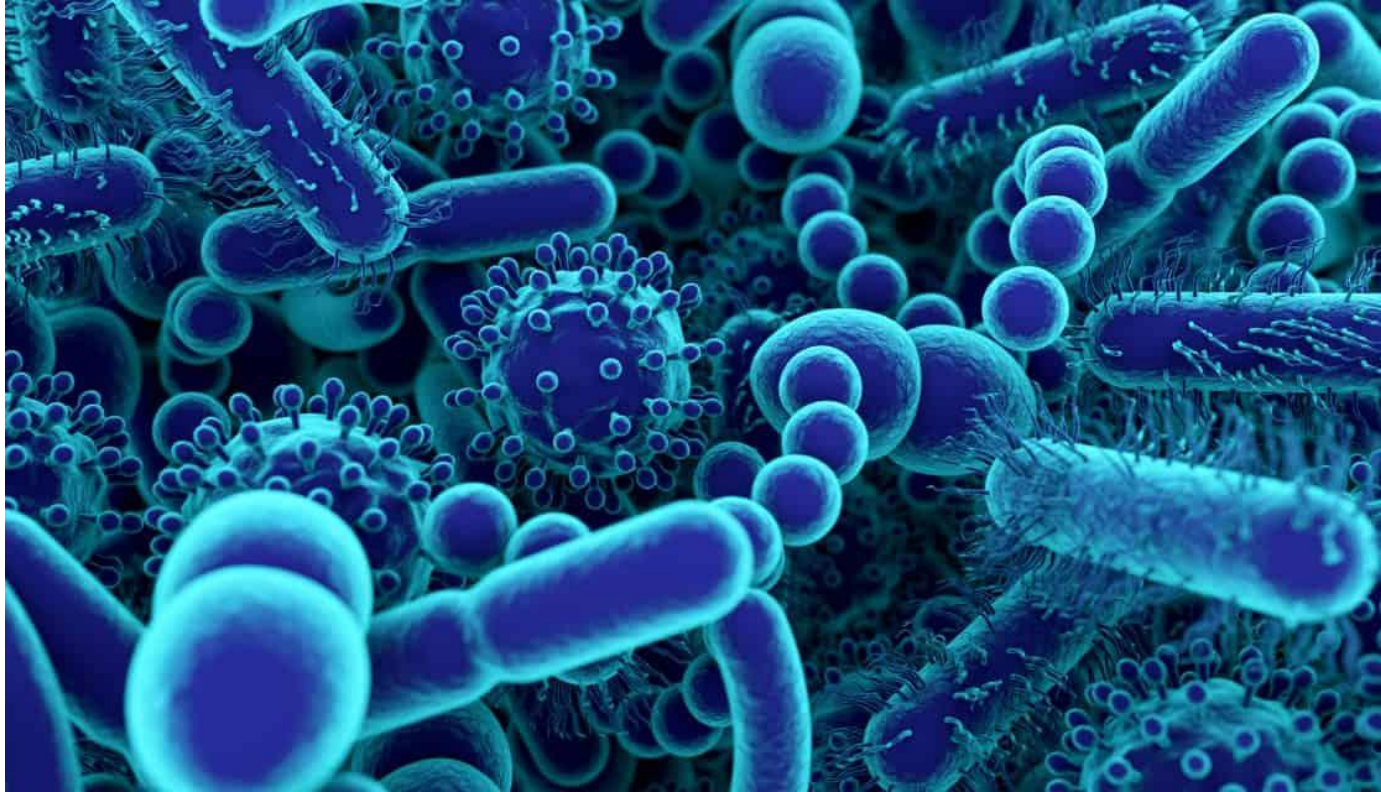


Aging Well from the Inside Out: Microbiome, Biotics, and Oral-Brain Health



Shalini Jain, Ph.D.

