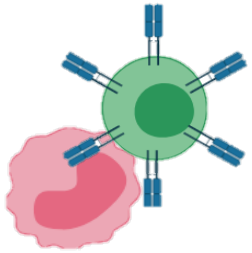
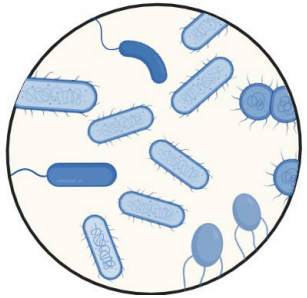
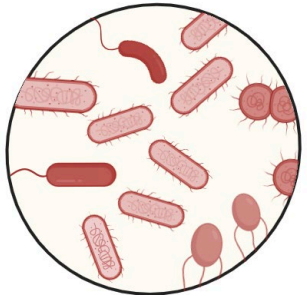
From Association to Action:

Unraveling the Importance of the Gut Microbiome during Aging



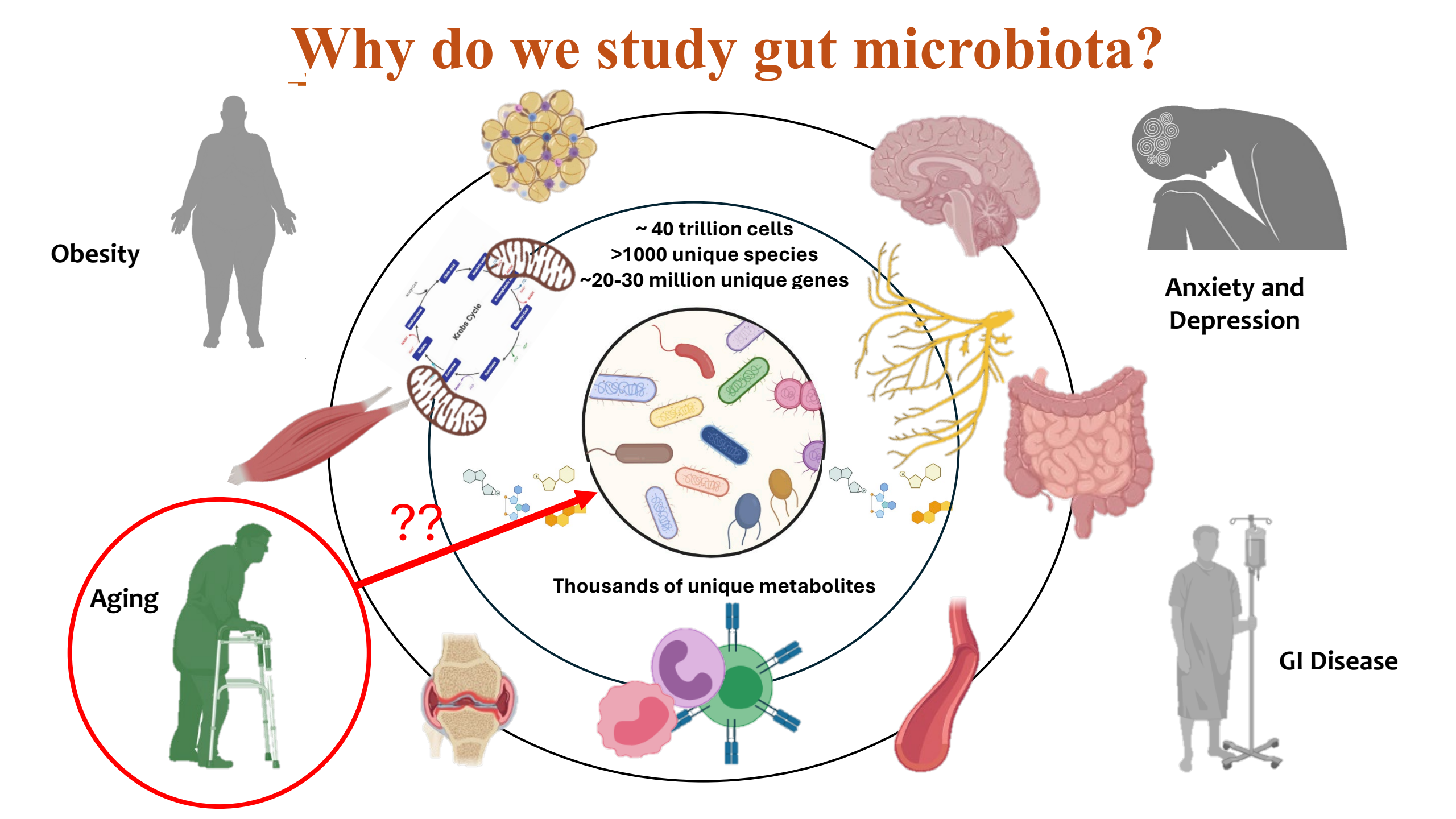
Jacob Allen, PhD

University of Illinois at Urbana-Champaign
Department of Health and Kinesiology
Institute for Genomic Biology
Microbiome Metabolic Engineering
Division of Nutritional Sciences

Microbial Systems Initiative

The Allen Lab
Integrative Microbiota & Physiology Lab

Why do we study gut microbiota?



Advanced age is associated with changes in microbiome composition

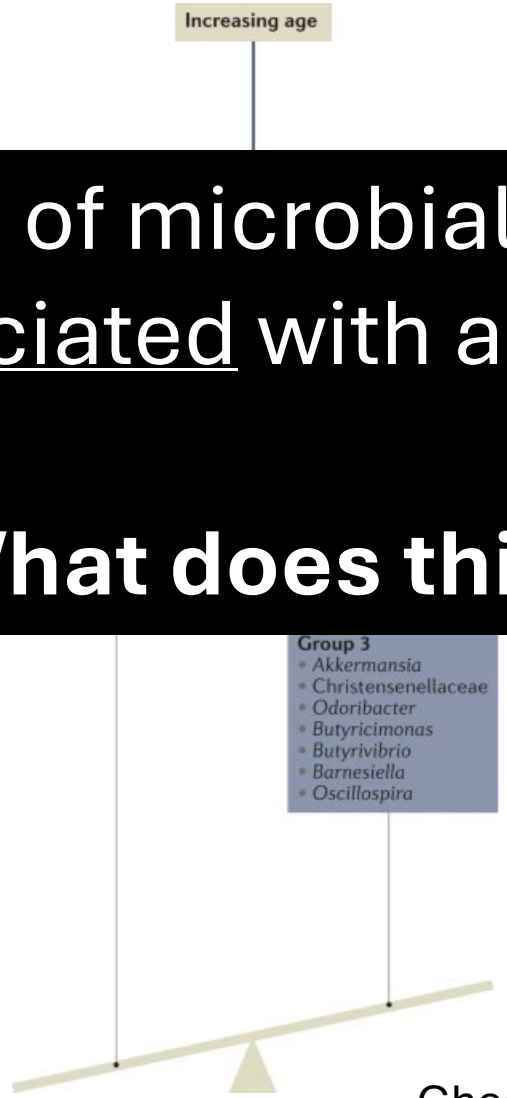
The gut microbiome as a modulator of healthy ageing

Tarini Shankar

Abstract | The g
non-communica
and functional c
studies of the gu
distinct populat
associated with

Summary: A range of microbial taxa have been associated with age

Problem: What does this mean?



