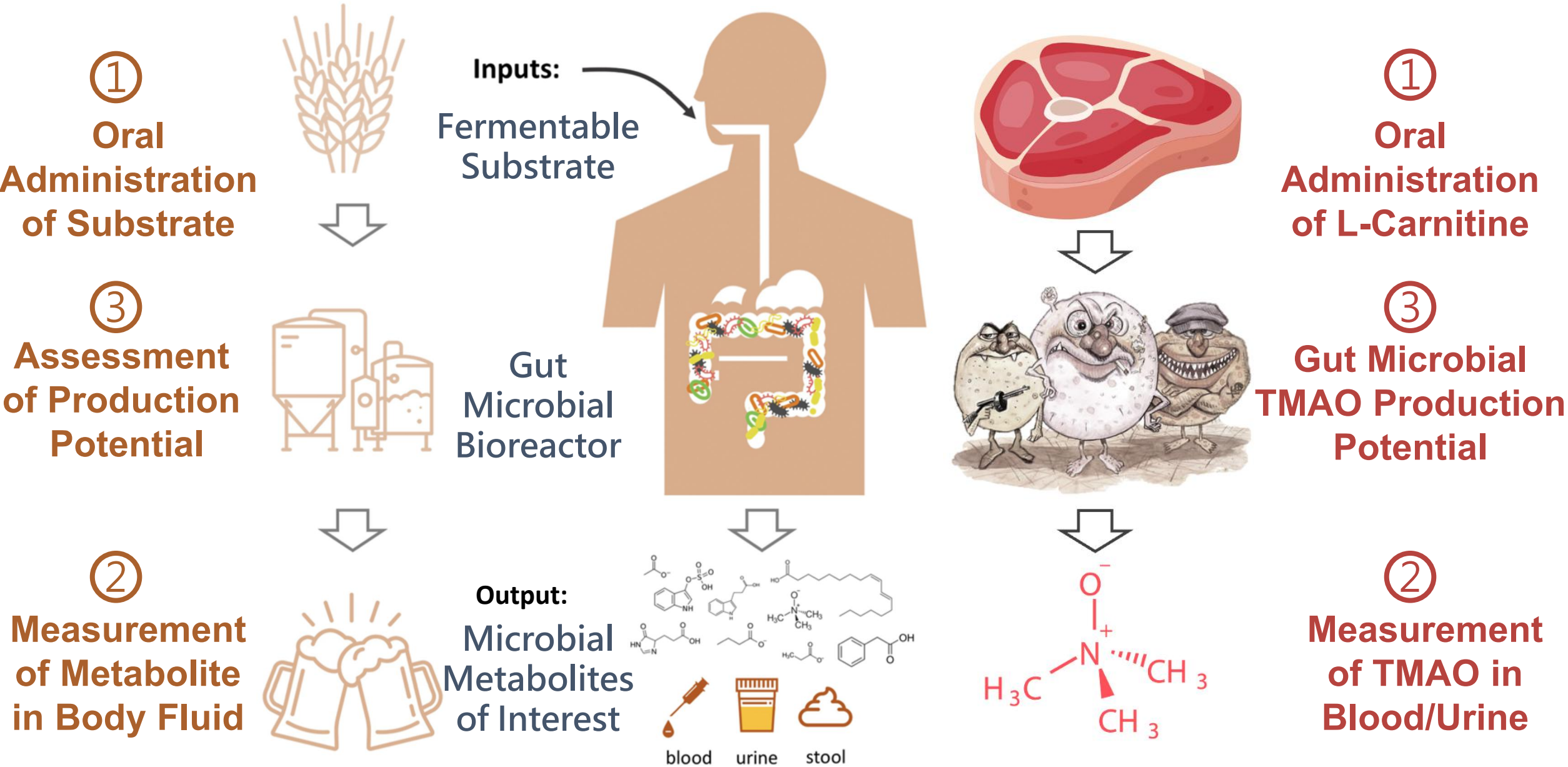
Broken-Heart Microbes
Hunting Project



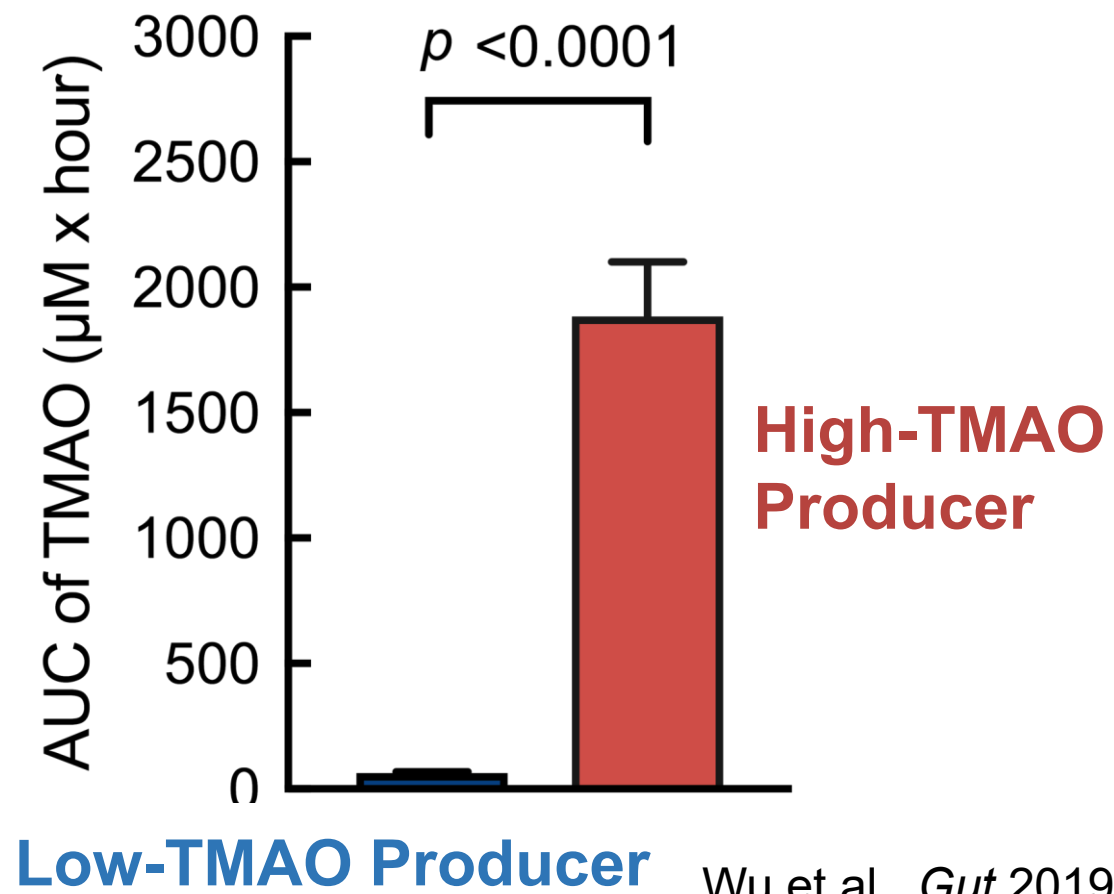
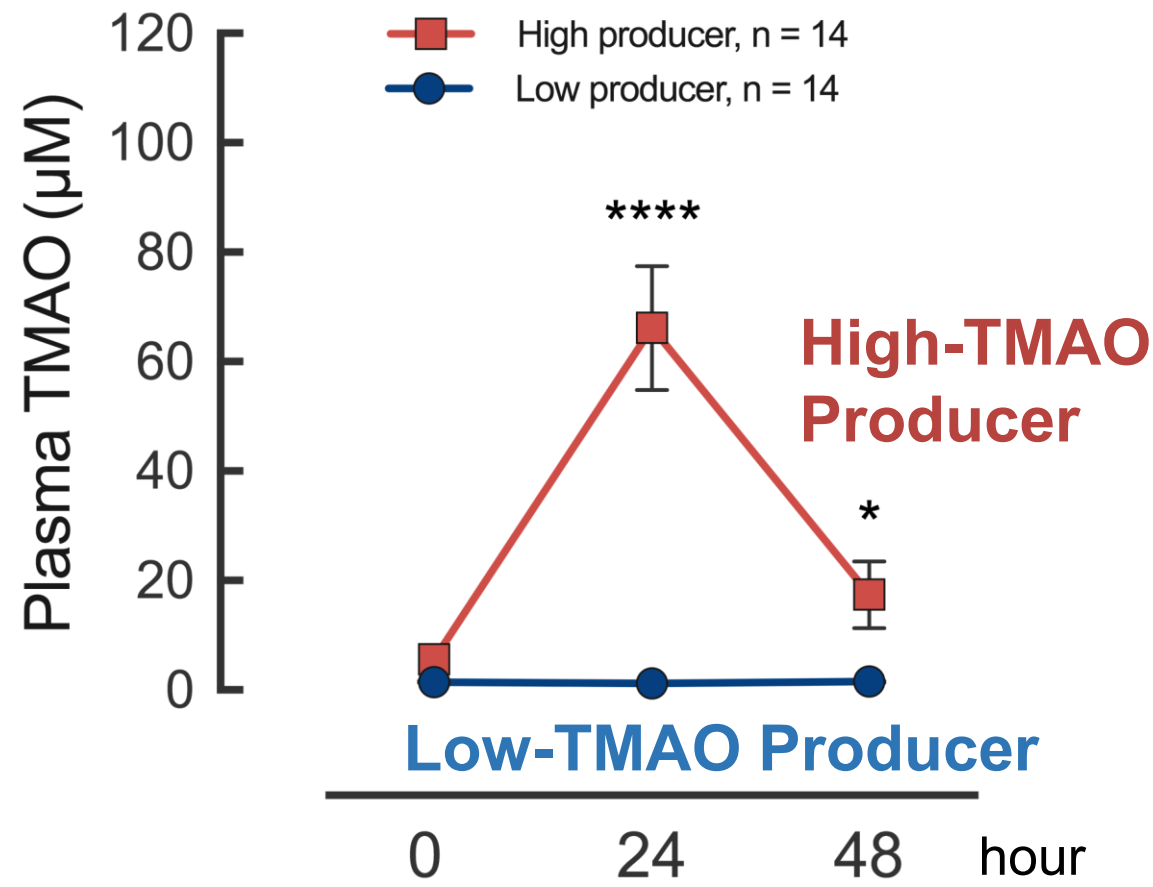
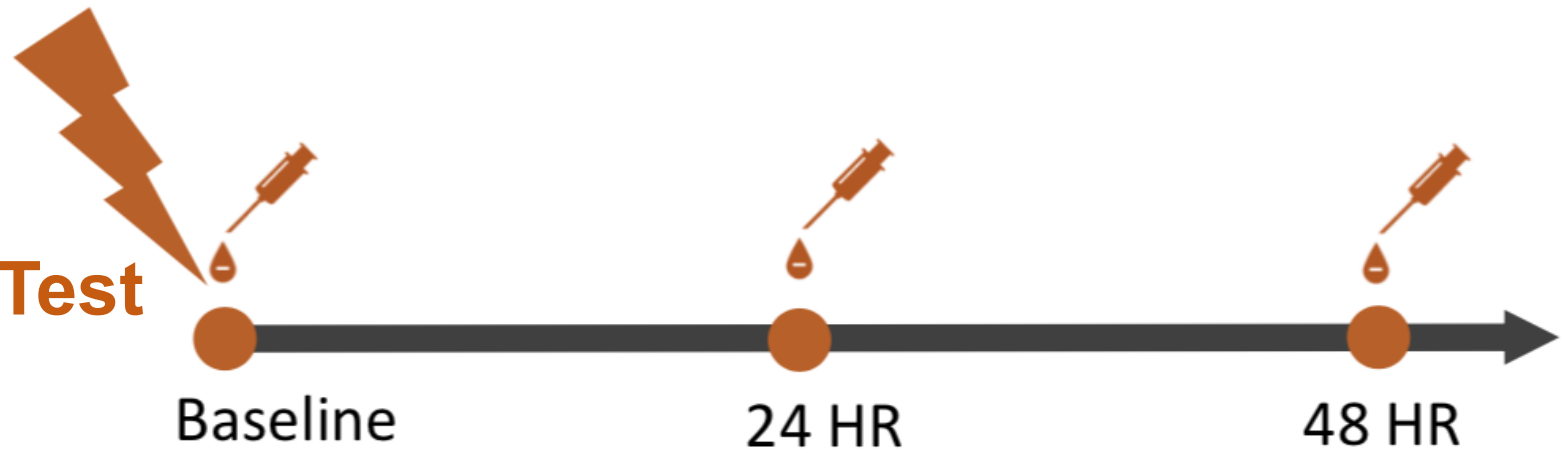
???

Who is it

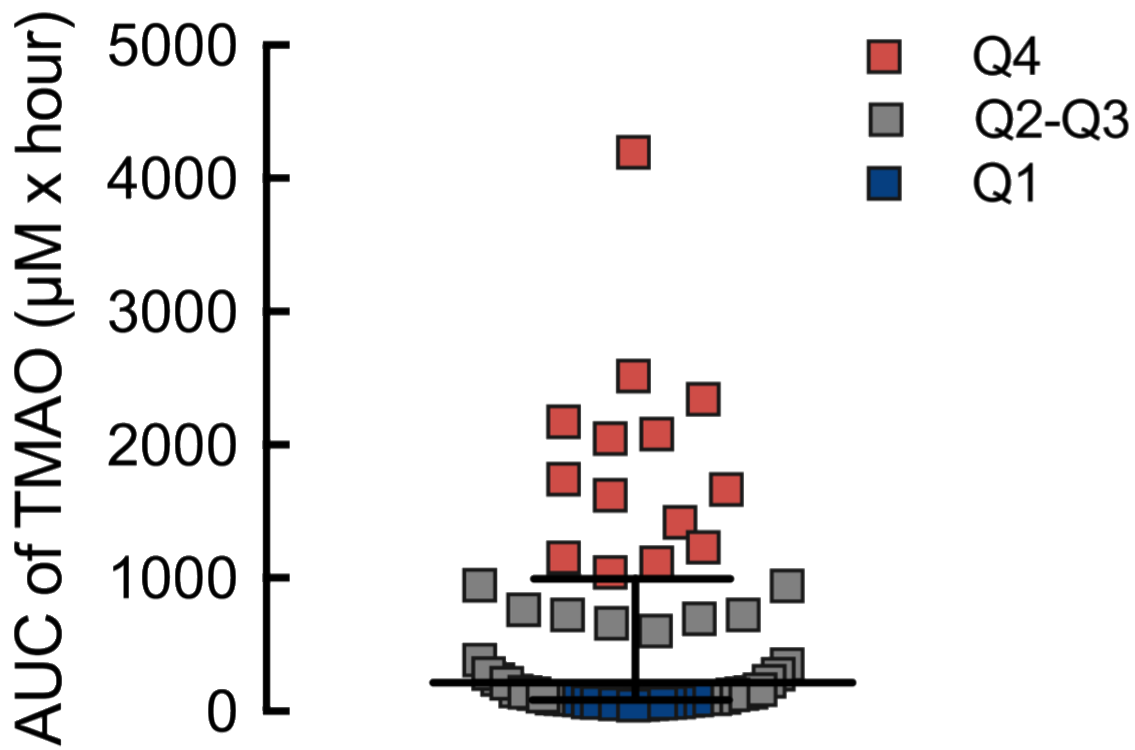
Oral Substrate Challenge Test: A Functional Assessment of Gut Microbiota