Assistant Professor,
Department of Neurosurgery and Brain Repair
USF Center for Microbiome Research
University of South Florida, Tampa

Overview of talk

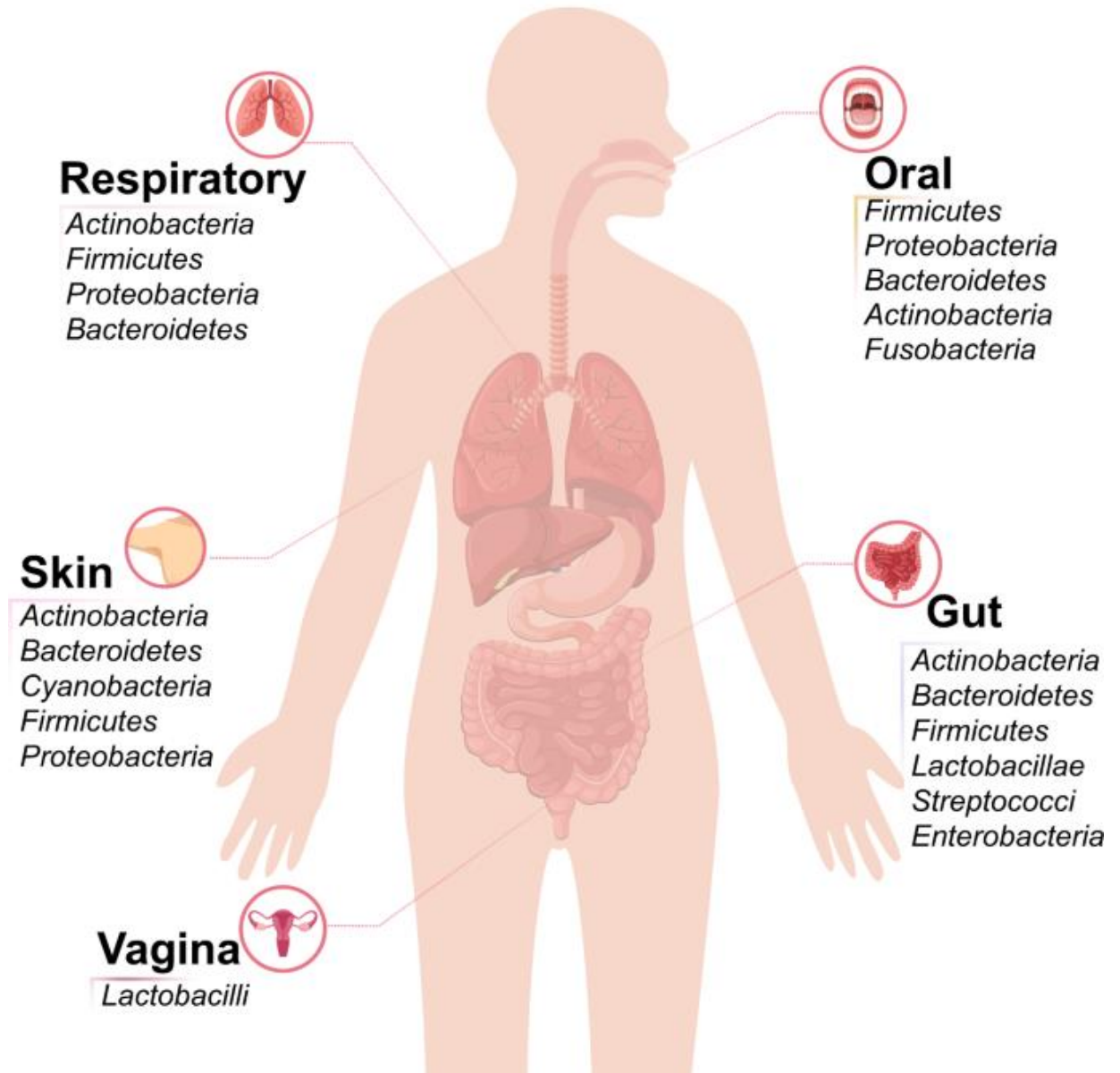
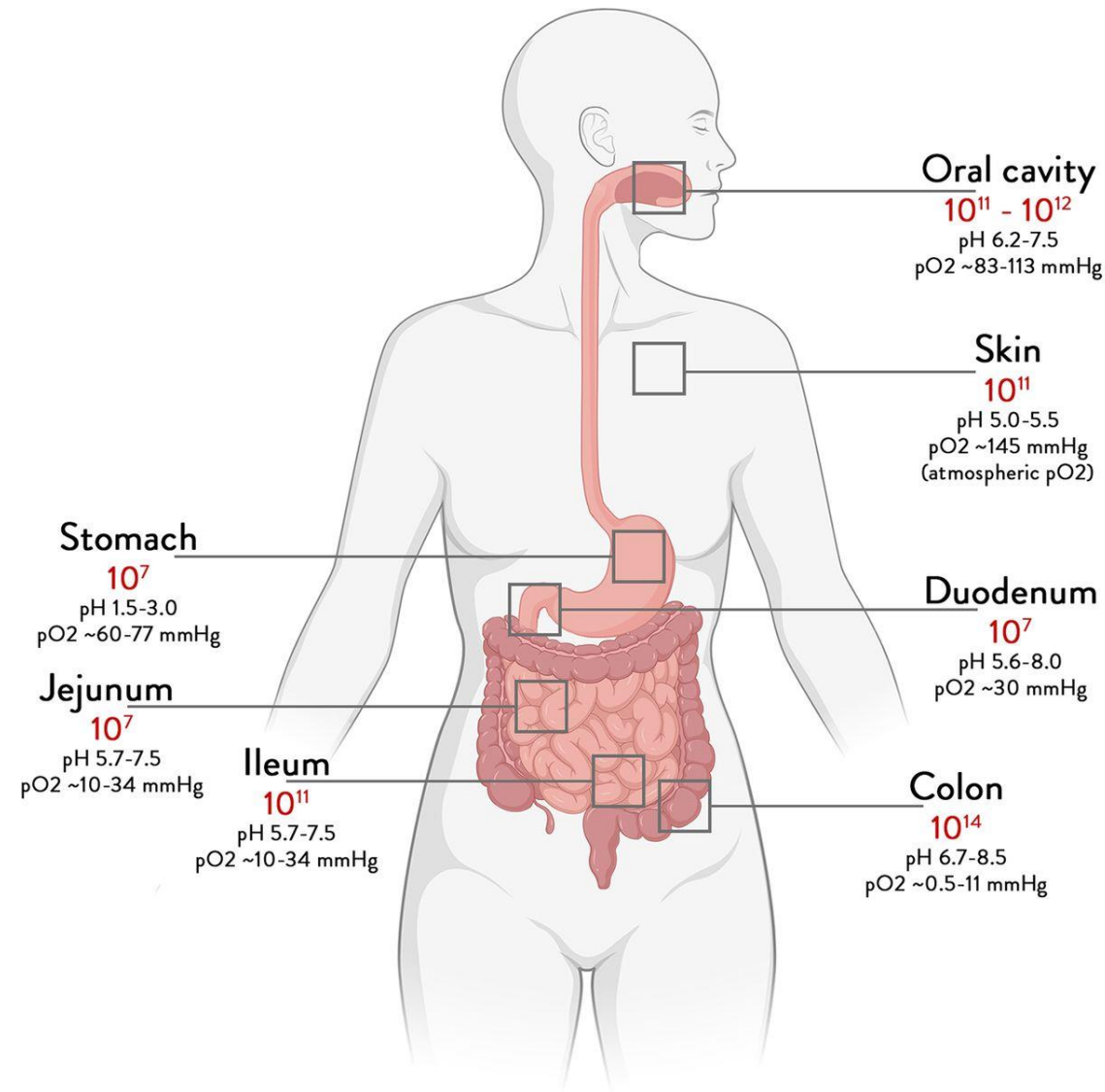
- Background
- Three topics
 - 1) Microbiome related comorbidities such as leaky gut and inflammation
 - 2) Biotics in aging and brain health
 - 3) Saliva based microbiome and proteomic signature can be used as biomarker for predicting the risk of cognitive decline