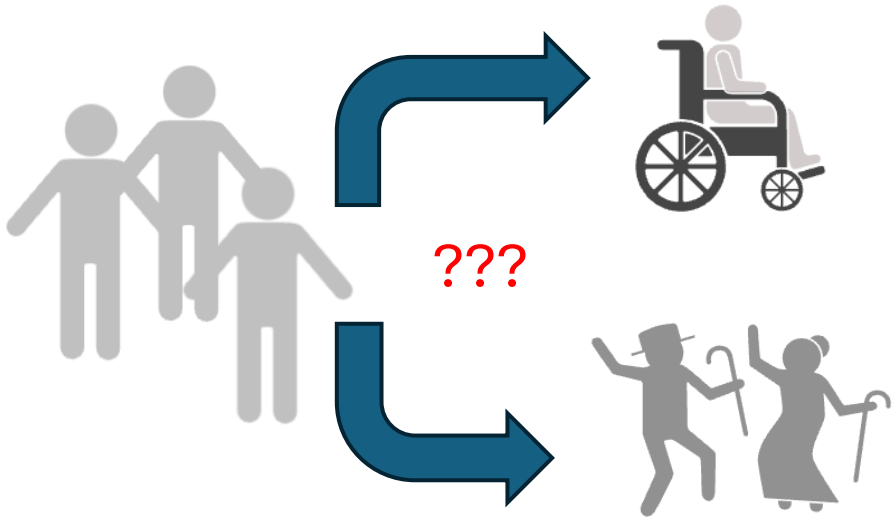
with younger age

Faecalibacterium
Roseburia
Copropcoccus
Eubacterium rectale
Bifobacterium
Prevotella

Anaerotruncus
Streptococcus
Escherichia

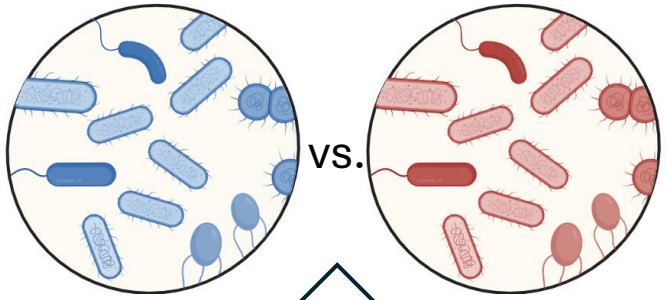
Ghosh et al. , *Nat Rev Gastroenterol Hepatol (2022)*

We all don't age the same way… perhaps the microbiome can tell us something more specific?



???

What does the microbiome tell us?



vs.

Chronological age

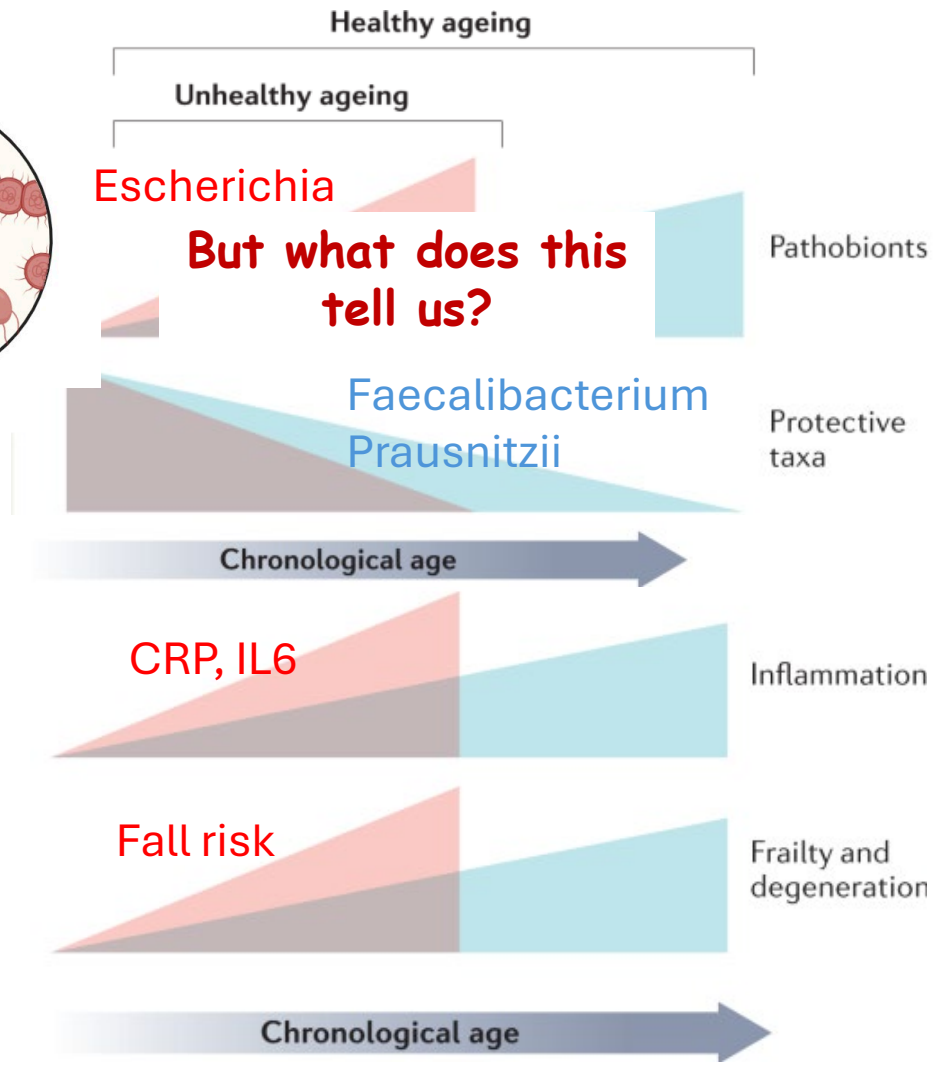
??

Healthy Aging

Unhealthy Aging

vs.