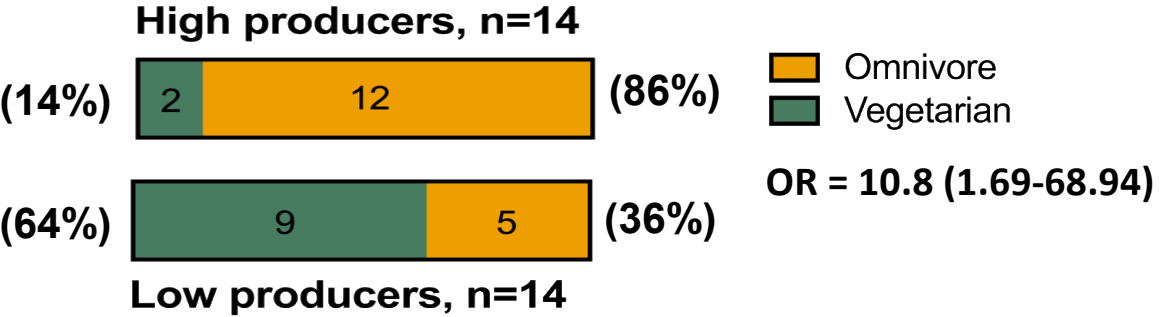
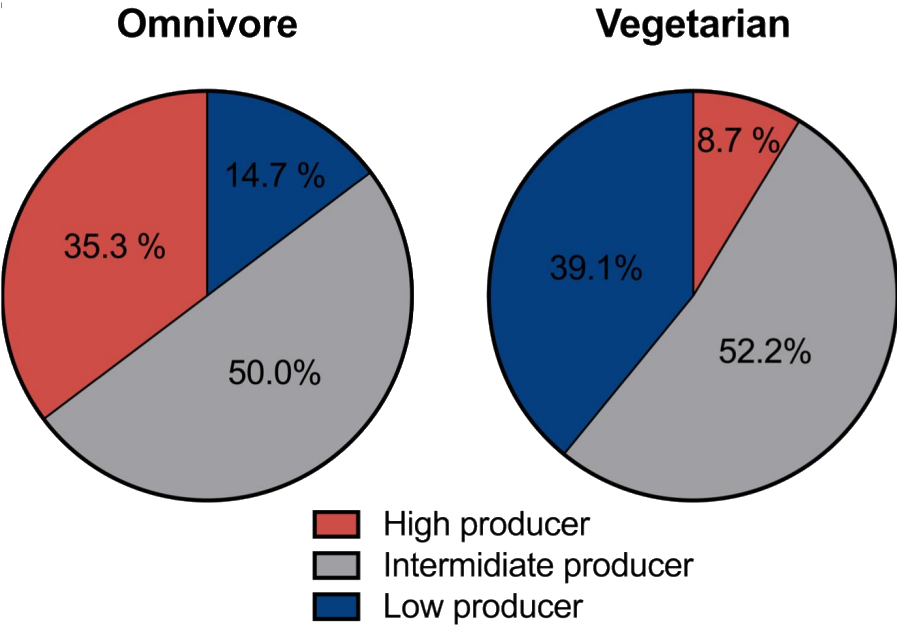
Oral Carnitine Challenge Test (OCCT)



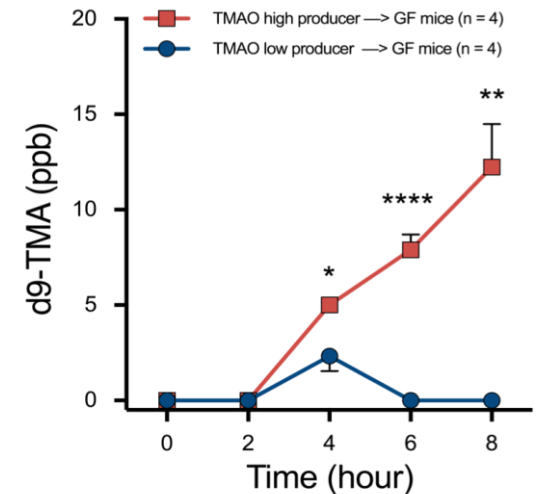
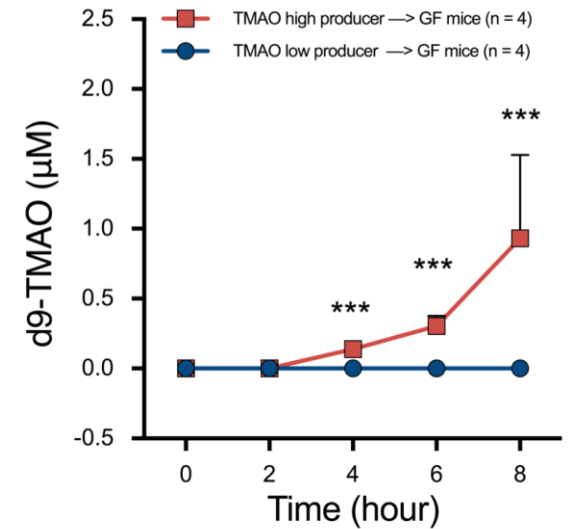
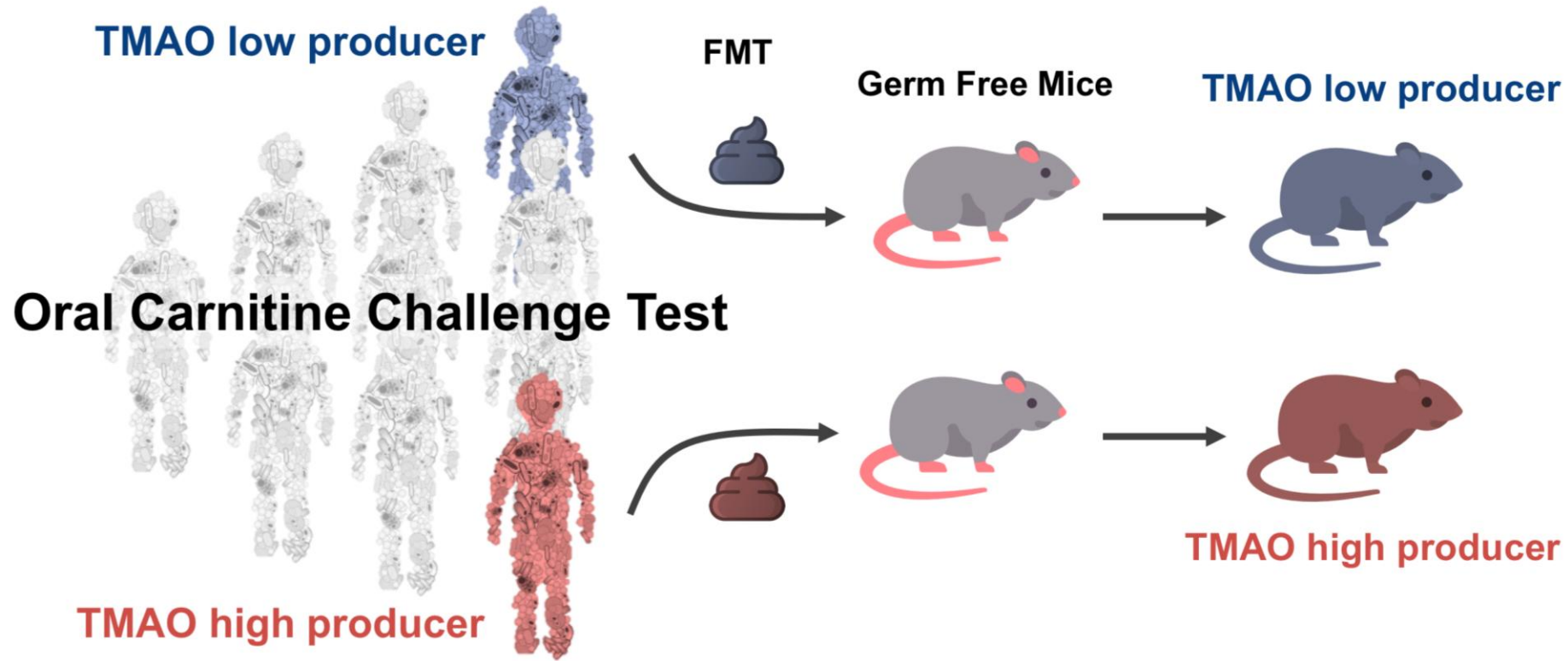
Omnivores Differs from Vegetarians in TMAO Producer Phenotype



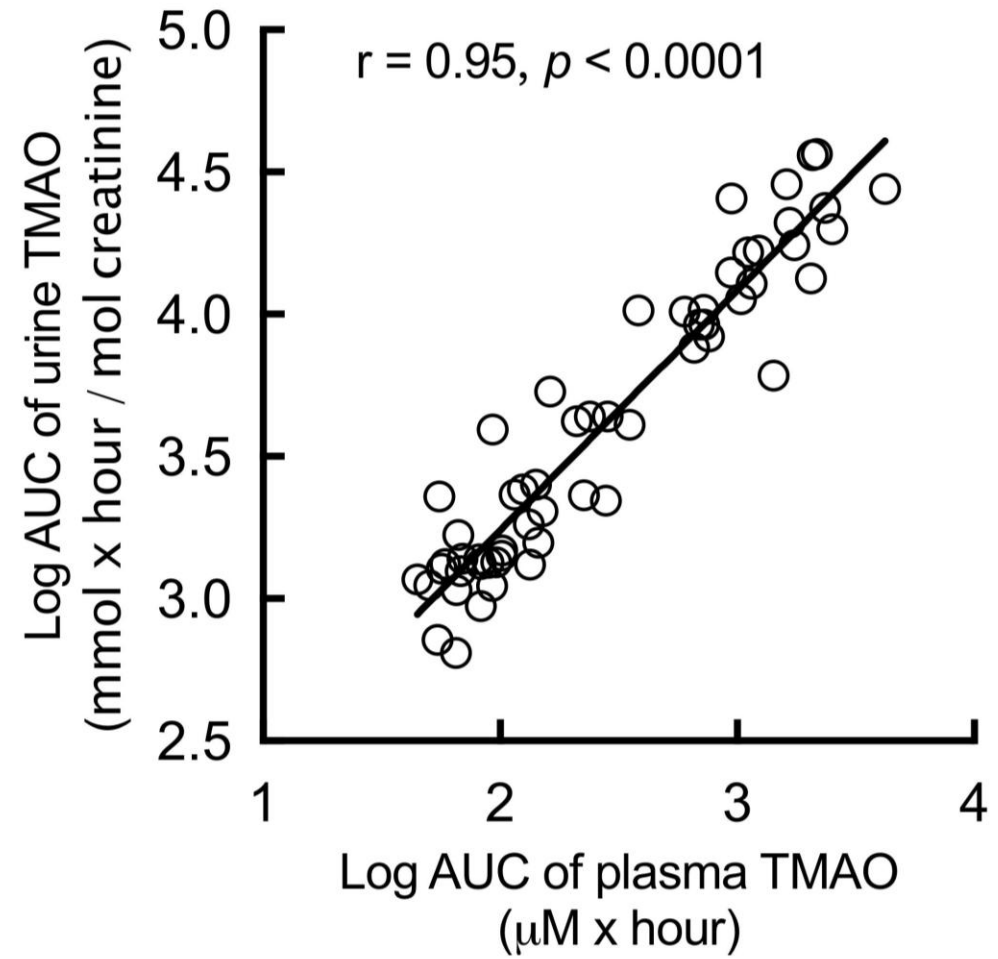
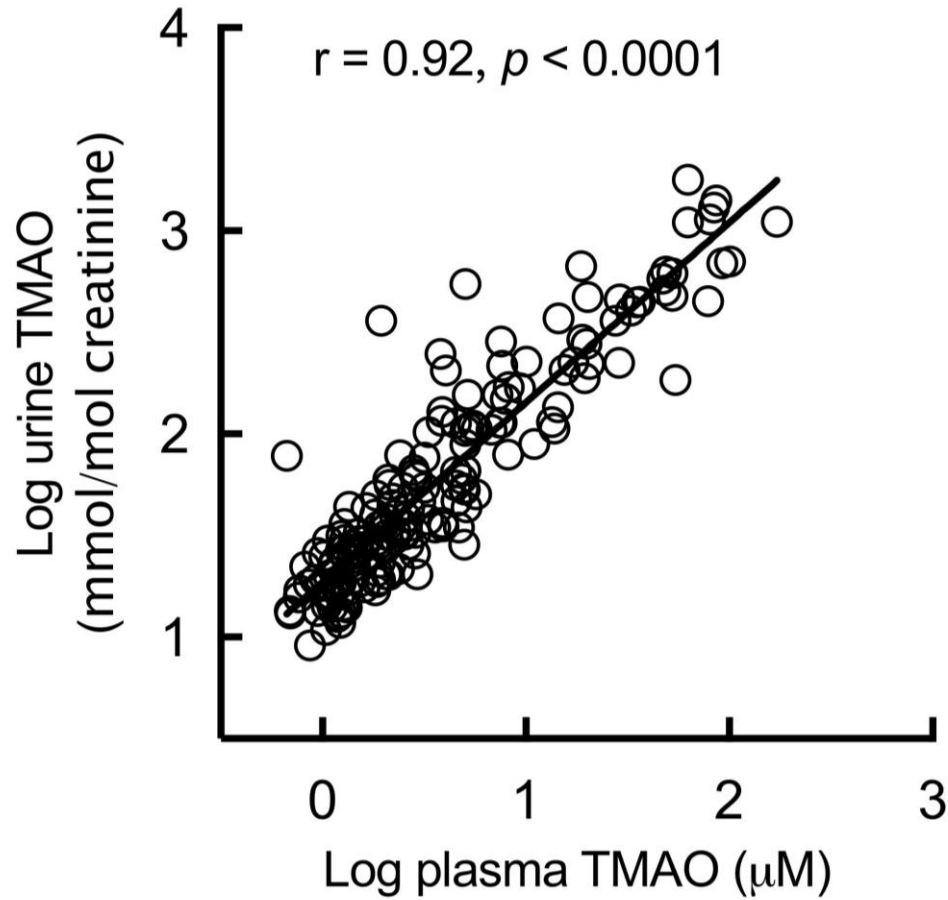
All participants
receiving CCT
n = 57