Microbiome- in and around us

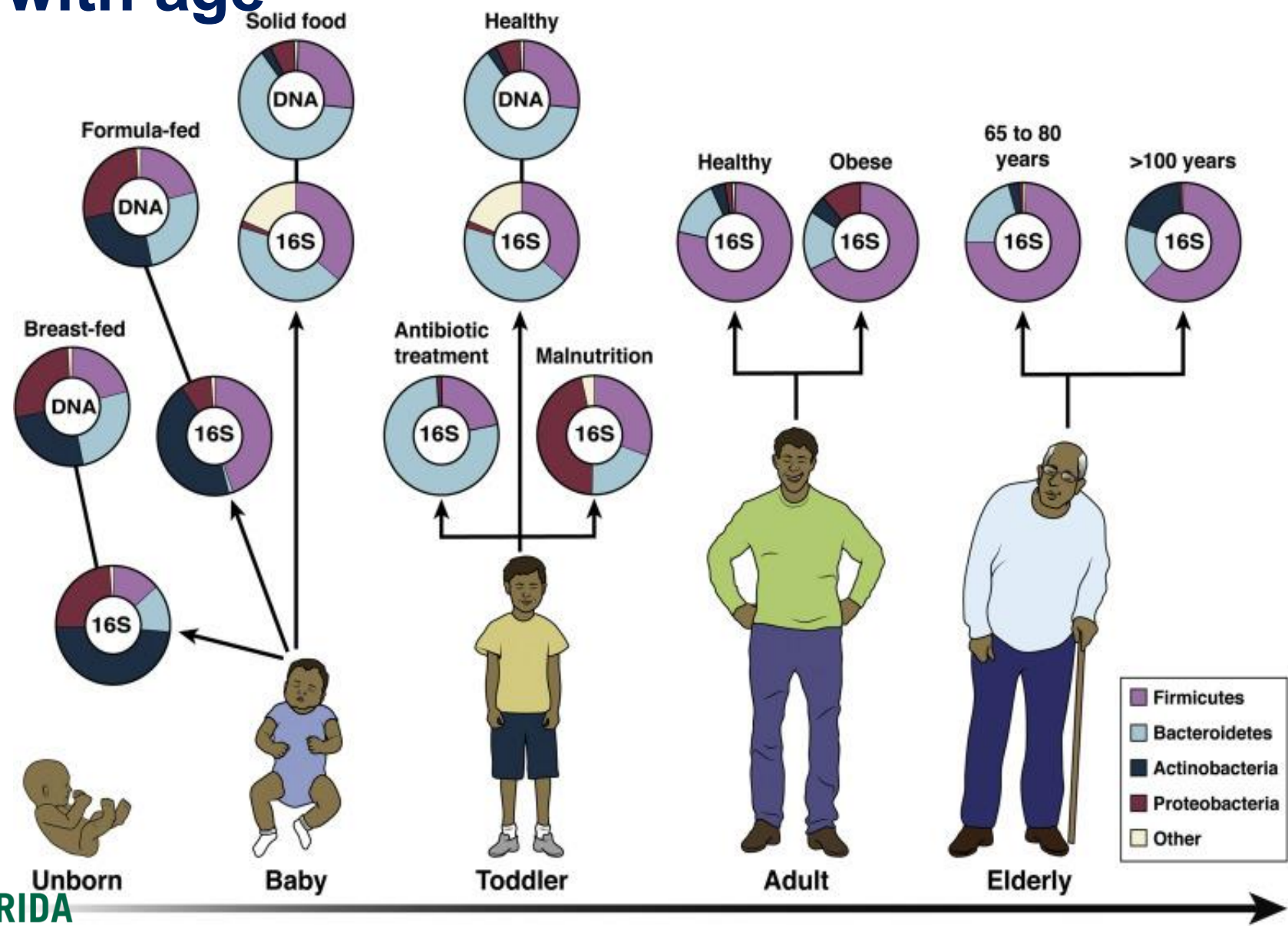
- Collection of microbes in and on our body including bacteria, viruses, fungi and archaea, is called microbiota
- More than 1000 species
- Biomarker as well as Therapeutic target