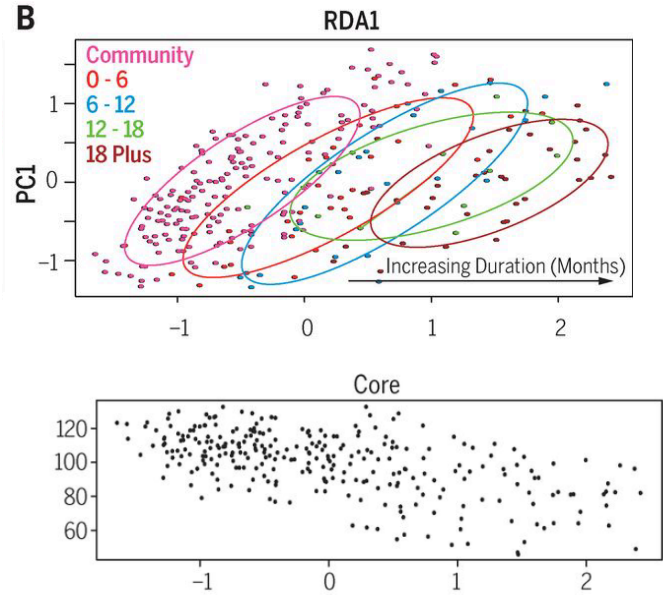
Host (Aging) phenotype



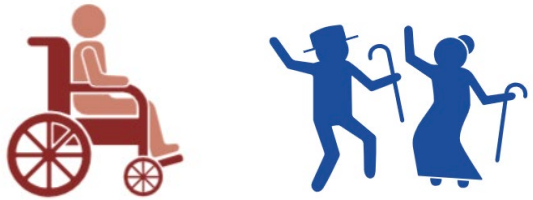
Ghosh et al. , *Nat Rev Gastroenterol Hepatol (2022)*

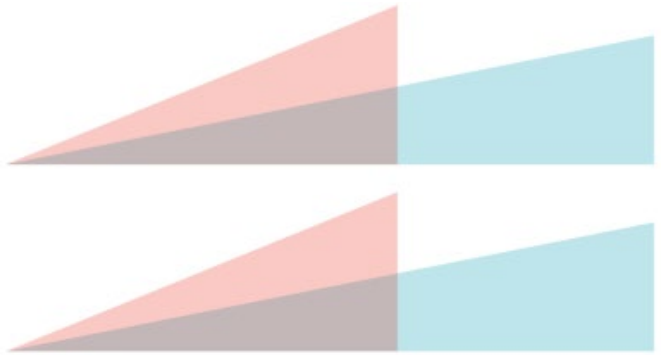
Microbiome shifts concordant to health indices

Time in Long-Stay Facility

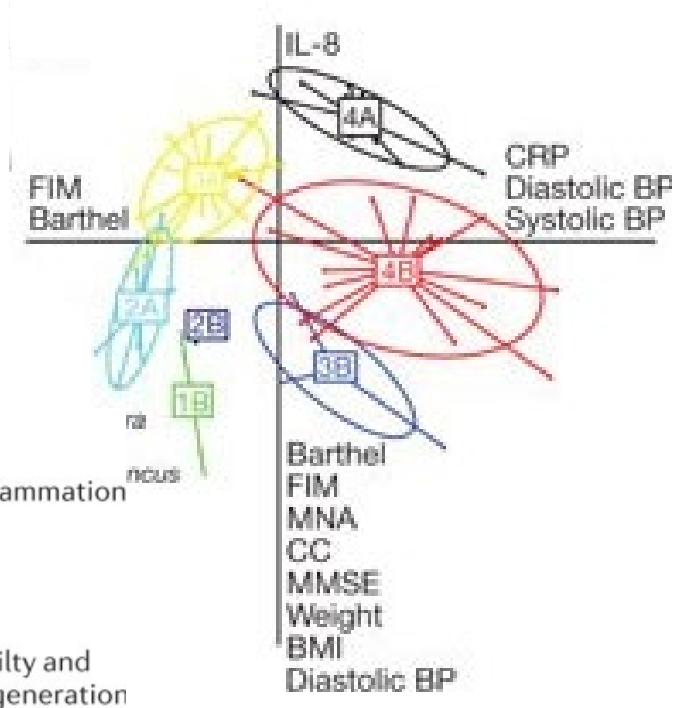


Loss of diversity in the core microbiota associated with <u>increased time in long-stay facilities</u>





Microbial composition <u>correlates</u> with health indices in long-stay facility occupants



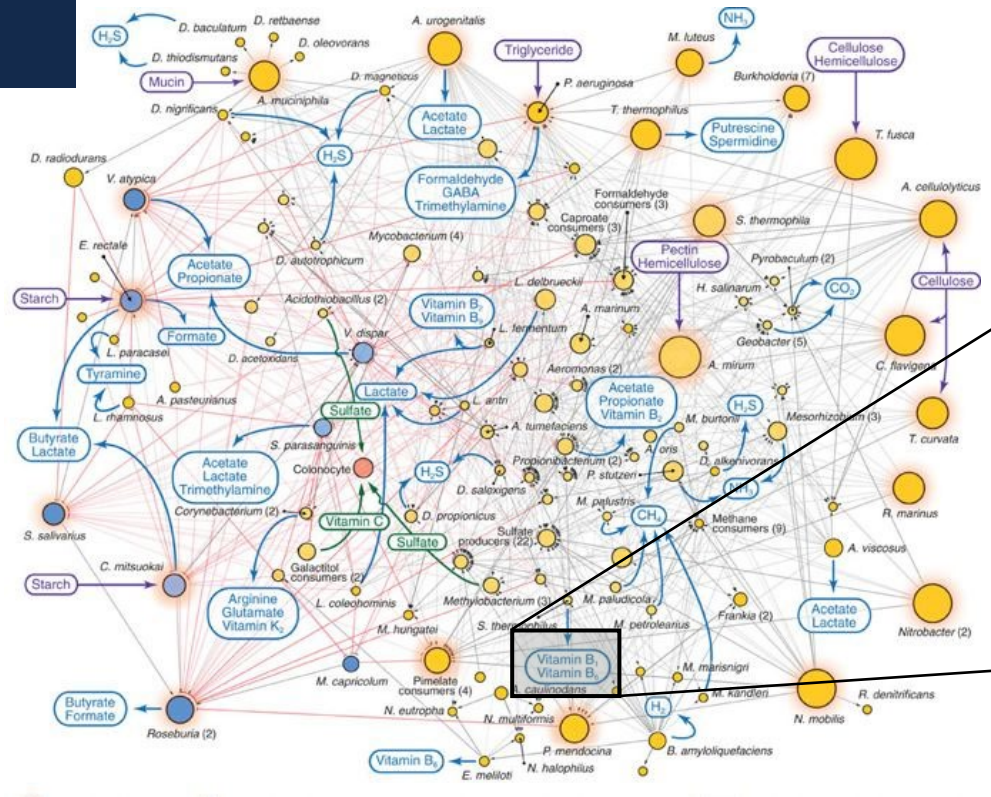
Claesson et al., *Nature* (2012)
O'toole and Jeffery, *Science* (2015)