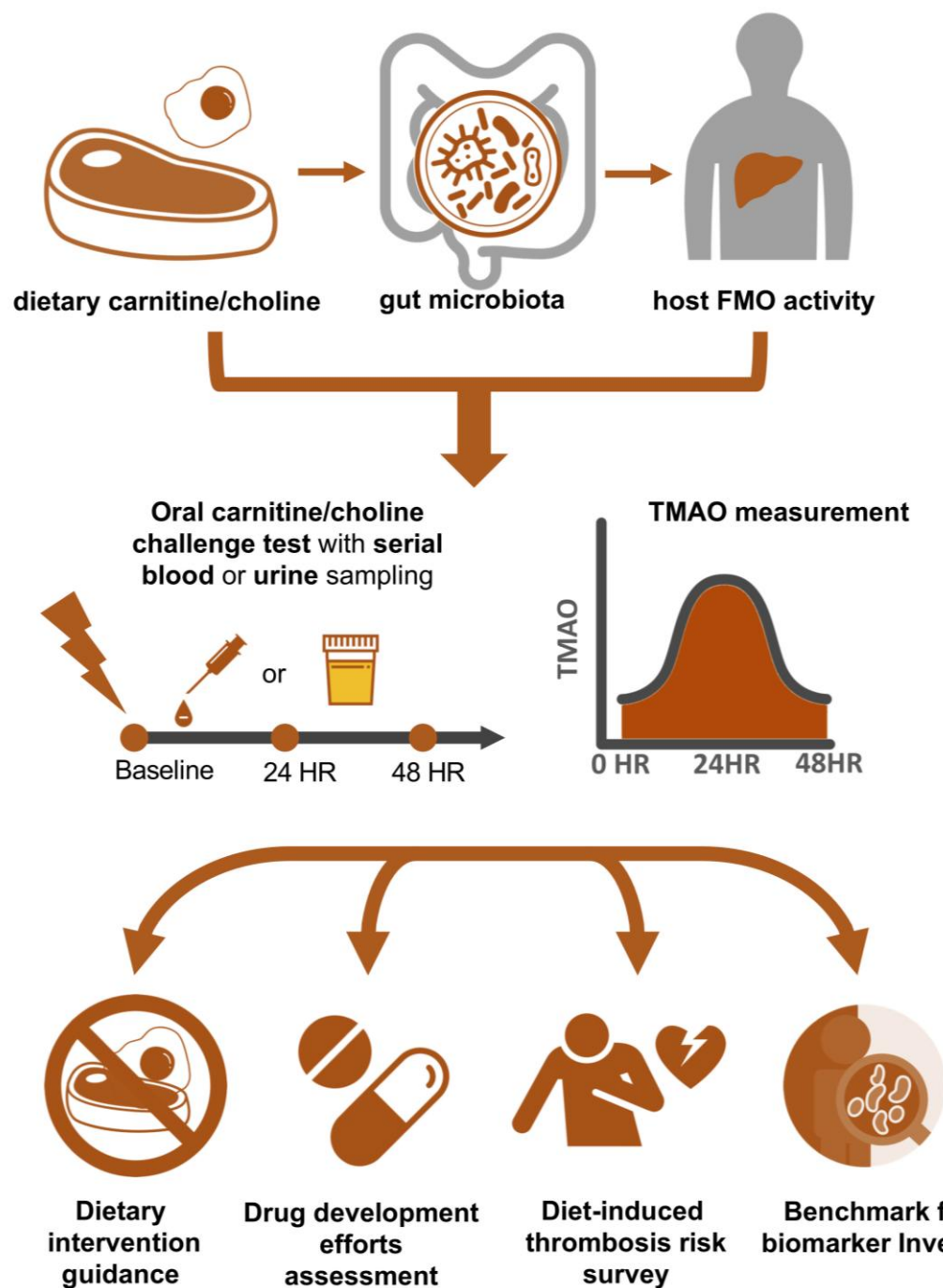


TMAO Producer Phenotypes Can be Transferred to GF mice by FMT



Blood and Urine TMAO were Highly Correlated

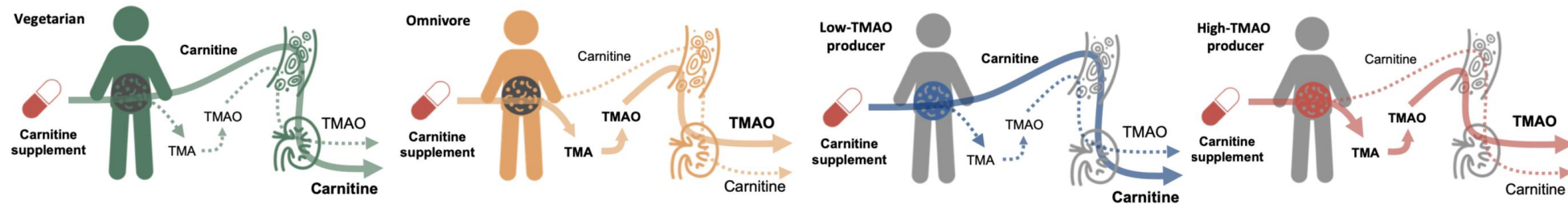
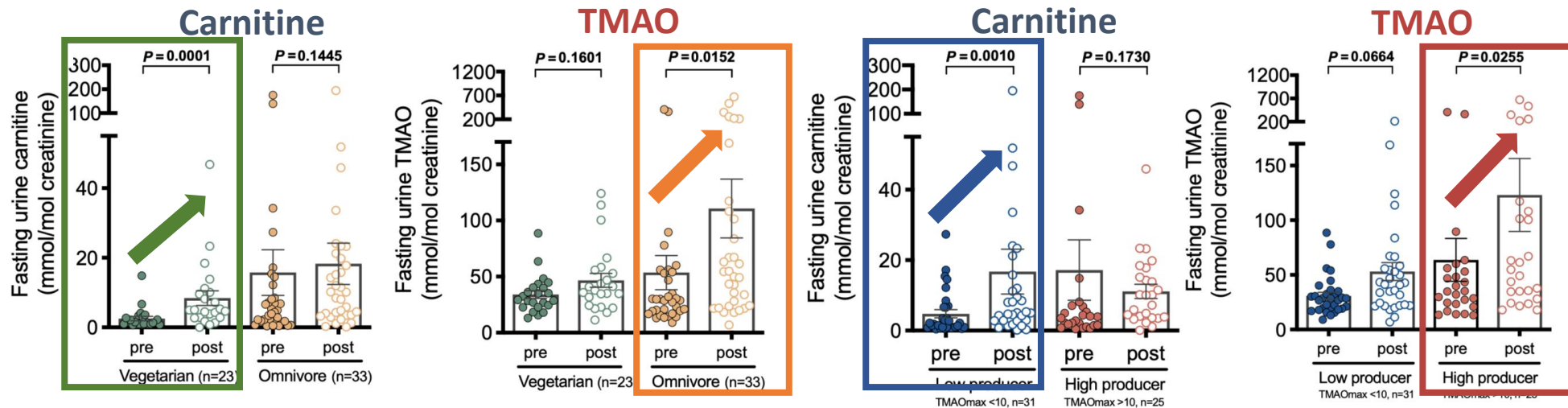
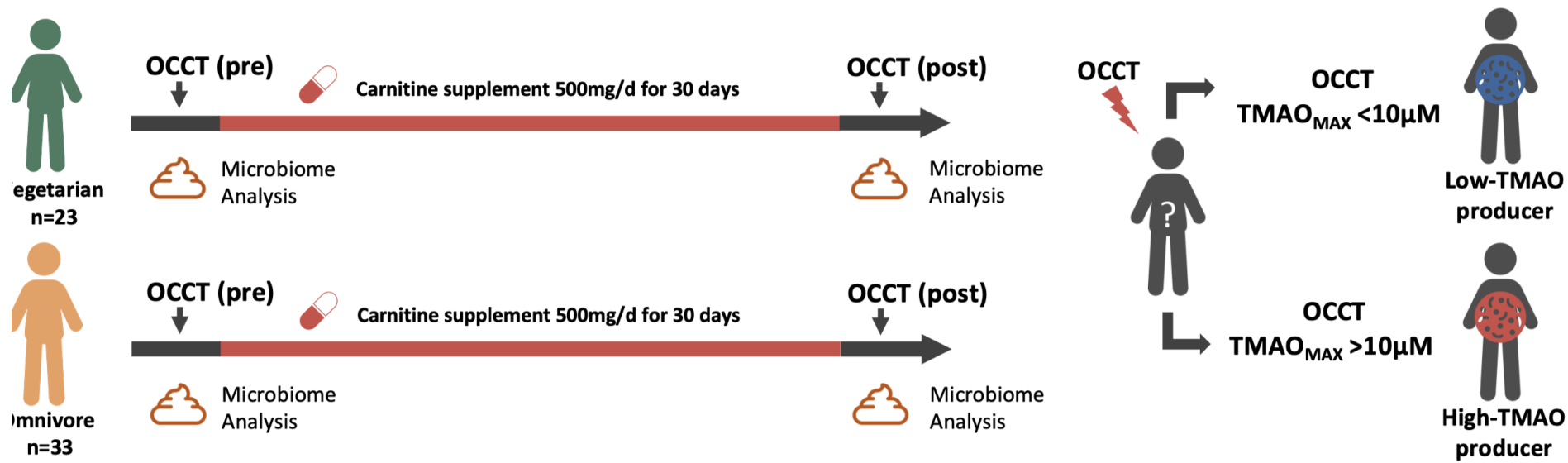




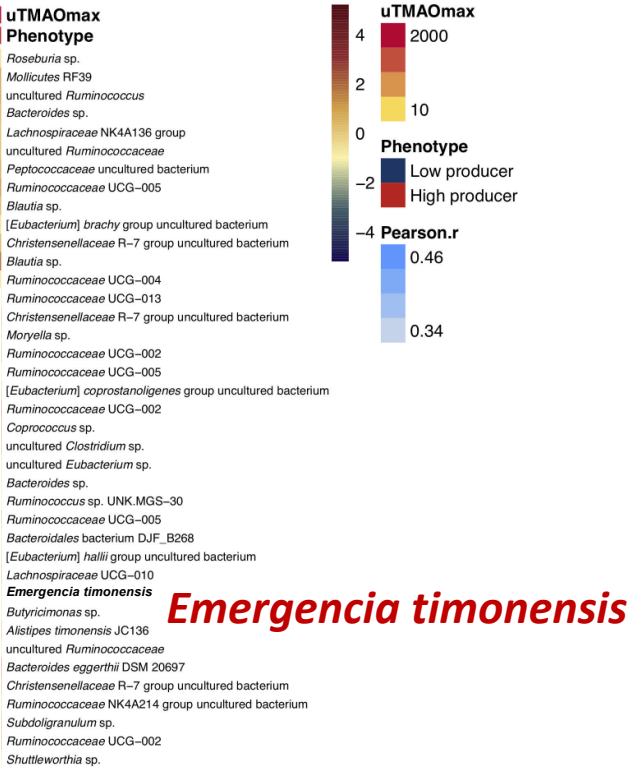
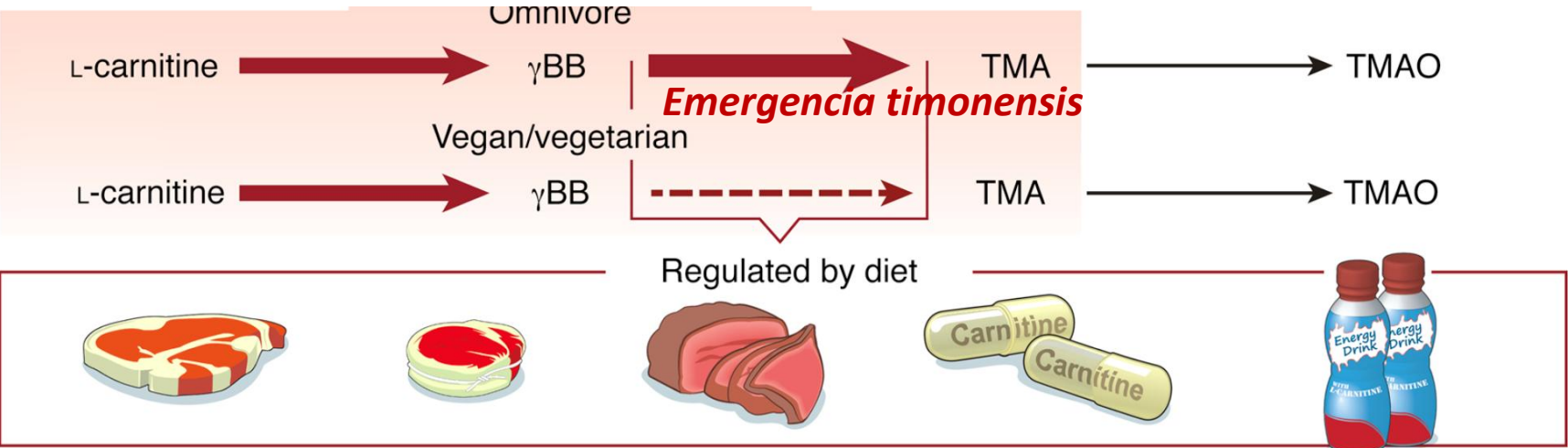
Wu et al., *Gut* 2019



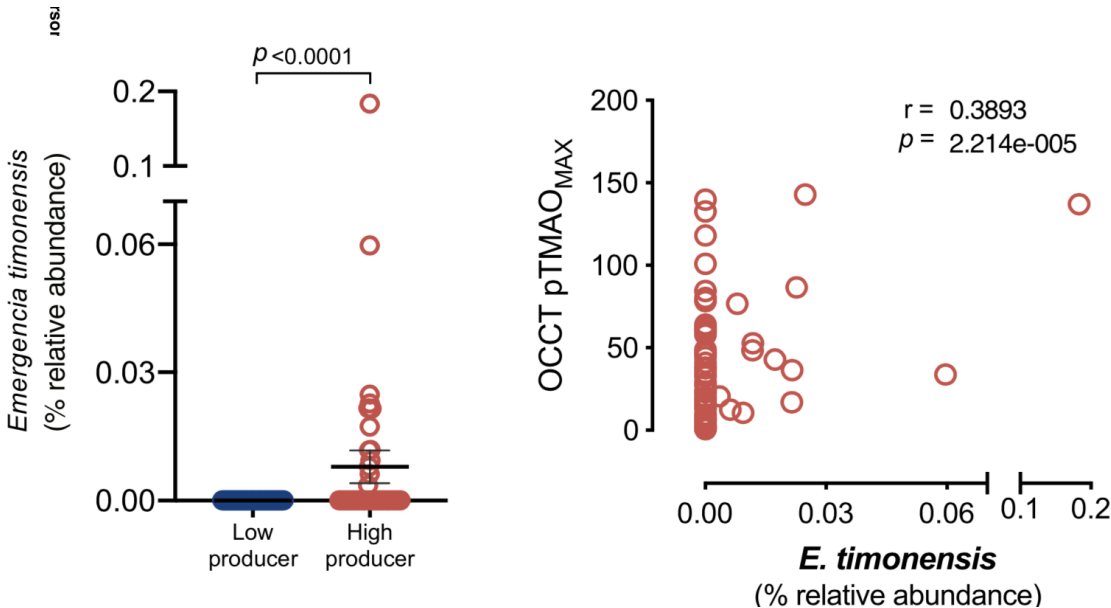
Patented in
US and Taiwan



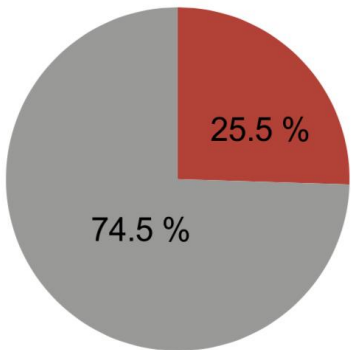
L-Carnitine in omnivorous diets induces an atherogenic gut microbial pathway in humans



Hazen et al., JCI 2019

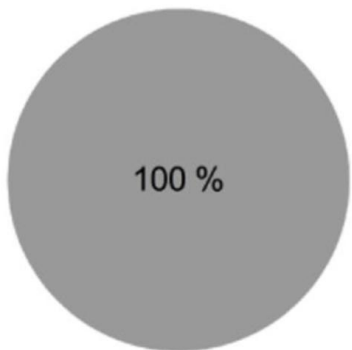


High-TMAO producer (n=51)



E. timonensis (+)
E. timonensis (-)

Low-TMAO producer (n=61)