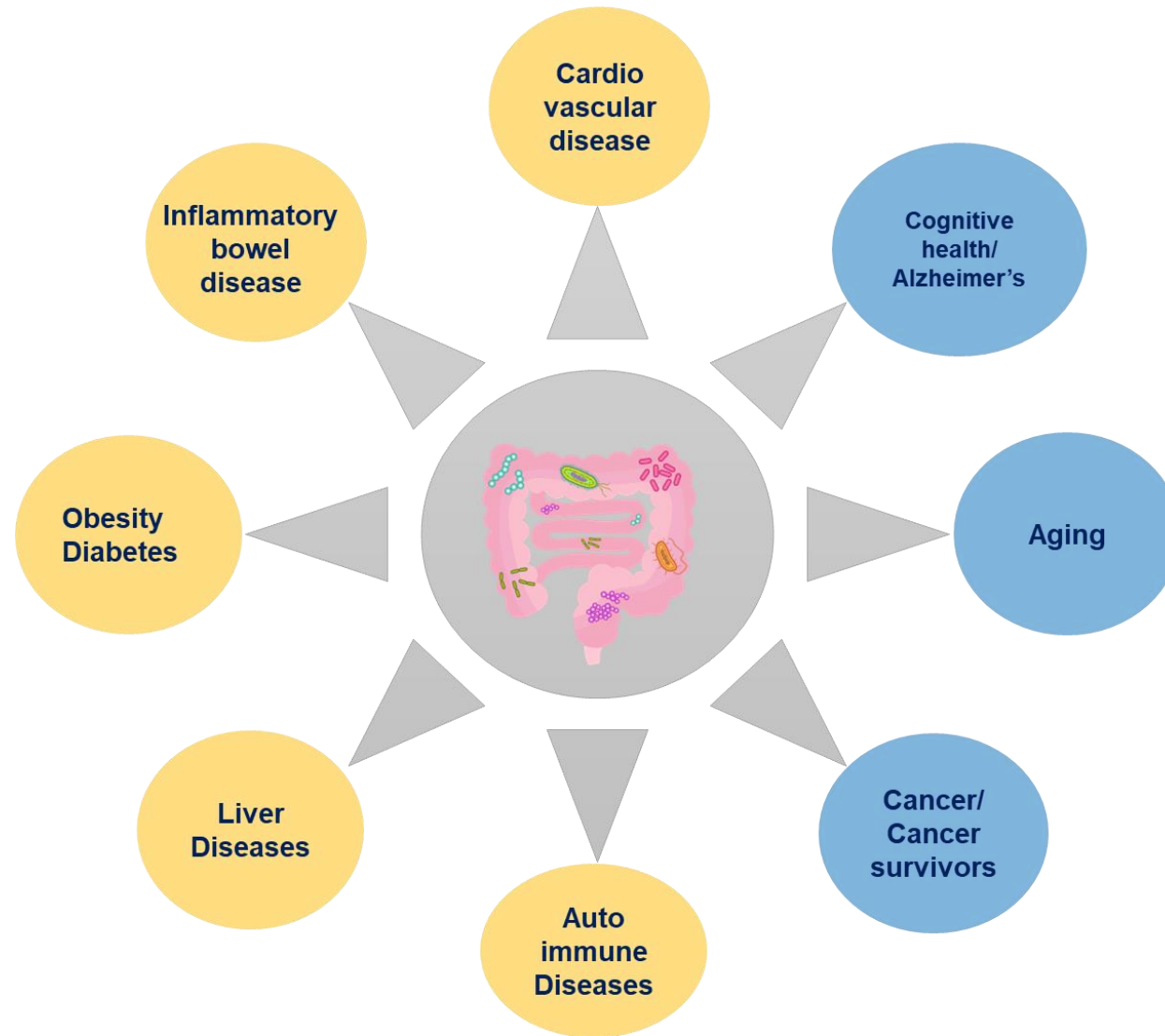
Microbiome in and around us



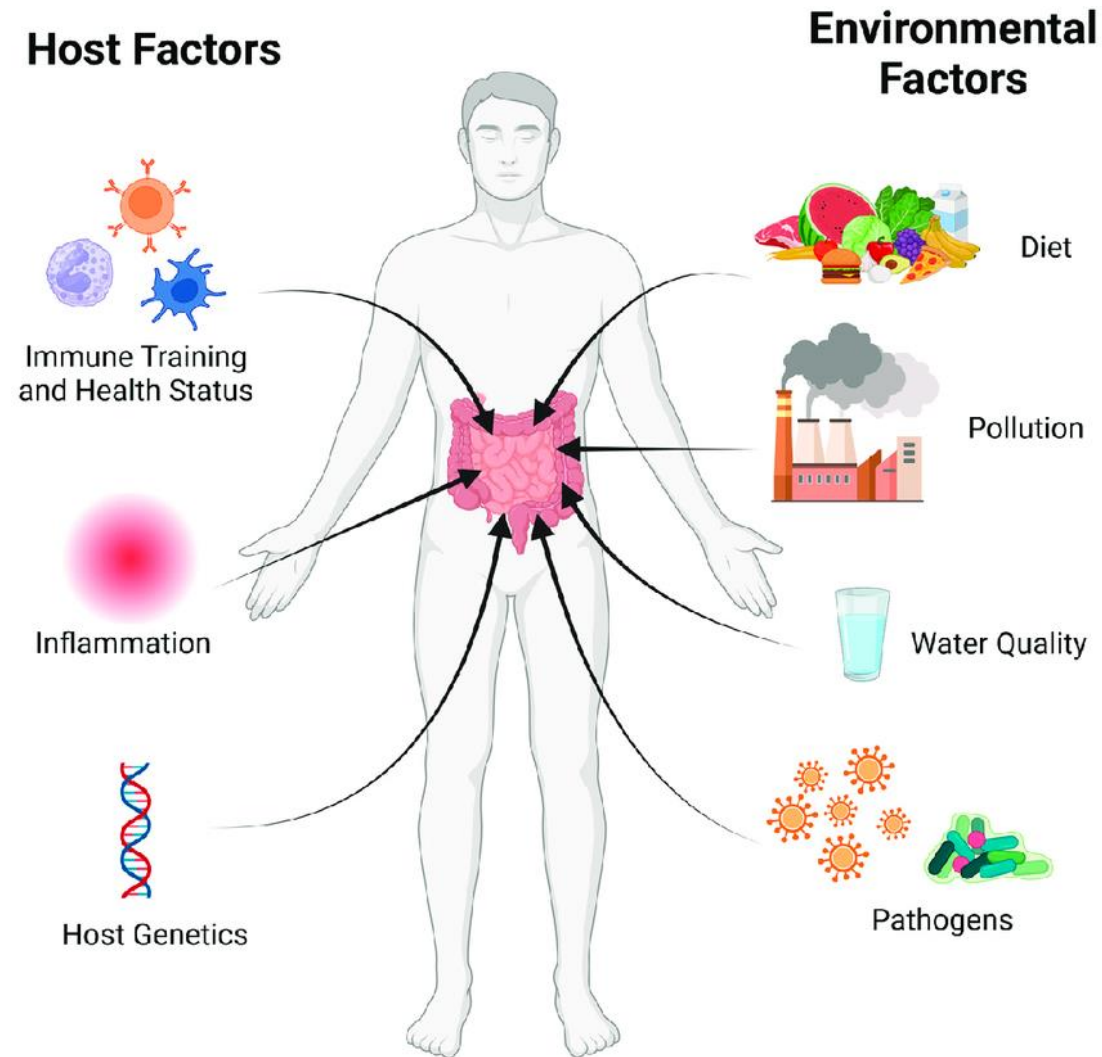
Microbiome composition is dynamic throughout the life and changes with age