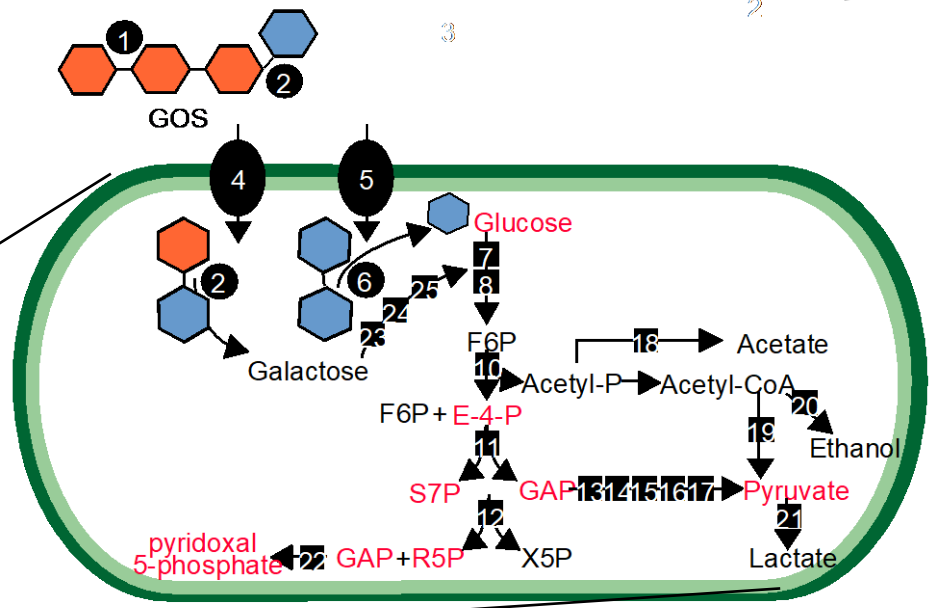
Microbiome composition associates with age and age-related health indices…

but can we learn more?

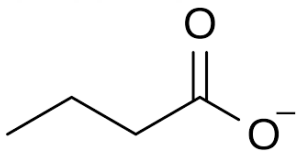
What do microbes produce?

1 -10 million unique genes

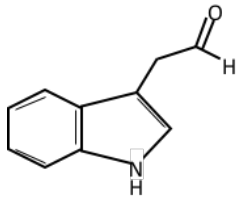




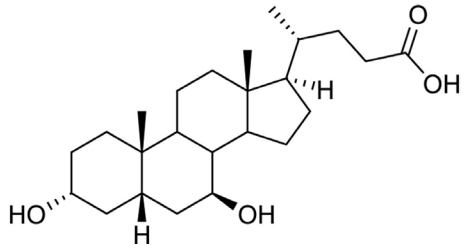
~ 10-20 percent of circulating metabolites are microbial-derived or modified



Short Chain fatty acids
(e.g. Butyrate)



Amino Acid Metabolites
(e.g. Indole-3-acetate)



Bile acids
(e.g. Deoxycholic Acid)

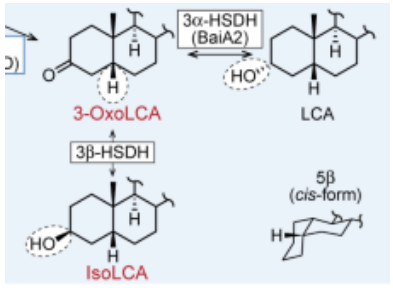
Centenarians harbor unique microbial-derived bile acids that limit pathogen growth

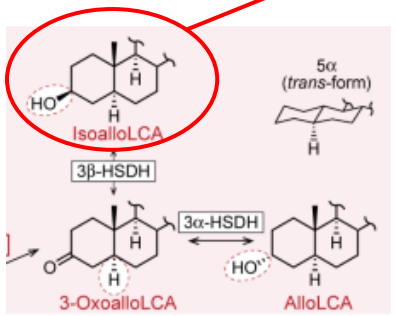
Article

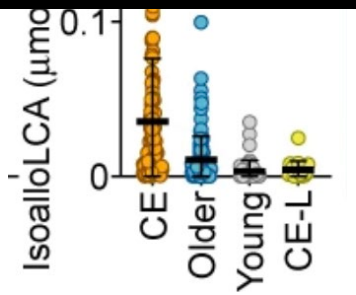
Novel bile acid biosynthetic pathways are enriched in the microbiome of centenarians

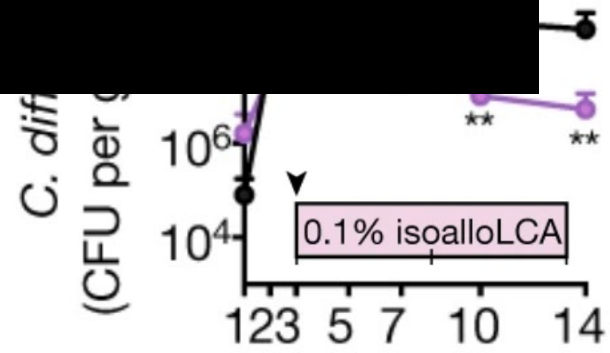
Summary: Microbes and their metabolites associate with aging biology

But does an 'aged microbiota' directly impact the host?