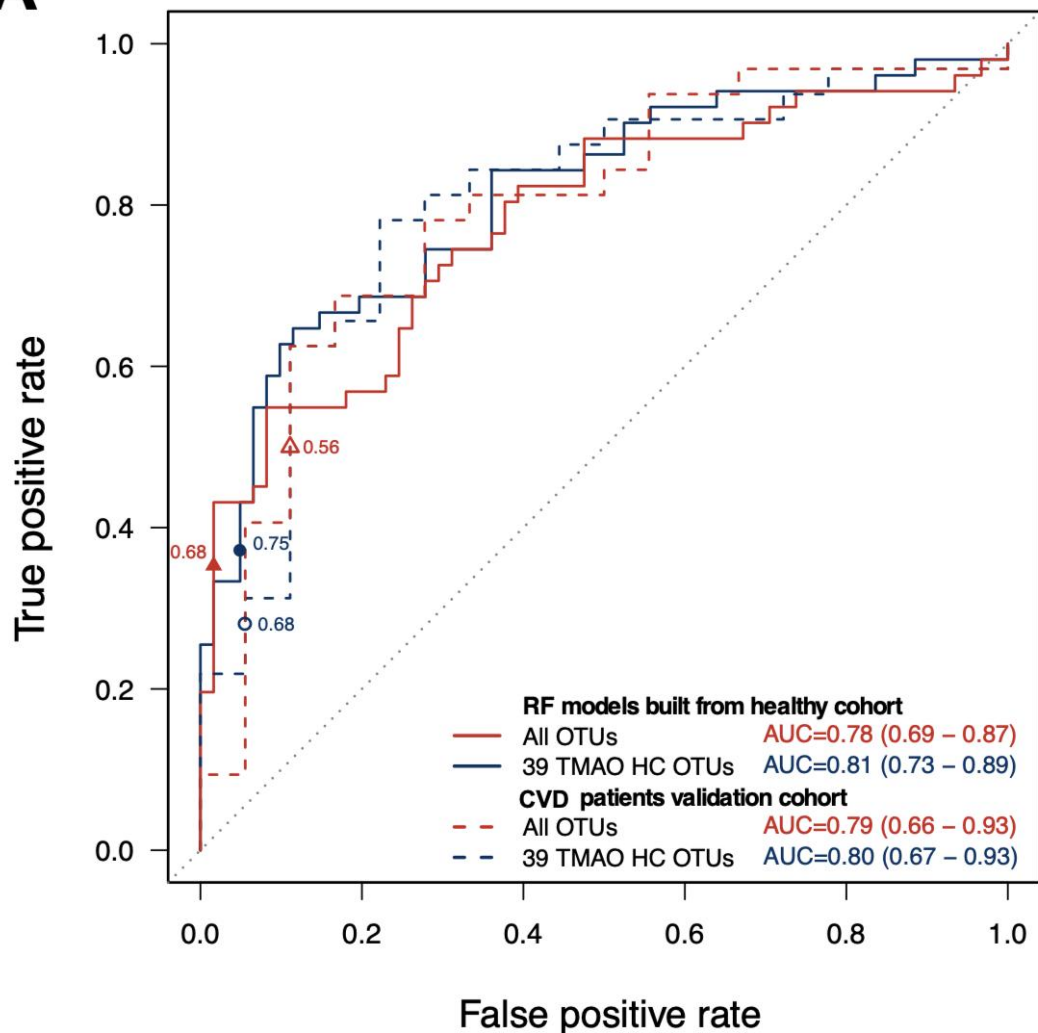


Sensitivity: 25.5%
Specificity: 100%

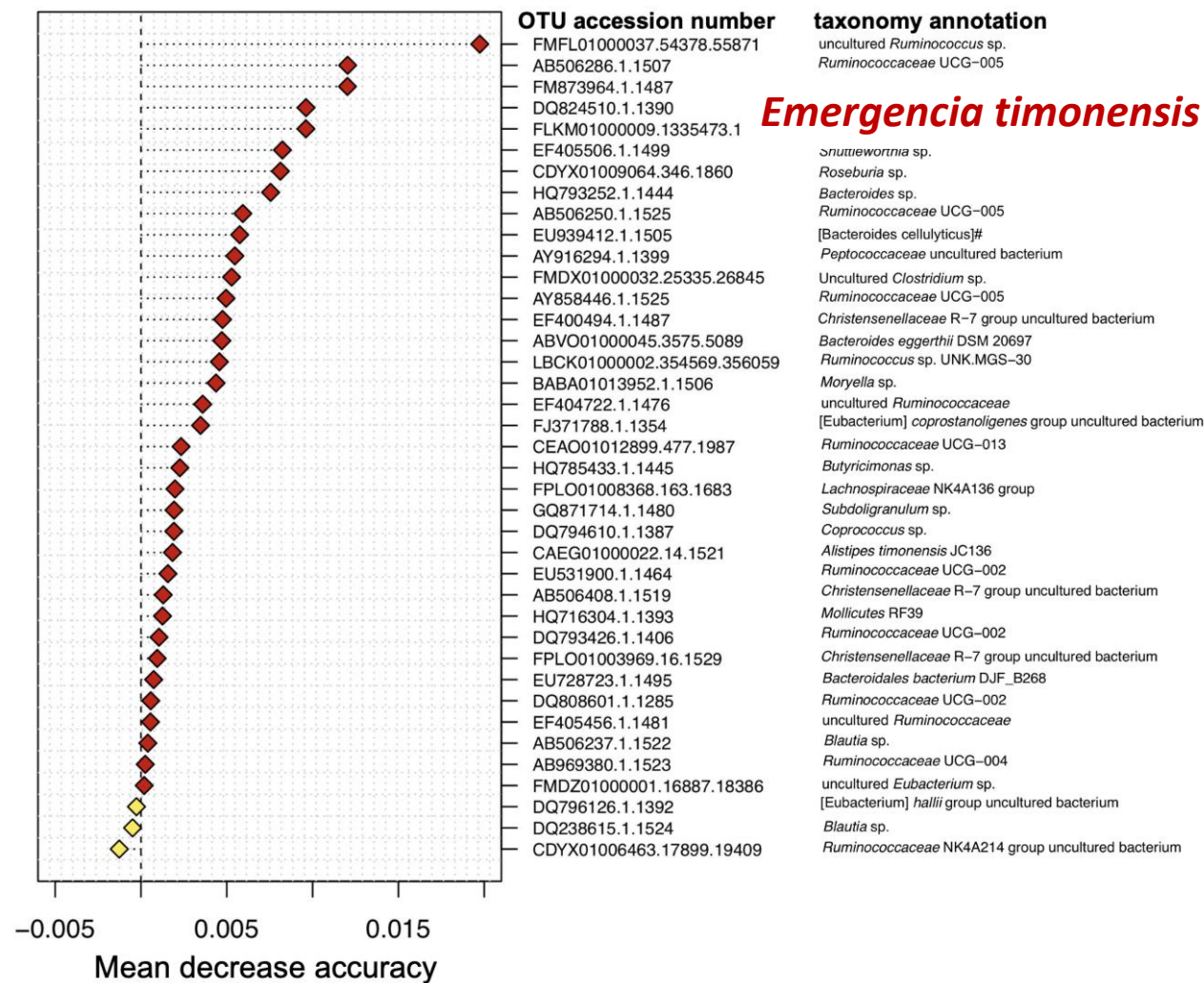
Wu et al.
Microbiome 2020

Random forest model built using 39 species strongly associated with TMAO production.

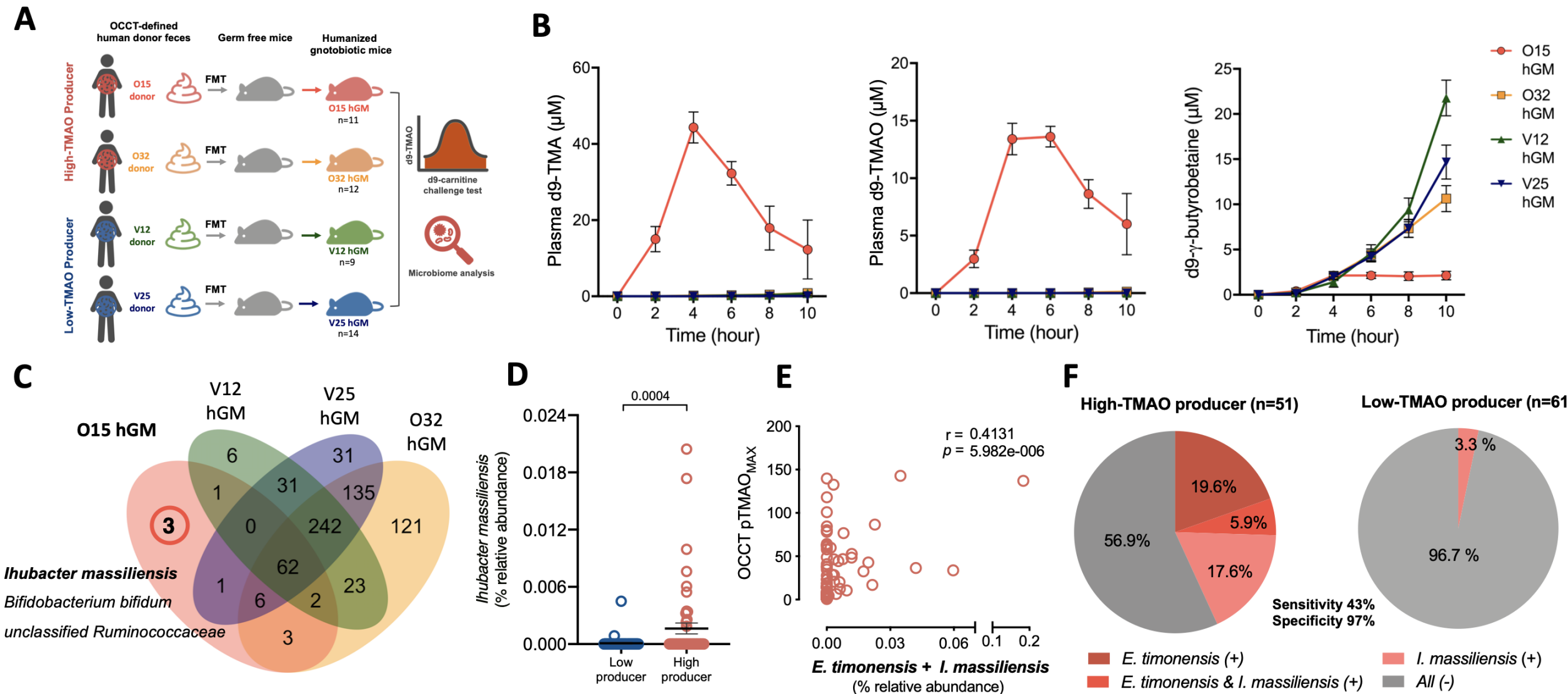
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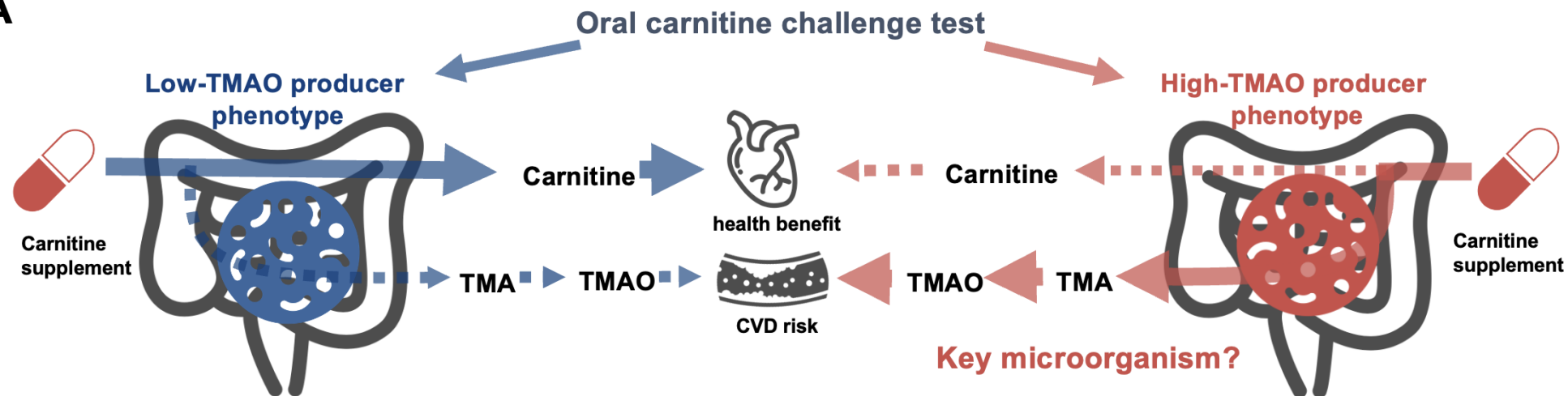
B



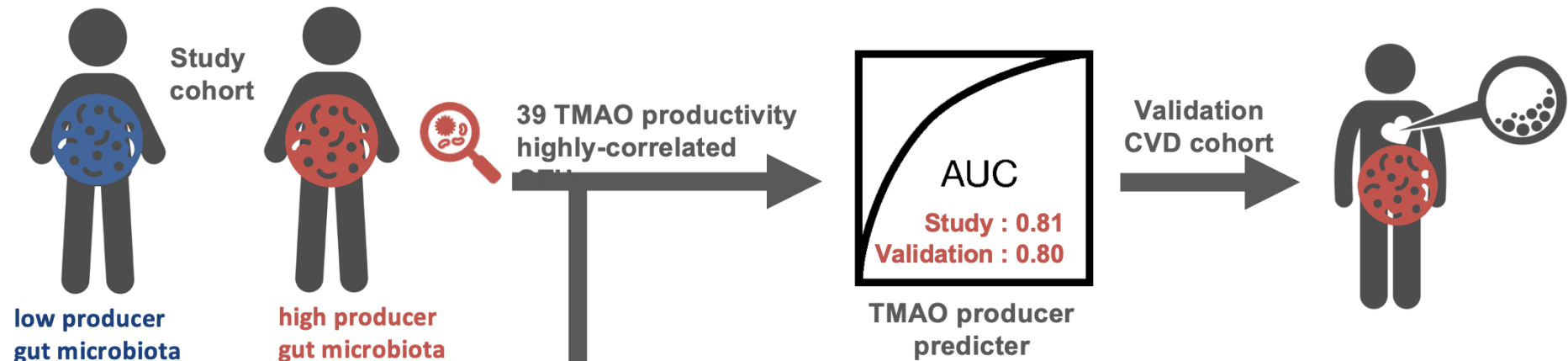
A new microbe highly correlated with TMAO production was identified using the human microbiota-associated mice model



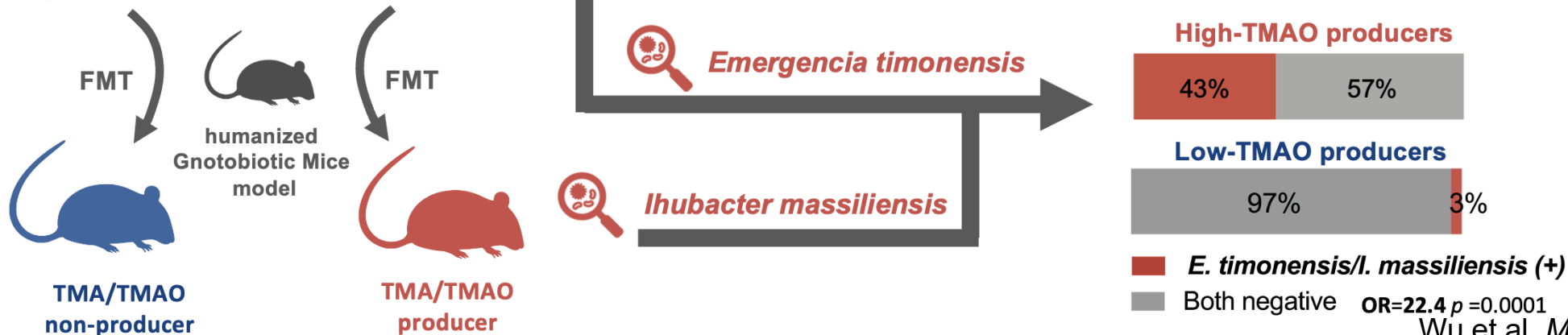
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B



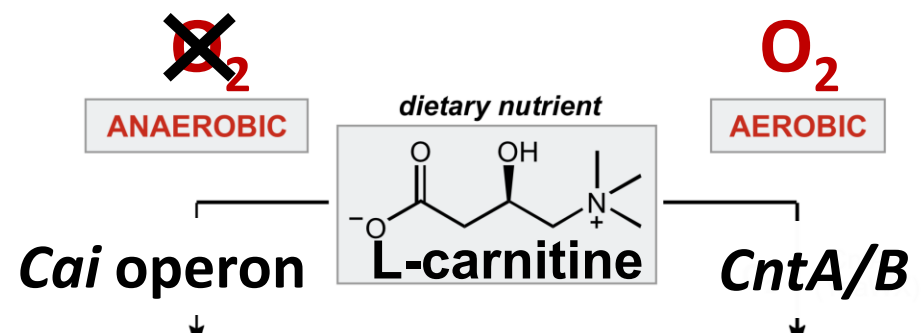
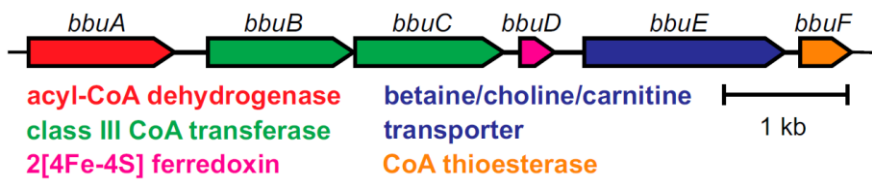
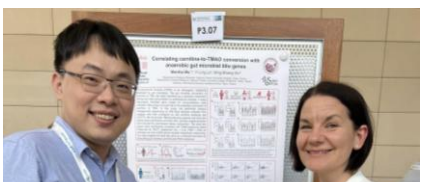
C