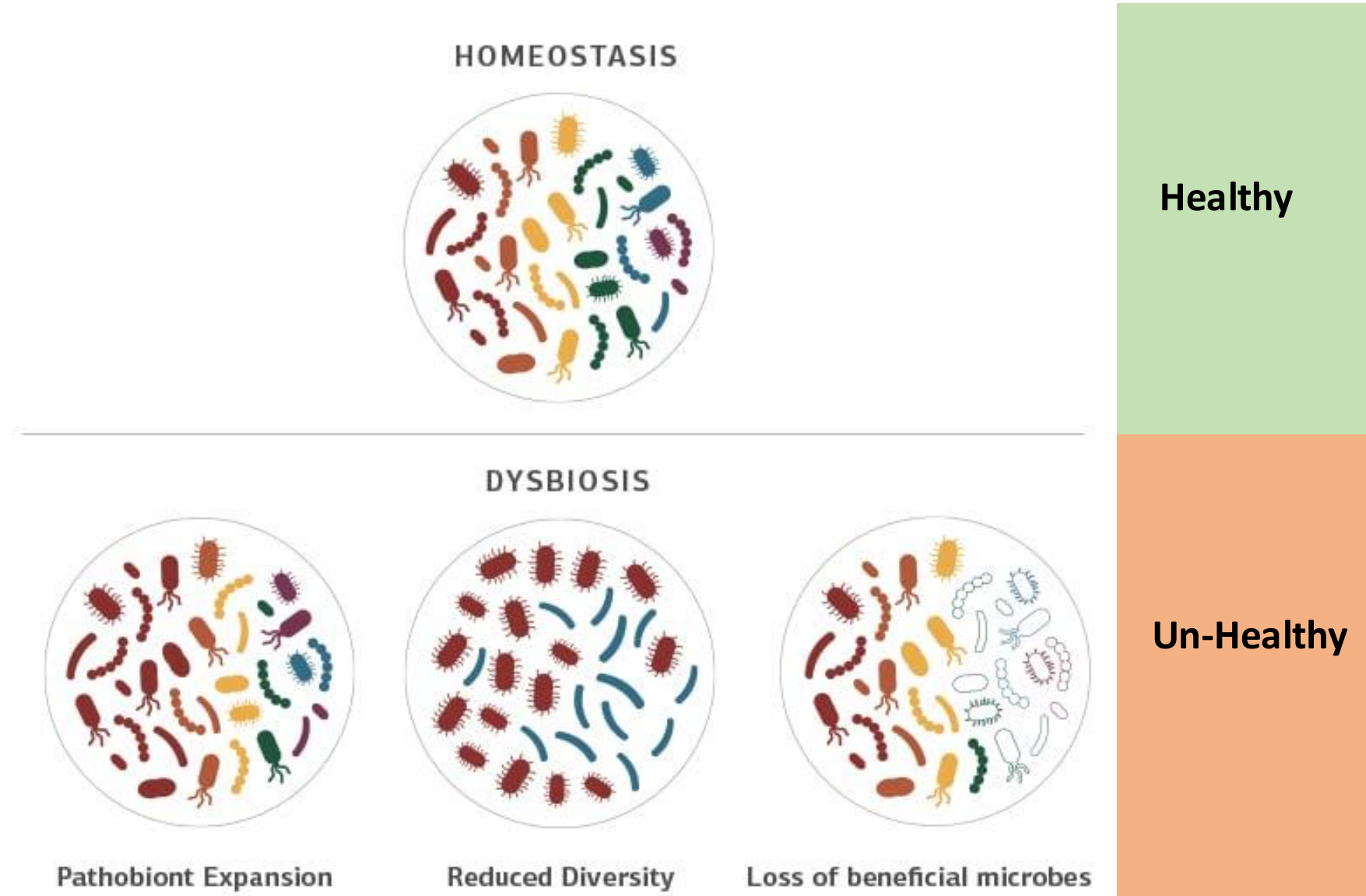
Role of gut microbiome in human diseases



Factors affecting the gut microbiome



Wrong and right turns of microbiome in human health



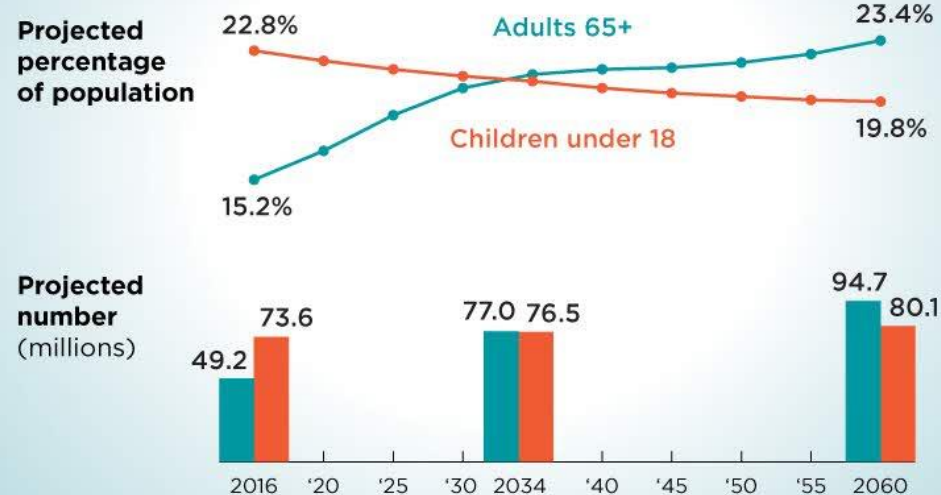
Advancing age is associated with an increased risk of various chronic diseases.