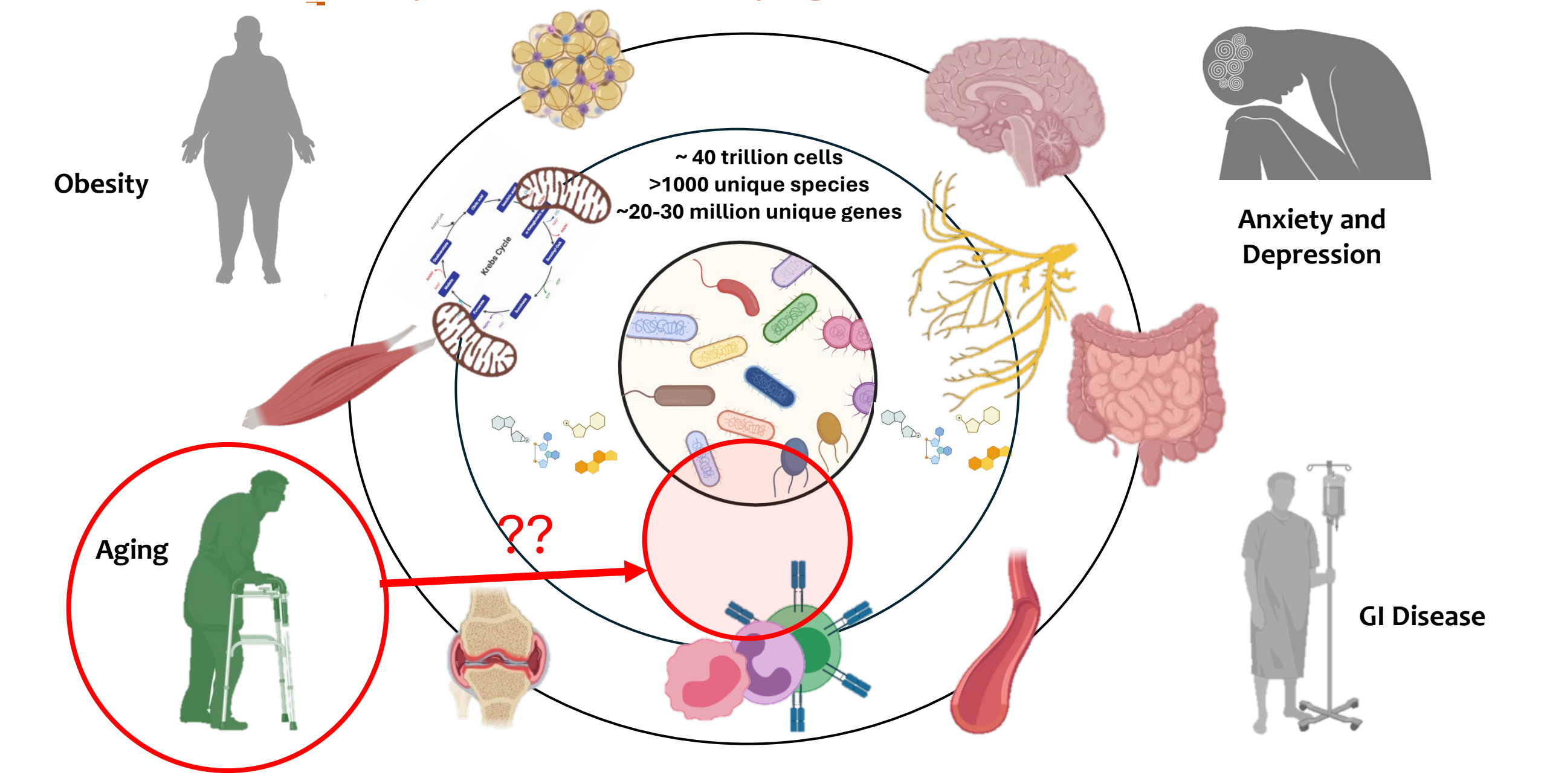






Sato et al. *Nature*, 2021

Why do we study gut microbiota?



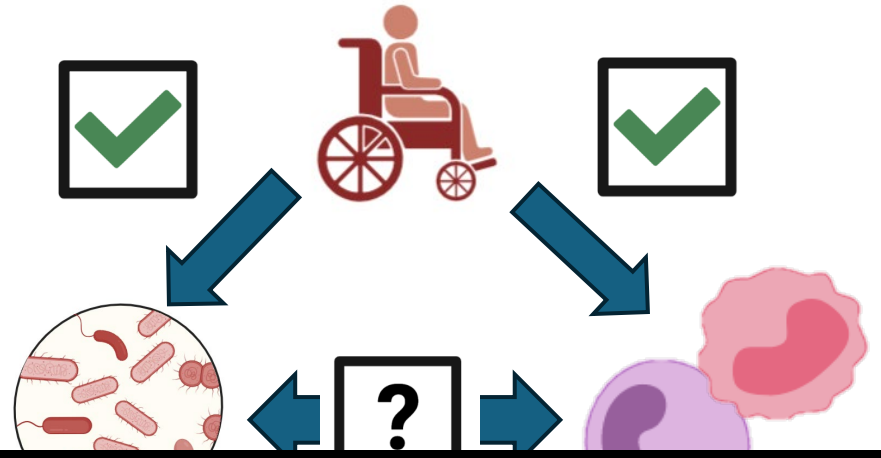
Microbiome composition associates with inflammation in aging humans?

ARTICLE

doi:10.1038/nature11319

Gut microbiota composition correlates with diet and health in the elderly

Marcus J. Claesson[1,2*], Ian B. Jeffery[1,2*], Susana Conde[3], Susan E. Power[1], Eibhlís M. O'Connor[1,2], Siobhán Cusack[1], Hugh M. B. Harris[1], Mairead Coakley[4], Bhuvaneswari Lakshminarayanan[4], Orla O'Sullivan[4], Gerald F. Fitzgerald[1,2], Jennifer Deane[1], Michael O'Connor[5,6], Norma Harnedy[5,6], Kieran O'Connor[6,7,8], Denis O'Mahony[5,6,8], Douwe van Sinderen[1,2], Martina Wallace[9], Lorraine Brennan[9], Catherine Stanton[2,4], Julian R. Marchesi[10], Anthony P. Fitzgerald[3,11], Fergus Shanahan[2,12], Colin Hill[1,2], R. Paul Ross[2,4] & Paul W. O'Toole[1,2]



Microbiome composition strongly correlates with inflammatory indices in aging humans….but is there a direct link?

Parameter	PC1		
	RC range	RC s.d.	*P*
GDT	−0.42	−0.11	0.6
Diastolic blood pressure	0.97	0.25	0.81
Weight	**−14.6**	**−3.8**	**0.033**
CC	**−3.9**	**−1.01**	**0.022**
IL-6	6.71	1.7	0.006
IL-8	4.23	1.1	0.43
TNF-α	1.1	0.28	0.31

Parameter	PC1		
	RC range	RC s.d.	*P*
Barthel	**−6**	**−1.5**	**0.004**
FIM	**−30.8**	**−7.8**	**0.046**
MMSE	−12.15	−3.08	0.14
MNA	−3.87	−0.98	0.23
BMI	−1.2	−0.31	0.69
CC	0.2	0.05	0.93
Diastolic blood pressure	**19.3**	**4.9**	**0.015**
Systolic blood pressure	**36.5**	**9.3**	**0.007**
Weight	−3.2	−0.81	0.69
IL-8	−2.56	−0.65	0.78
CRP	13.9	3.53	0.02

Does the microbiome directly facilitate aging-induced inflammation?

Received: 23 February 2024 | Revised: 20 April 2024 | Accepted: 22 April 2024
DOI: 10.1111/acel.14190