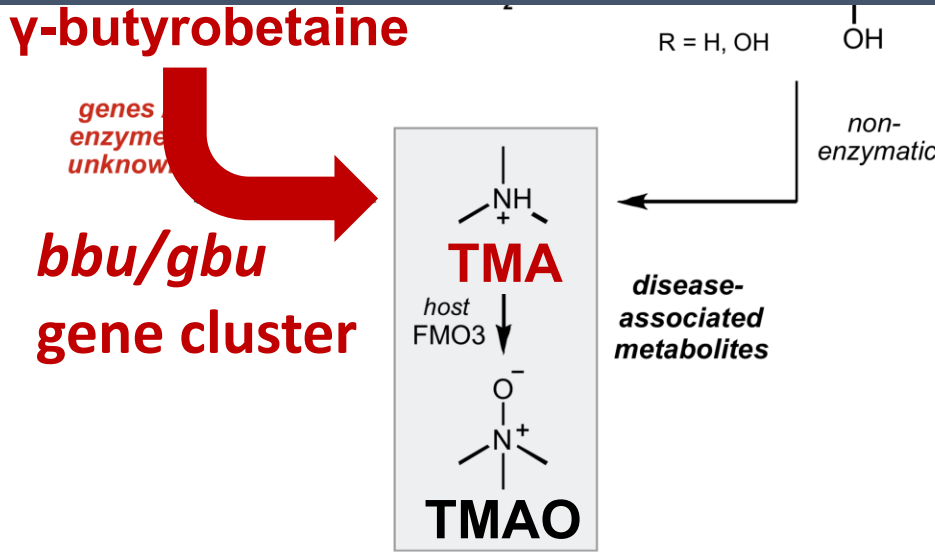
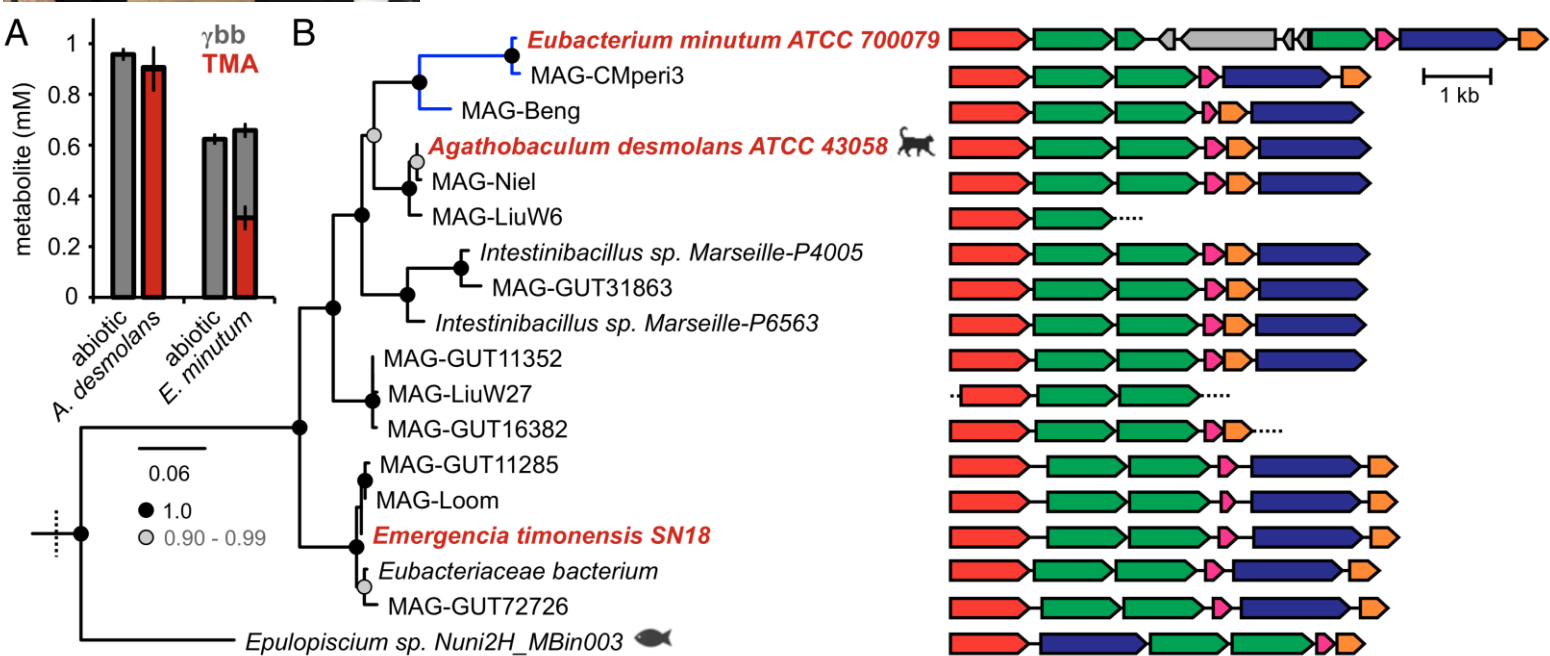
Elucidation of an anaerobic pathway for metabolism of L-carnitine-derived γ -butyrobetaine to trimethylamine in human gut bacteria

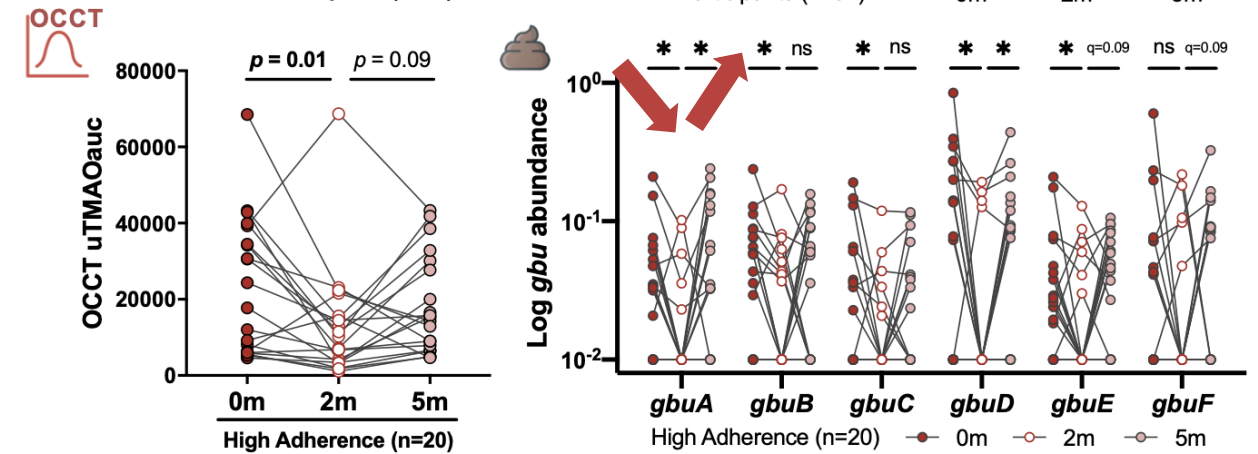
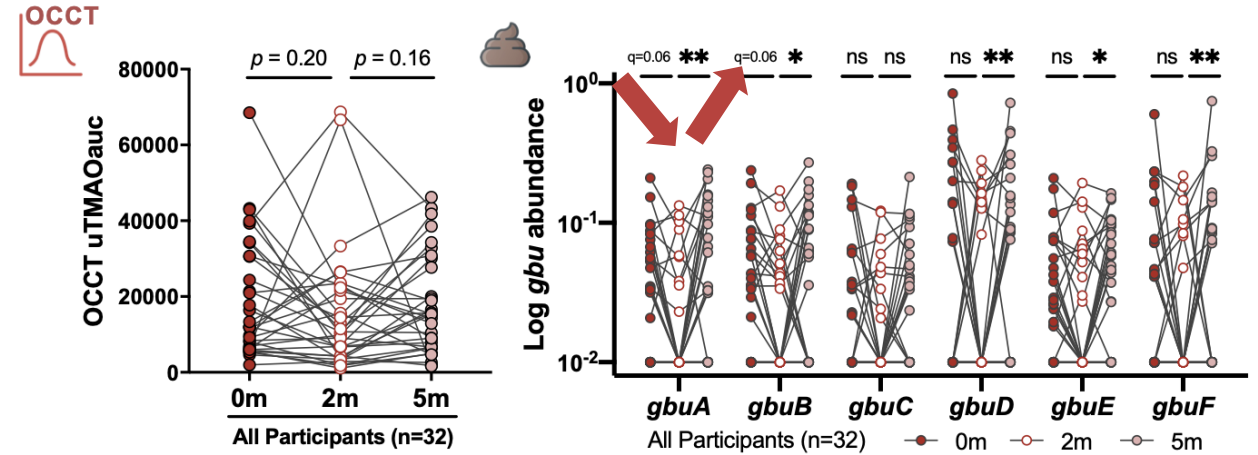
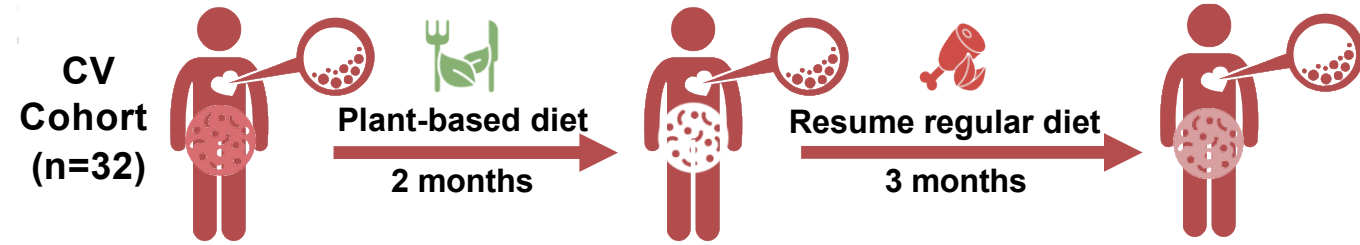
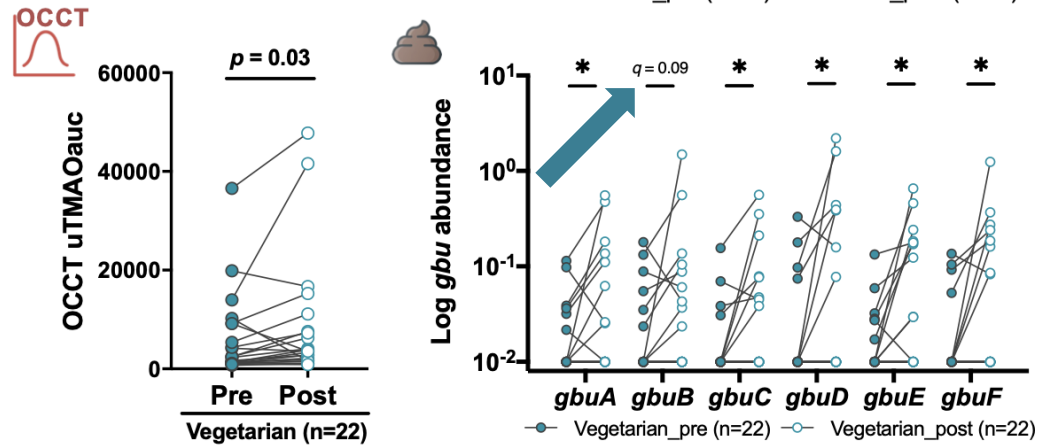
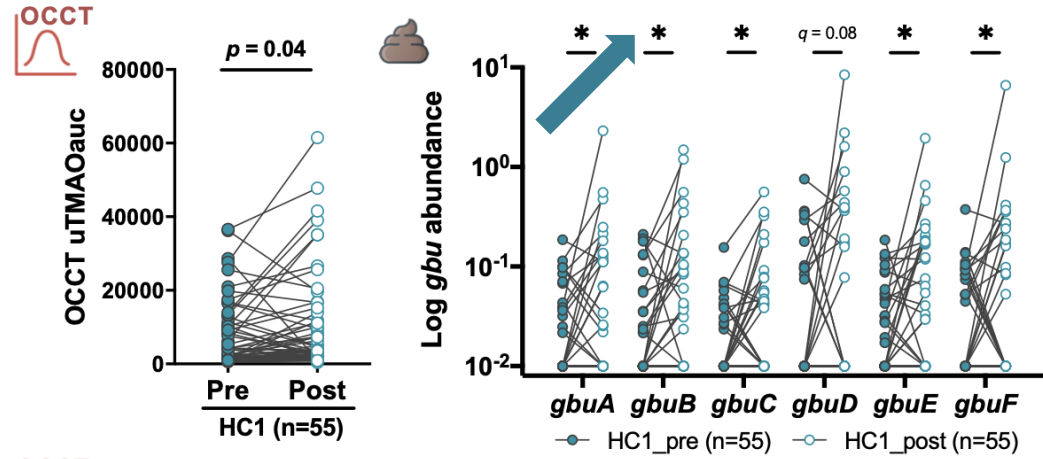
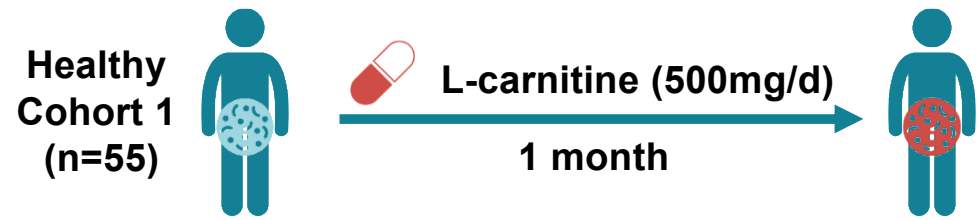
Lauren J. Rajakovich^a, Beverly Fu^a, Maud Bollenbach^a, and Emily P. Balskus^{a,1}

^aDepartment of Chemistry and Chemical Biology, Harvard University, Cambridge, MA 02138

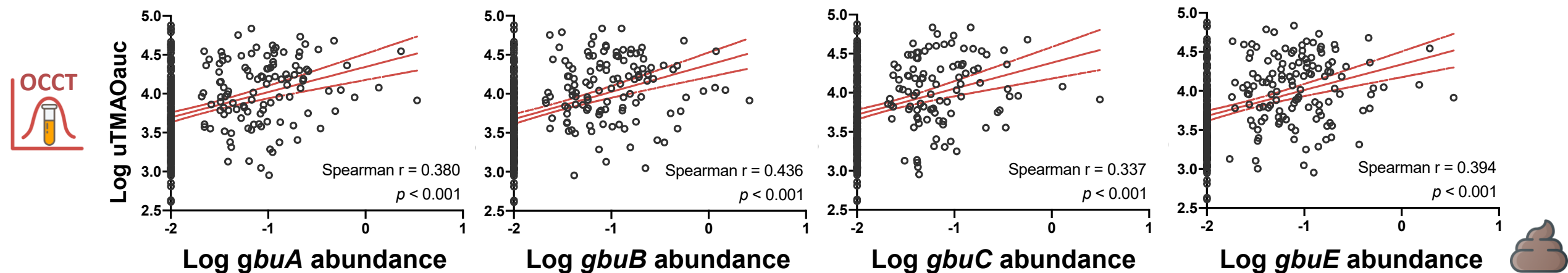


How essential is the *gbu* cluster for TMAO production from carnitine in humans?

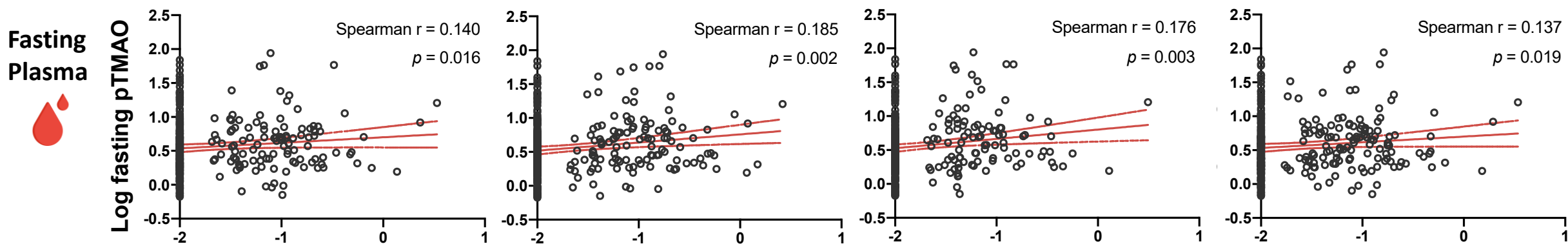




Stronger correlation of *gbu* genes with OCCT than with fasting TMAO



OCCT correlation coefficient = 0.337-0.436, all $p < 0.001$



Fasting plasma TMAO correlation coefficient = 0.137-0.185, $p = 0.002-0.019$

gbu genes-mapping bacteria

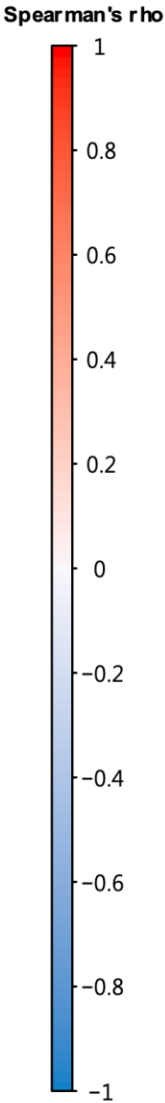
gbuA

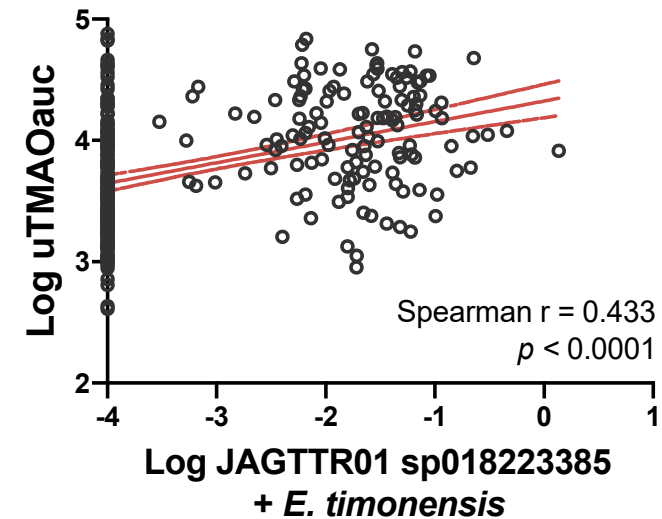
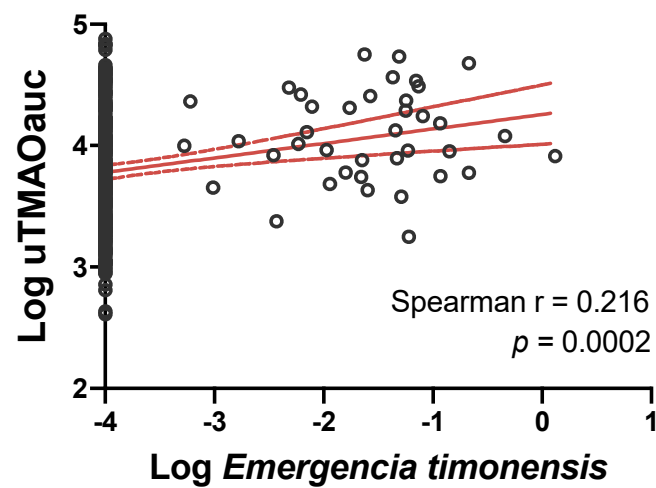
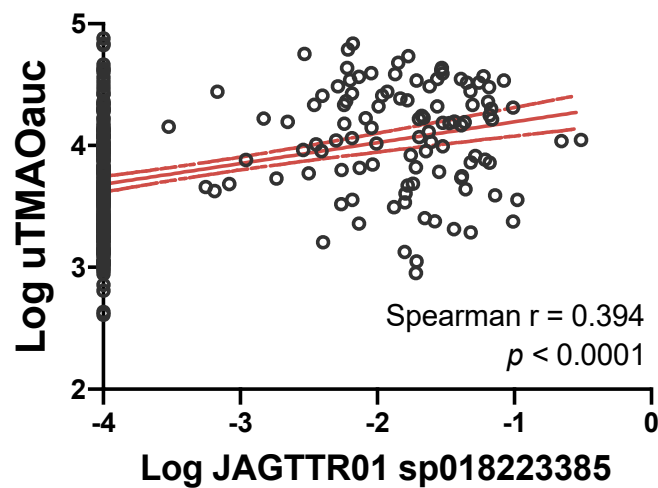
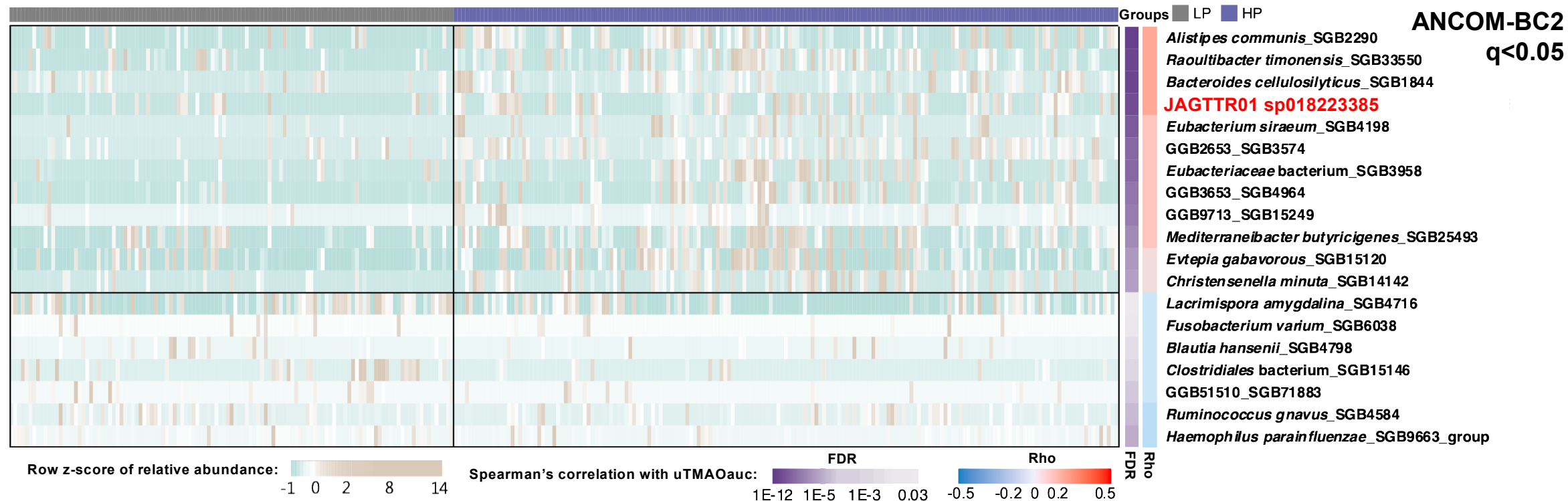
gbuB

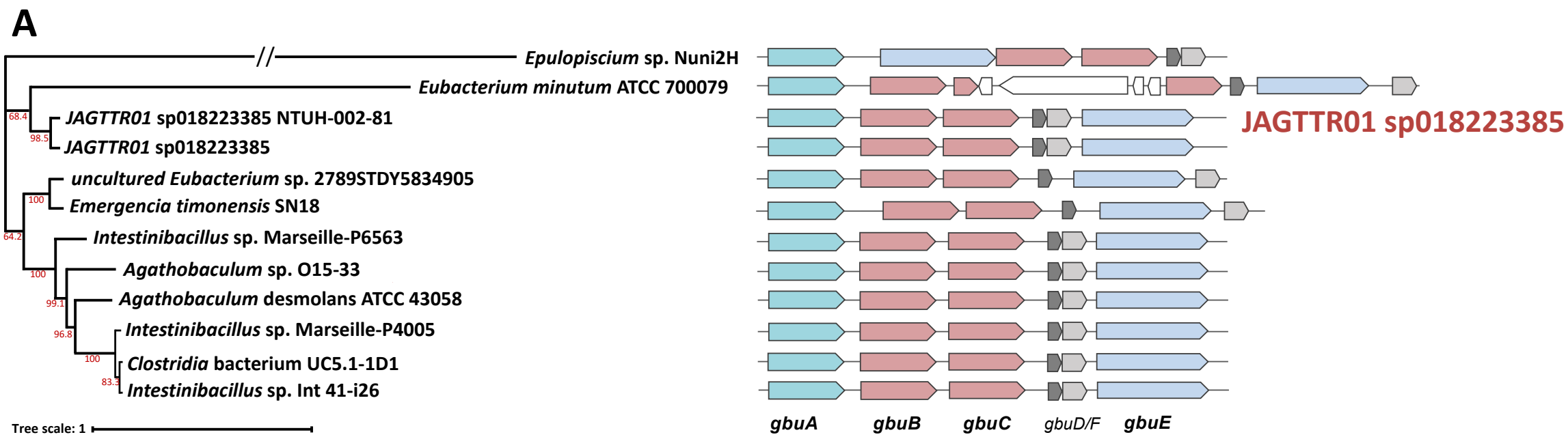
gbuC

gbuE

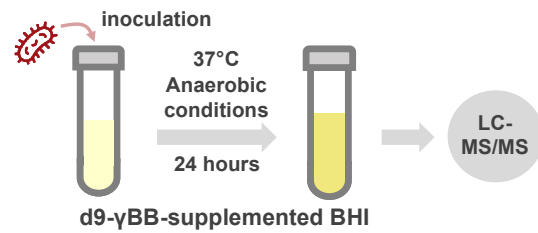
	pTMAO	uTMAOmax	uTMAOauc	pTMAO	uTMAOmax	uTMAOauc	pTMAO	uTMAOmax	uTMAOauc	pTMAO	uTMAOmax	uTMAOauc
Agathobaculum desmolans ATCC 43058												
Agathobaculum sp. NSJ-28	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Agathobaculum sp._O15-33												
Clostridia bacterium UC5.1-1D1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Emergencia timonensis strain SN18		**	*		***	***		**	**		*	*
Epulopiscium sp. Nuni2H	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Eubacterium minutum ATCC 700079	NA	NA	NA							NA	NA	NA
Intestinibacillus sp. Marseille-P4005				NA	NA	NA	NA	NA	NA	NA	NA	NA
Intestinibacillus sp. Marseille-P6563												
JAGTTR01 sp018223385		****	****	*	****	****		**	***		****	****
Uncultured Eubacterium sp. 2789STDY5834905			*								*	*