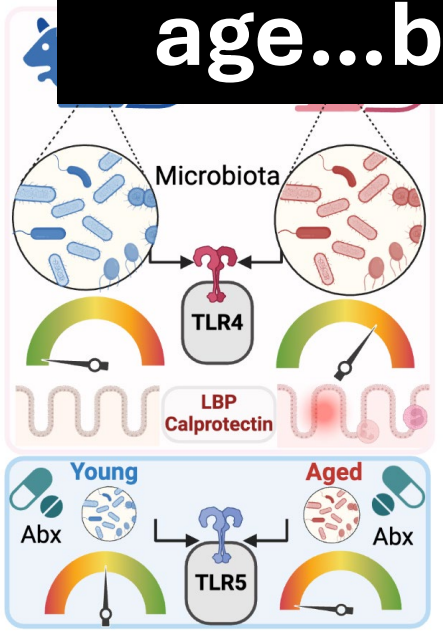
RESEARCH ARTICLE

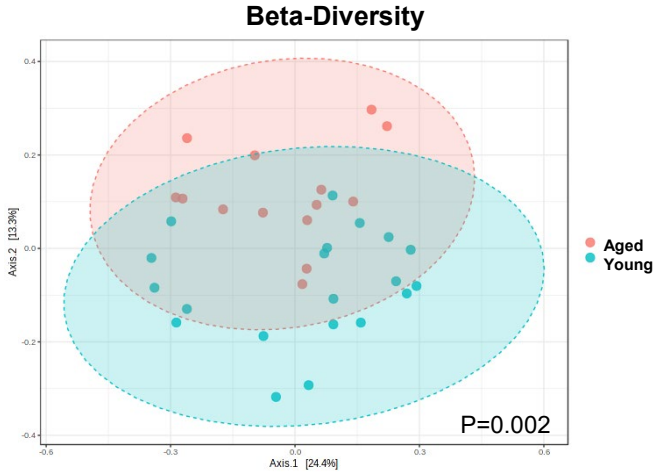
Aging Cell WILEY

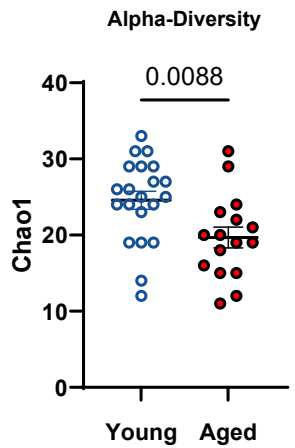
Aging amplifies a gut microbiota immunogenic signature linked to heightened inflammation

Maria Elisa Caetano-Silva[1,2] | Akriti Shrestha[2] | Audrey F. Duff[3] | Danica Kontic[3] |
Patricia C. Brews
Diego Hernande
Thomas W. Bufo

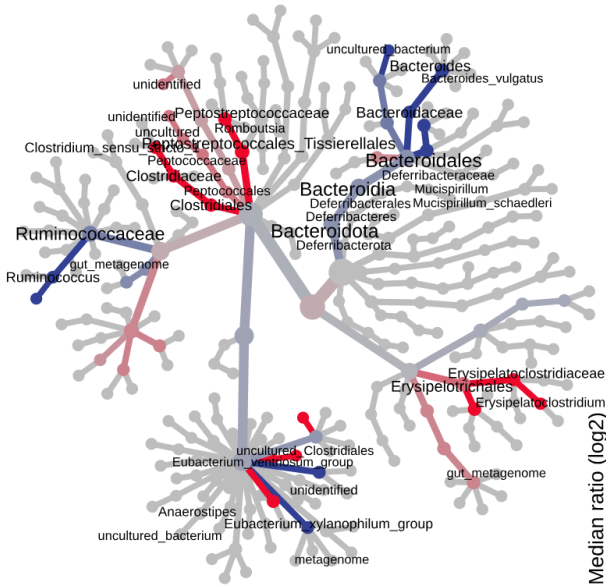
Microbiome changes with age…but what does this mean?





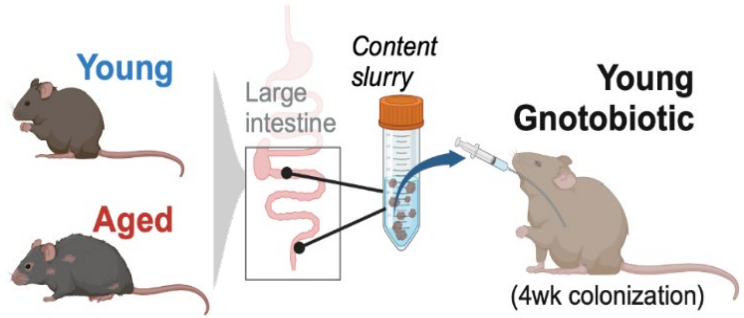


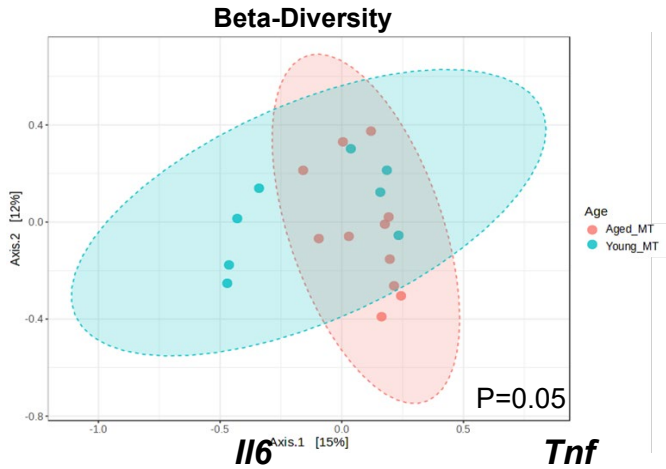
Elisa Caetano-Silva, PhD

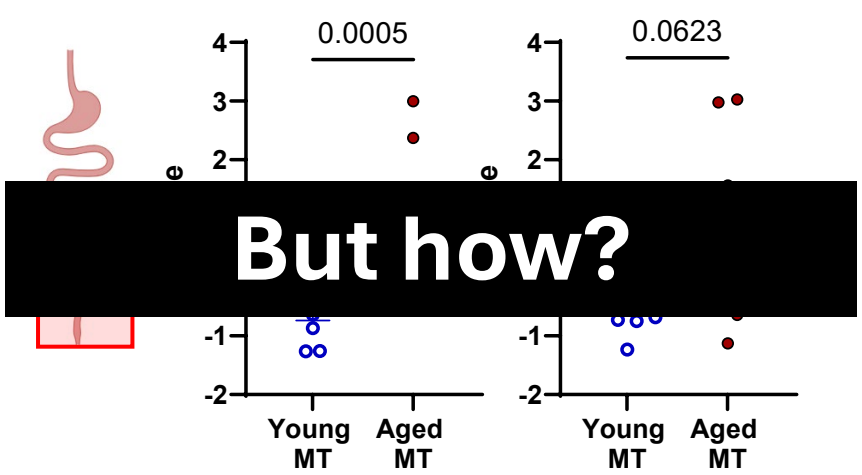


Caetano-Silva et al. *Aging Cell*, 2024

Microbiome correlates with host inflammation…can we learn more?