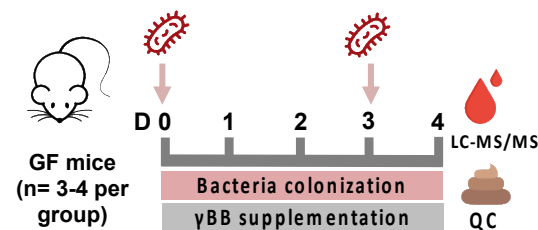




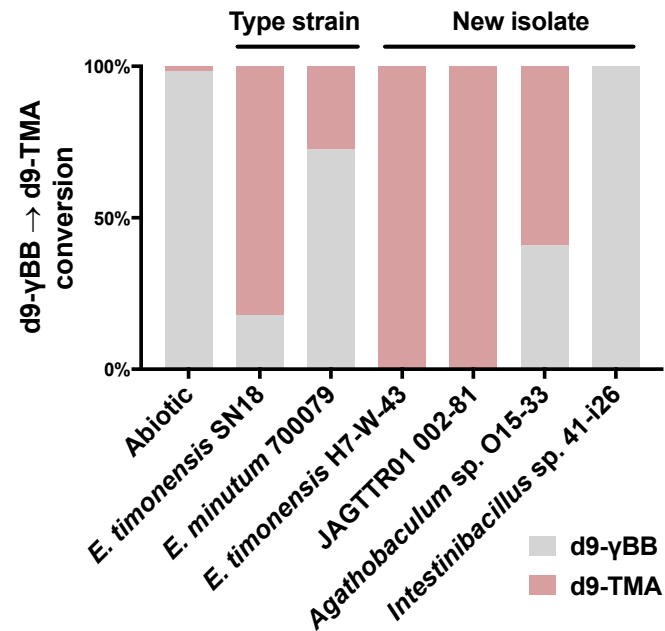
B *in vitro*



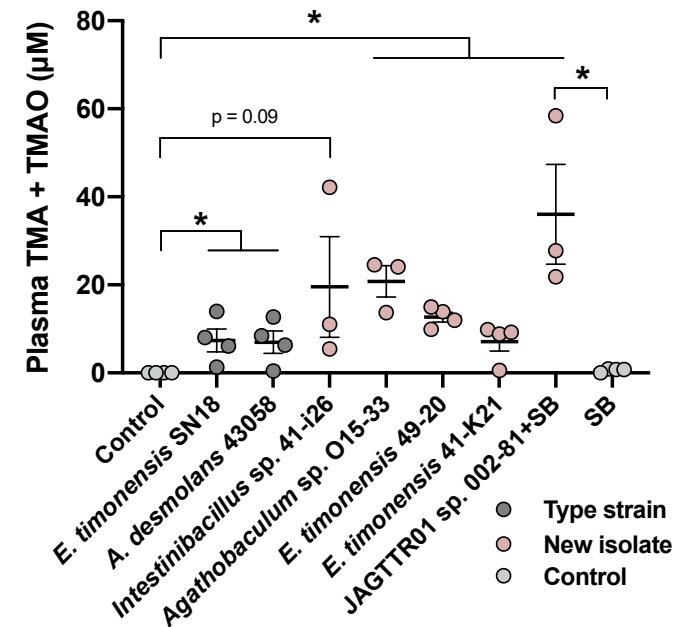
C *in vivo*



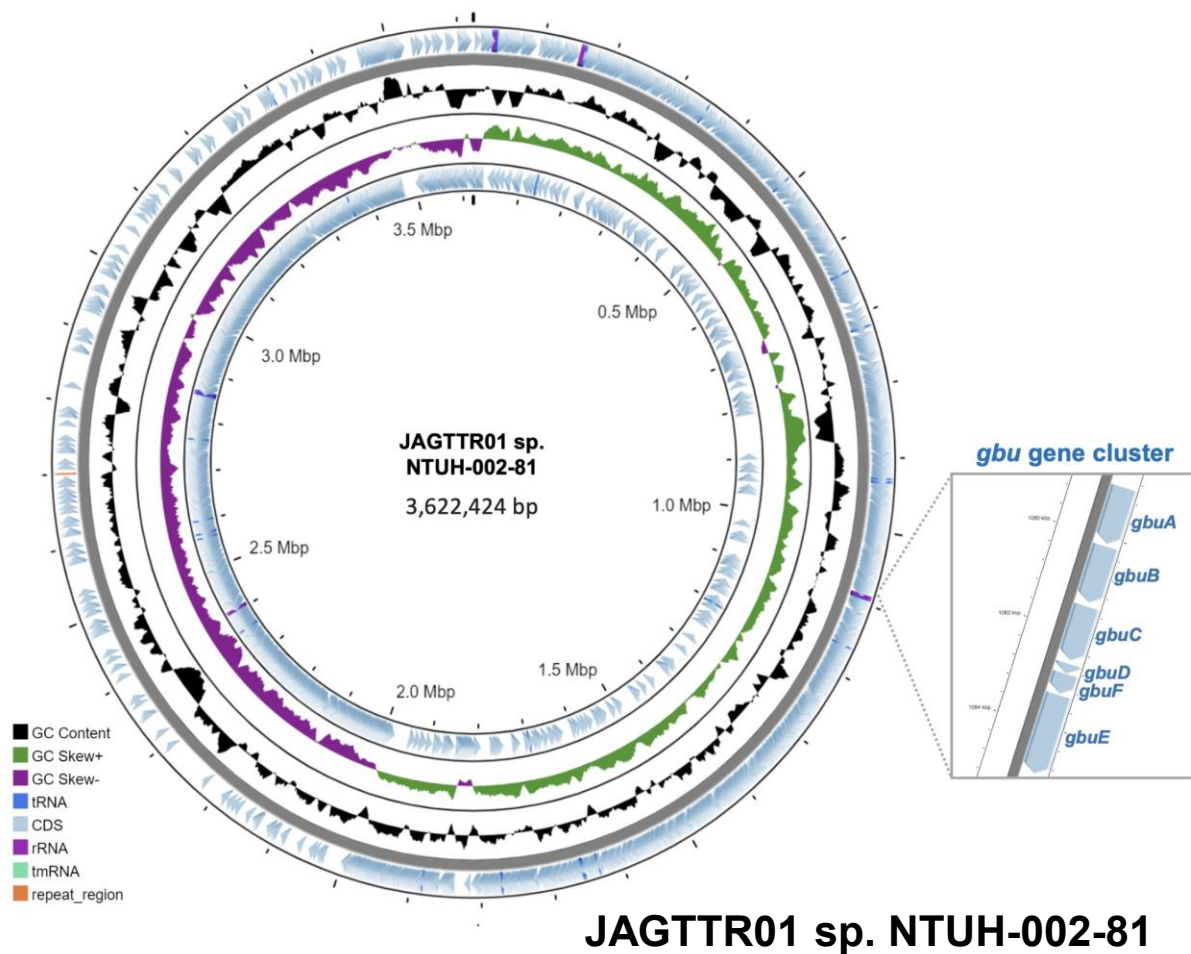
D *in vitro*



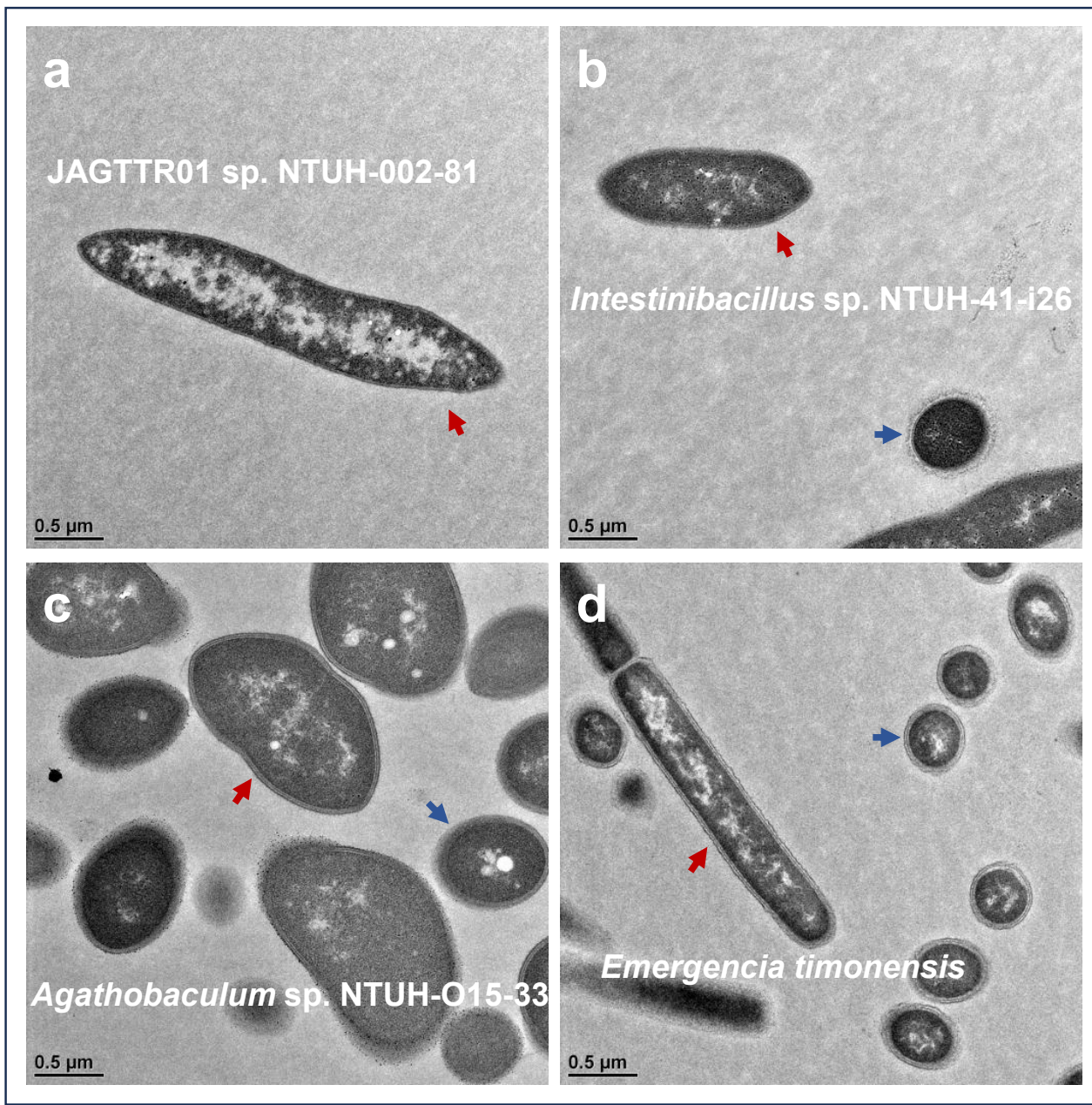
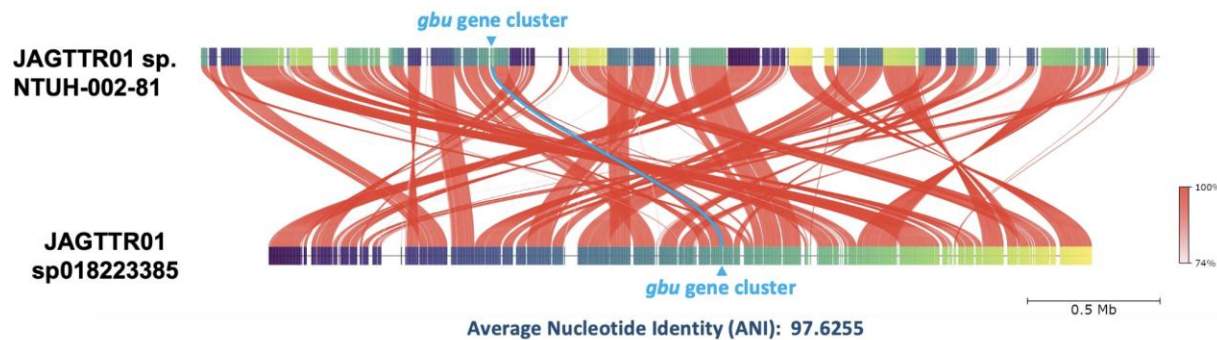
E *in vivo*



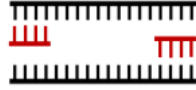
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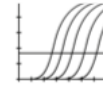
B



Design degenerate
primer for qPCR of
gbuB using templates
of six *gbu* gene
cluster-containing
bacteria

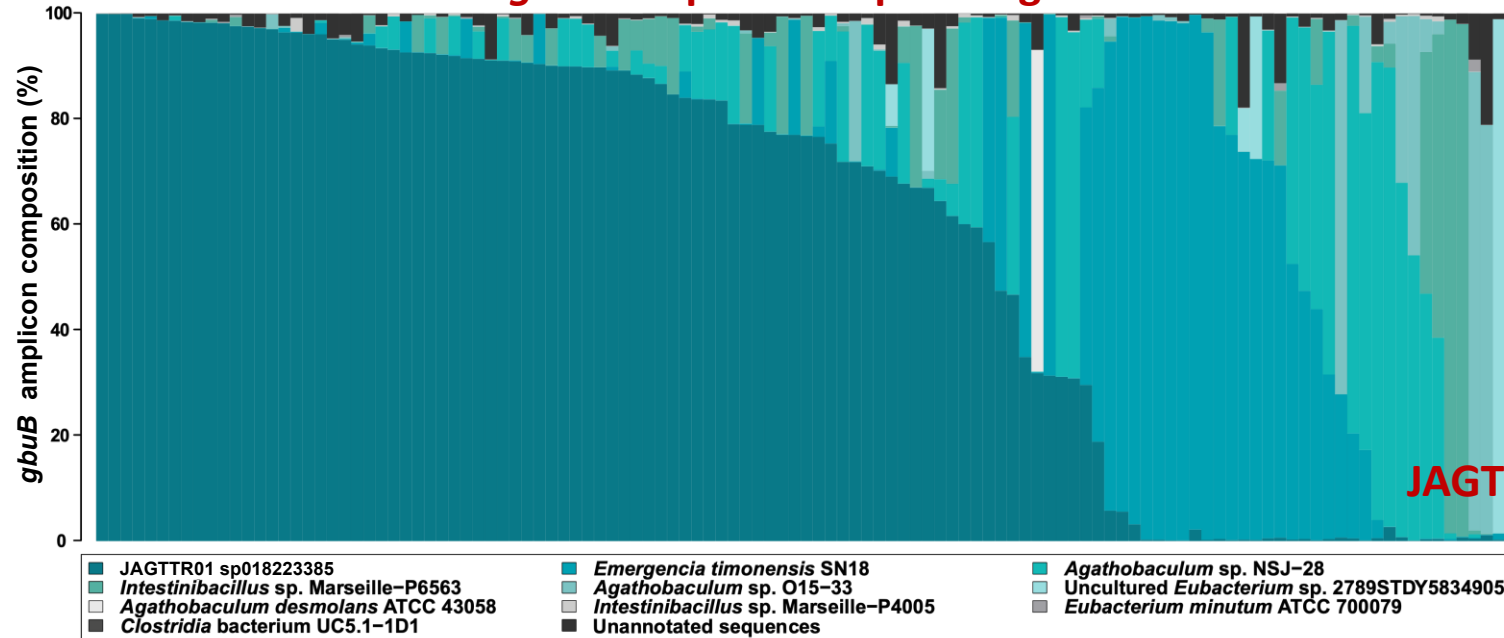


fecal DNA



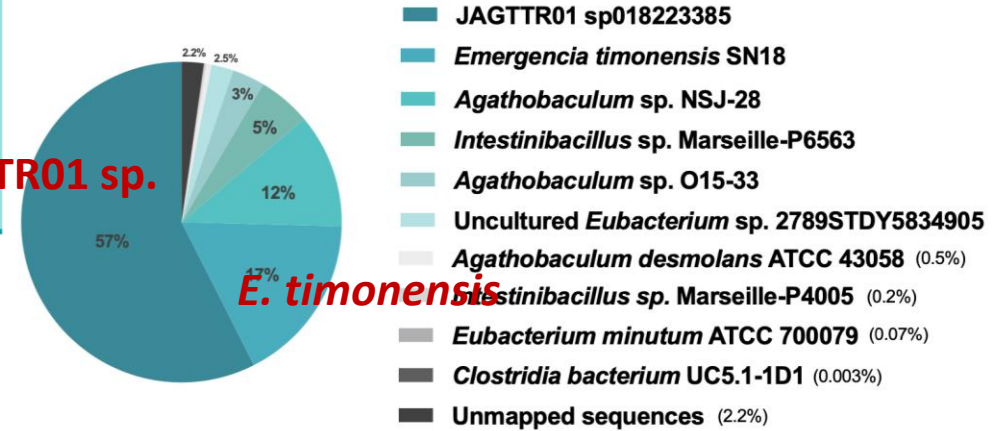
qPCR

gbuB amplicon sequencing



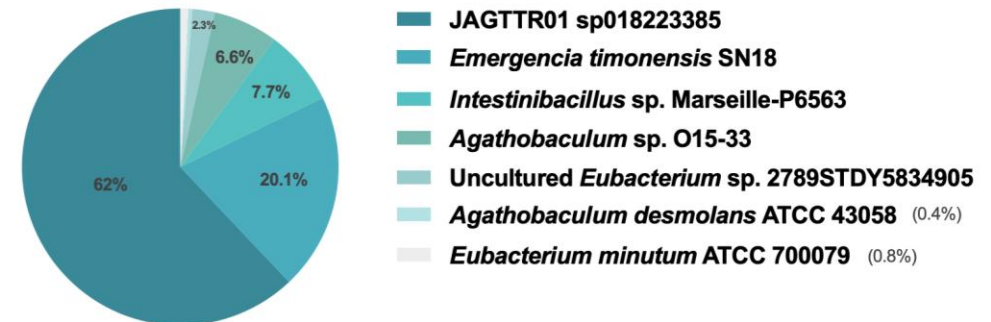
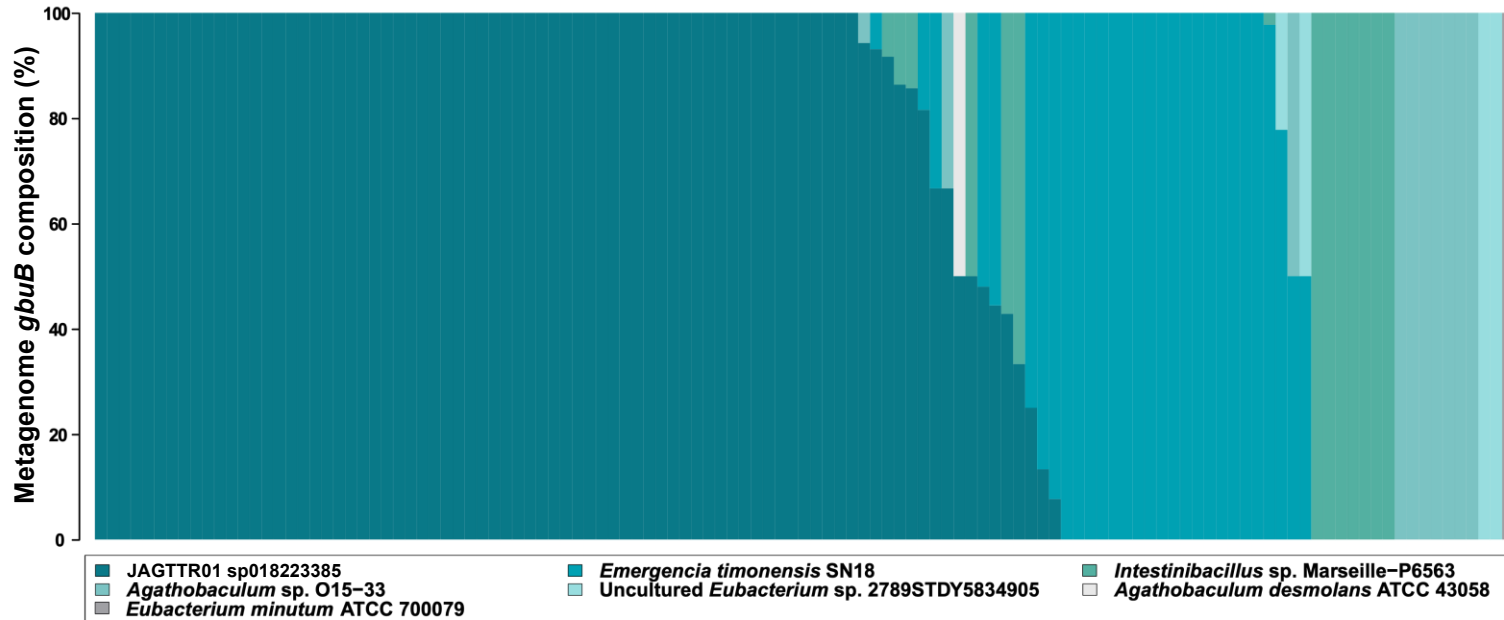
JAGTTR01 sp.