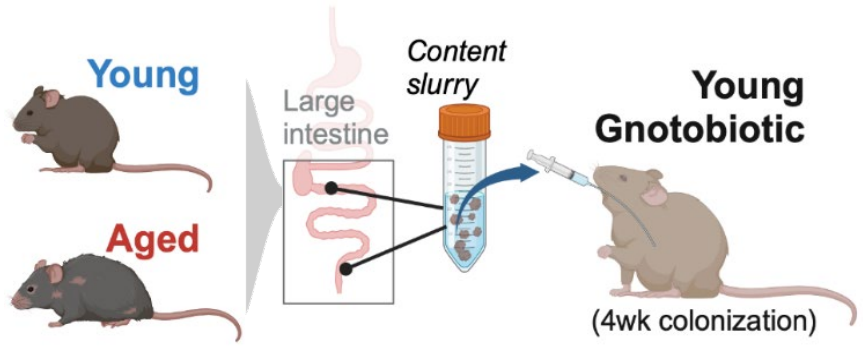




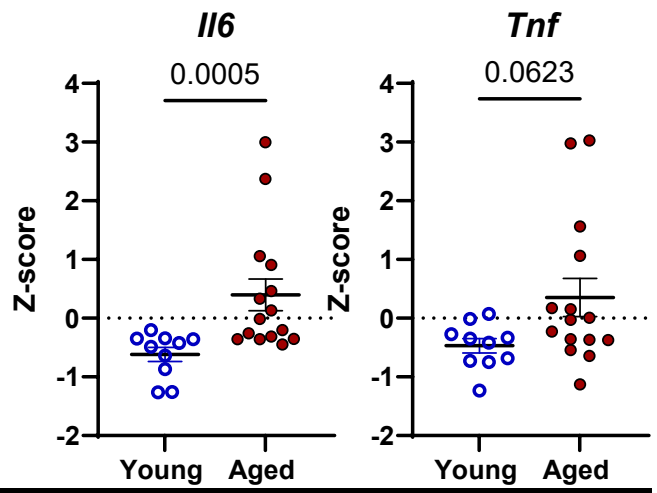


But how?

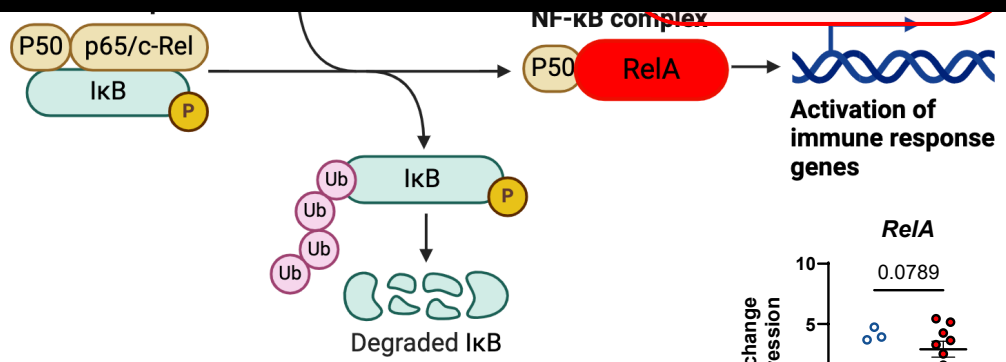
Caetano-Silva et al. *Aging Cell*, 2024

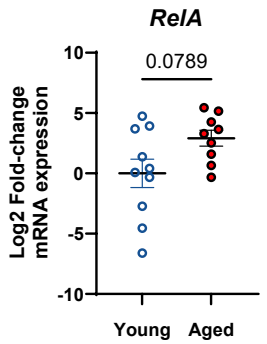


??



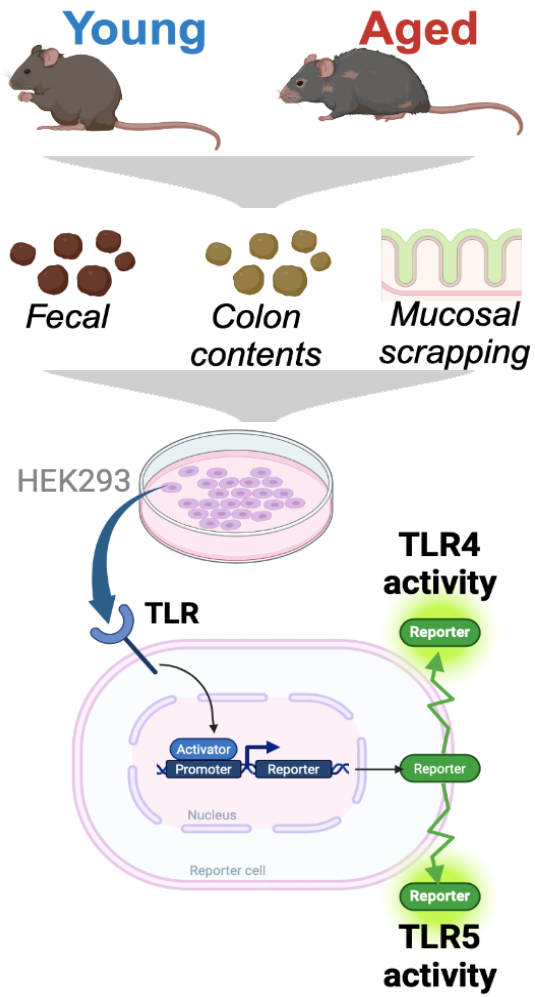
Signs of enhanced TLR4 signaling in aged colons… Perhaps an 'aging microbiota' has a propensity to activate this pathway?



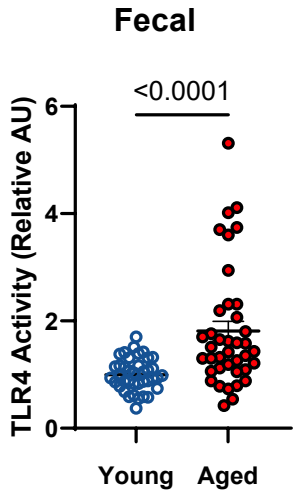


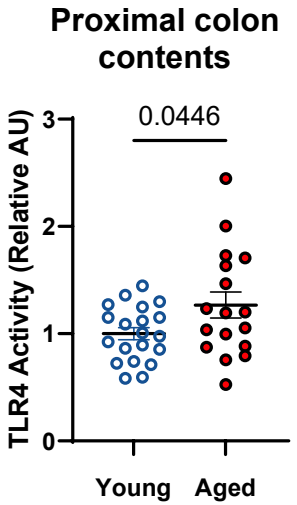
Caetano-Silva et al. *Aging Cell*, 2024

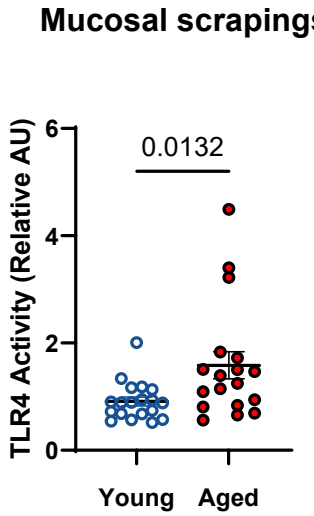
Microbiome of aged mice harbors elevated capacity to activate host TLR4