JAGTTR01 may serve as a key gut microbes for determining TMAO level from Carnitine Consumption

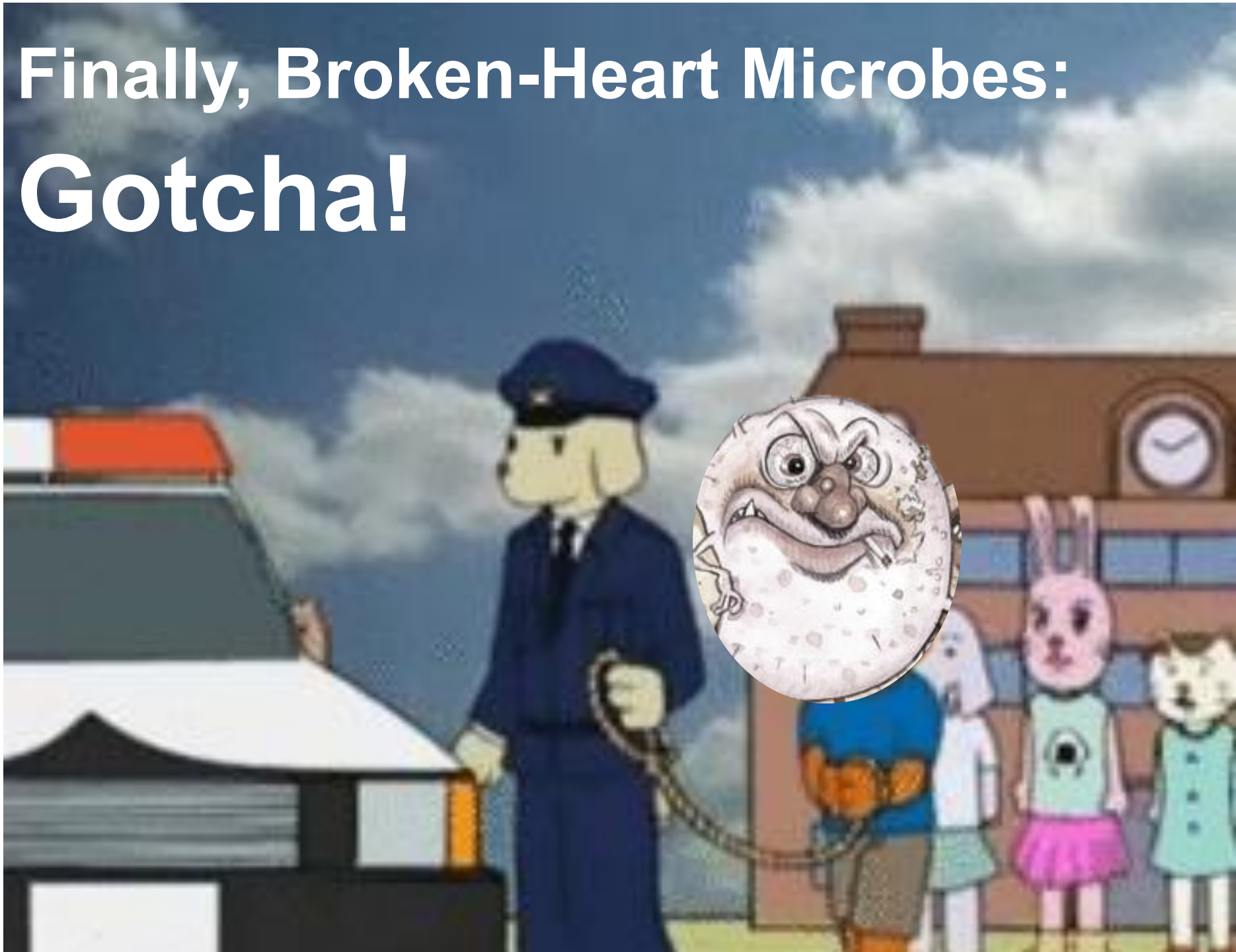


E. timonensis

Metagenome sequencing

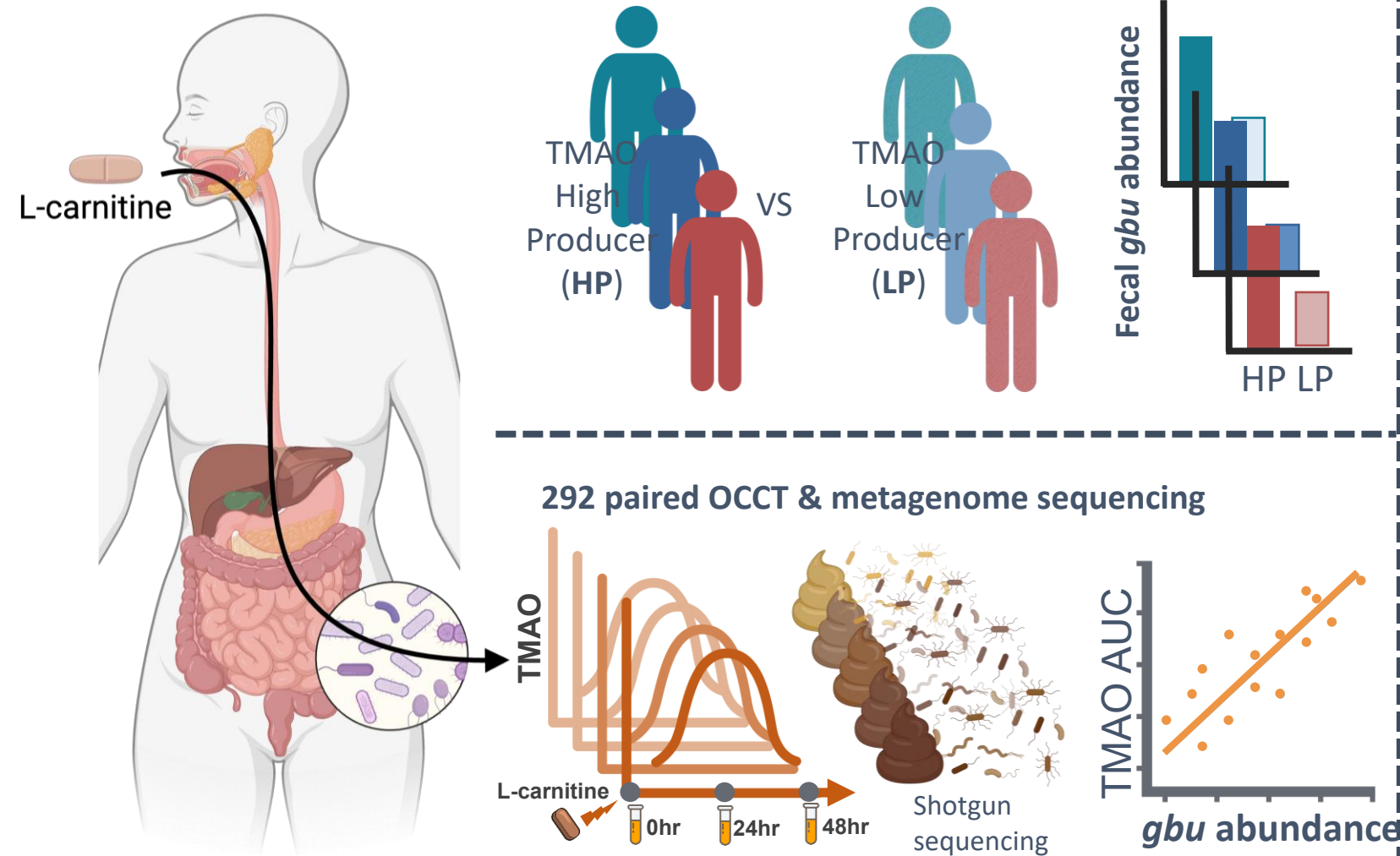


Finally, Broken-Heart Microbes: Gotcha!

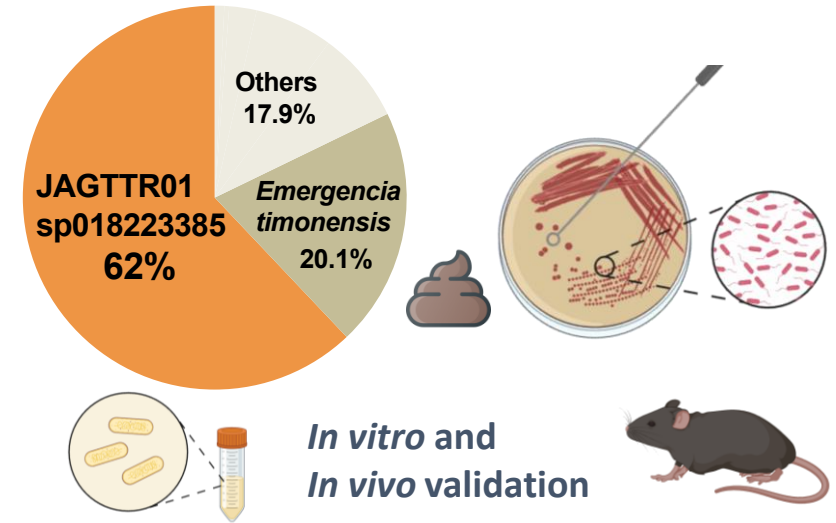


A Gut Microbiome-based Personalized Nutrition

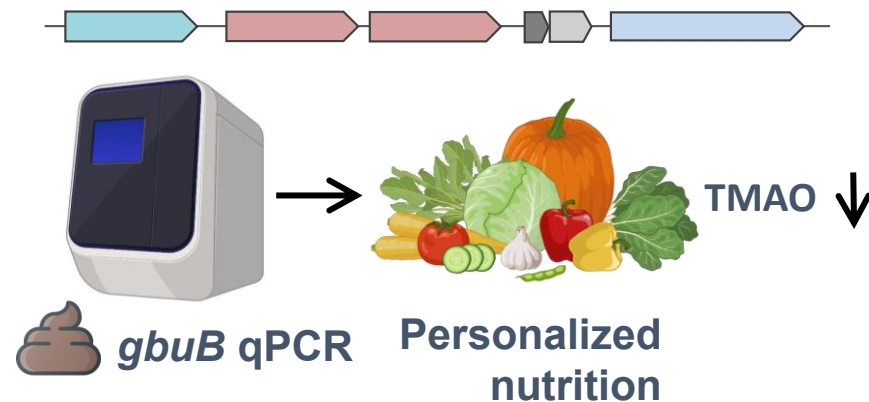
Oral Carnitine Challenge Test (OCCT)



gbu-containing bacteria ID and isolation

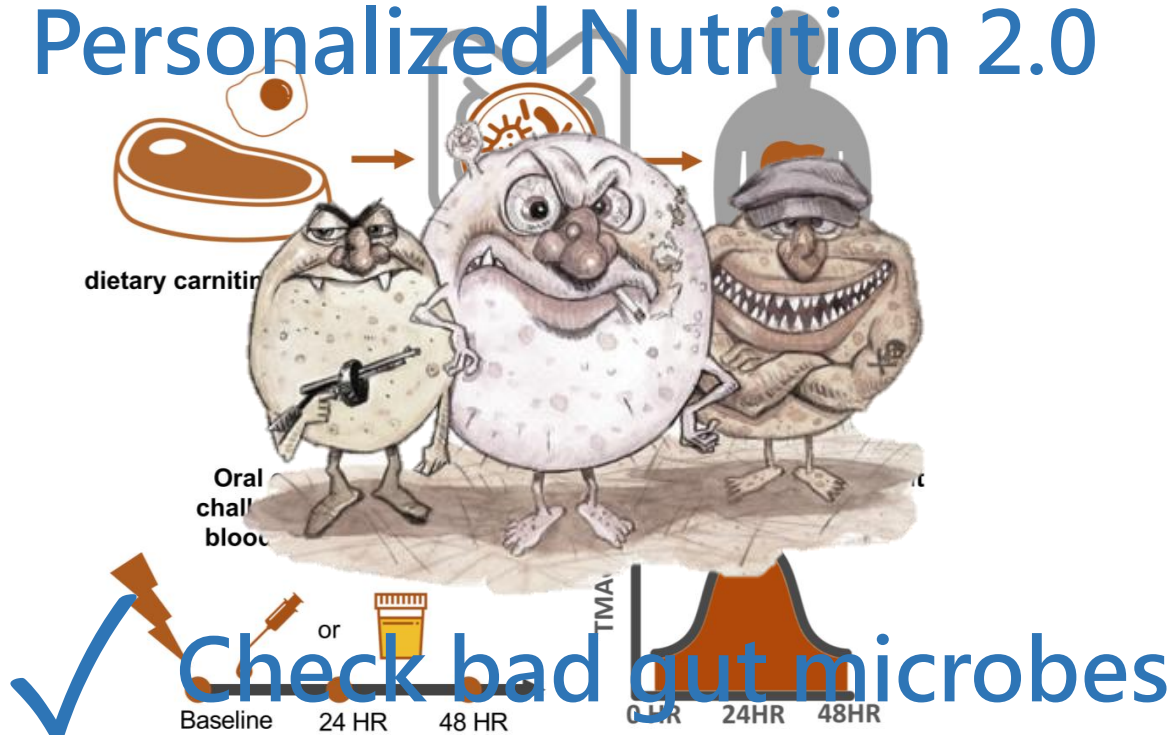


gbu gene cluster collection



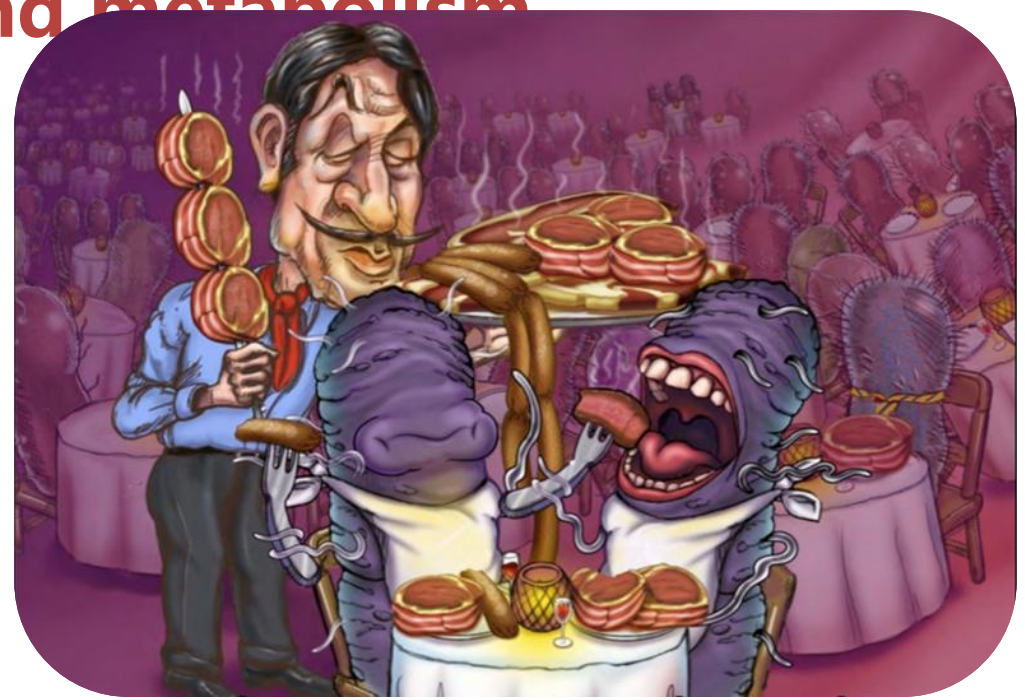
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Microbiome-based Personalized Nutrition 2.0



Q: Why don't I eat Red Meat?

A: My doctor discover that my gut bacteria **love** eating meat, producing harmful toxins that are **bad for my heart, kidney and metabolism**



Check fecal gbu gene

Dietary intervention guidance Drug development efforts assessment Diet-induced thrombosis risk survey Benchmark for fecal biomarker Investigation

Thanks for your attention

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