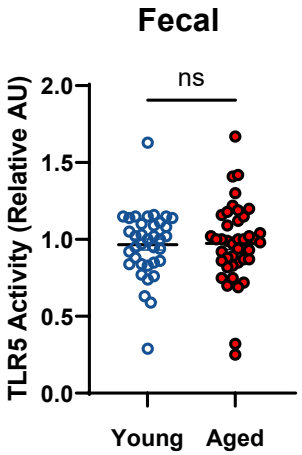
TLR4

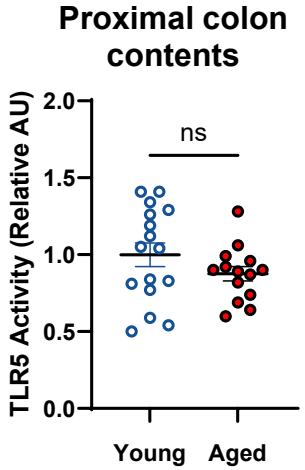


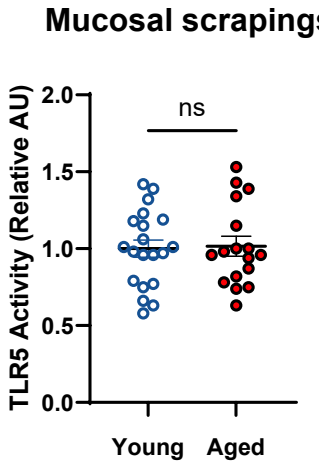




TLR5



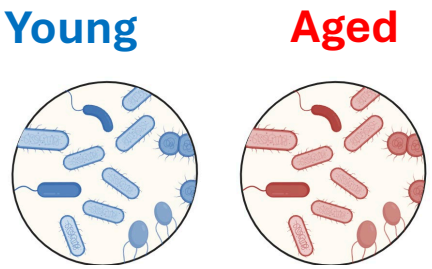


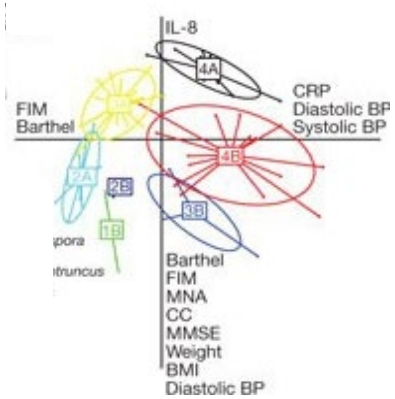


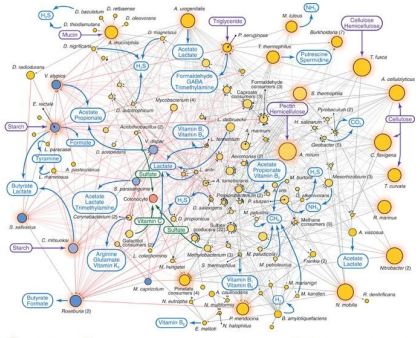
Caetano-Silva et al. *Aging Cell*, 2024

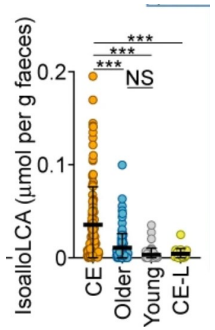
Microbiome and aging: what have we learned?

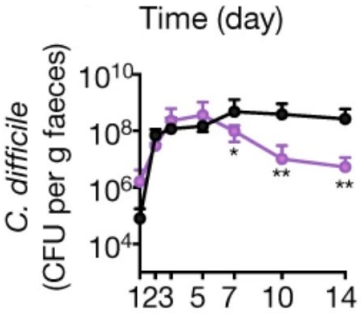
- Microbiome composition changes with age.....but there are many ‘microbial trajectories’ that could determine healthy vs. unhealthy aging
- Microbial metabolites are also age sensitive and may facilitate (or inhibit) health span
- Microbial immunogenic properties are impacted by age and facilitate host inflammation

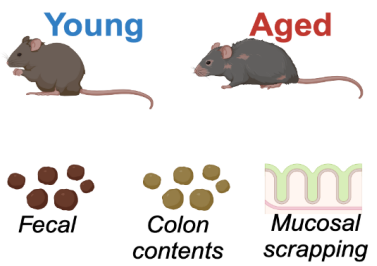


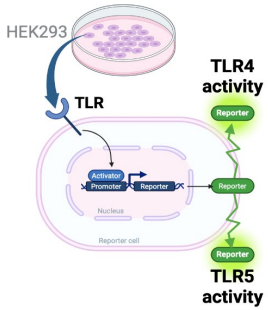


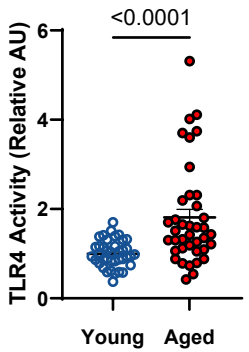








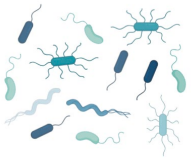


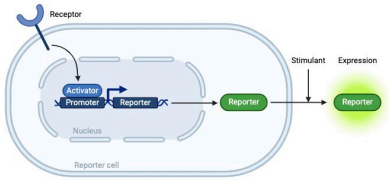


Microbiome and aging: where do we need to go?

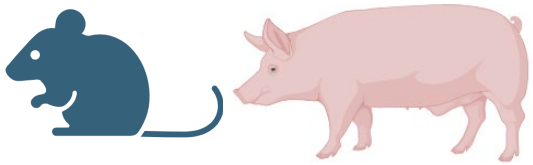
Towards a mechanistic understanding of an ‘aging microbiome’

I. Functional readouts
   a) Larger Biobanks of cultured microbes
   b) Metabolites and their bioactivity



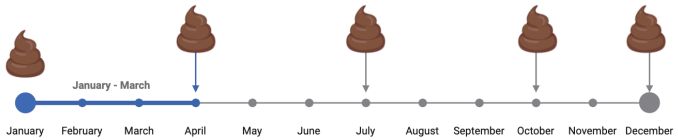


II. Mechanistic microbe-host pathways
   a) Gnotobiotic models with defined consortia
   b) FMTs humans to → mice, pigs, other (zebrafish)



Teasing out signal from noise in human studies

I. Longitudinal designs
   a) e.g. Randomized Crossover



II. DIET,DIET,DIET !!
   a) Need better controls

III. Medications-
   a) Polypharmacy, antibiotics
   b) Need better controls

THANK YOU!

Microbial Systems Initiative

Allen Lab

Elisa Caetano-Silva, PhD
Akriti Shrestha
Bob McCusker
Mikaela Kasperek
John Lin
Casey Lim
Ivan Valishev

The Allen Lab

Integrative Microbiota & Physiology Lab

University of Illinois Urbana-Champaign

Collaborators

Tom Buford, PhD (UAB)
Suzanne Devkota (Cedars-Sinai)
Derek Wainwright (Loyola)
Diego Hernandez-Saavedra, PhD (UIUC)

Department of Kinesiology
Microbial Systems Initiative
Division of Nutritional Sciences
Microbiome Metabolic Engineering

NIH National Institutes of Health
R01DK131133 NIDDK
R56 AG068747 NIA

USDA NIFA
2023-67017-39053

ILLINOIS Personalized Nutrition Initiative

jmallen5@illinois.edu

@JacobAllenPhD