An Aging Nation

Projected Number of Children
and Older Adults

For the First Time in U.S. History Older Adults Are
Projected to Outnumber Children by 2034



Note: 2016 data are estimates not projections.

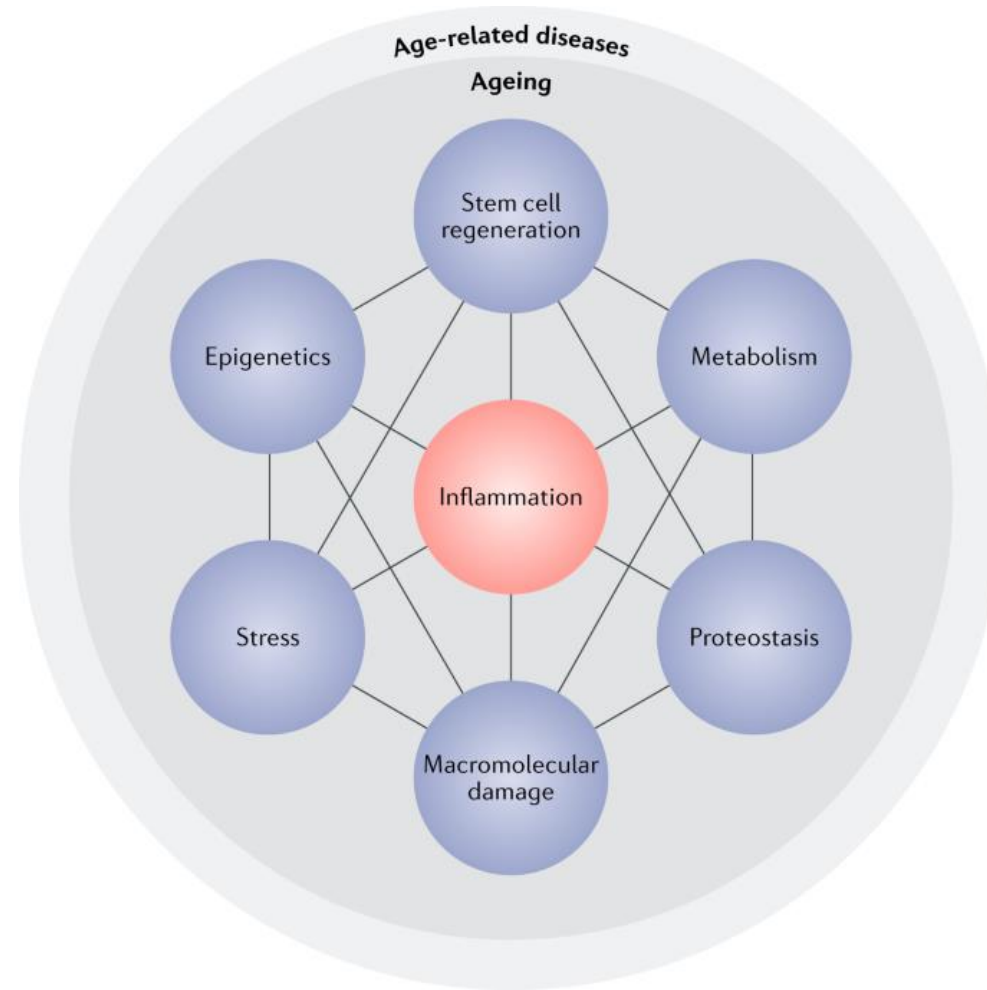
United States®
Census
Bureau

U.S. Department of Commerce
U.S. CENSUS BUREAU
[census.gov](https://www.census.gov)

Source: National Population
Projections, 2017
www.census.gov/programs-surveys/popproj.html

- Aging is not a disease, therefore no FDA approved anti-aging drugs are available
- However, aging is a key risk factor for several chronic diseases
 - But how remains largely unknown
 - Also, how we can prevent or treat aging-related conditions

Inflammation is a key risk factor for increasing risk of aging related conditions



Pillars of aging

Source: Franceschi, et al (2018).
Nature Reviews Endocrinology; 14: 576–590.

With age systemic inflammation increases, and mid life inflammation can determine healthspan in later part of life

aging

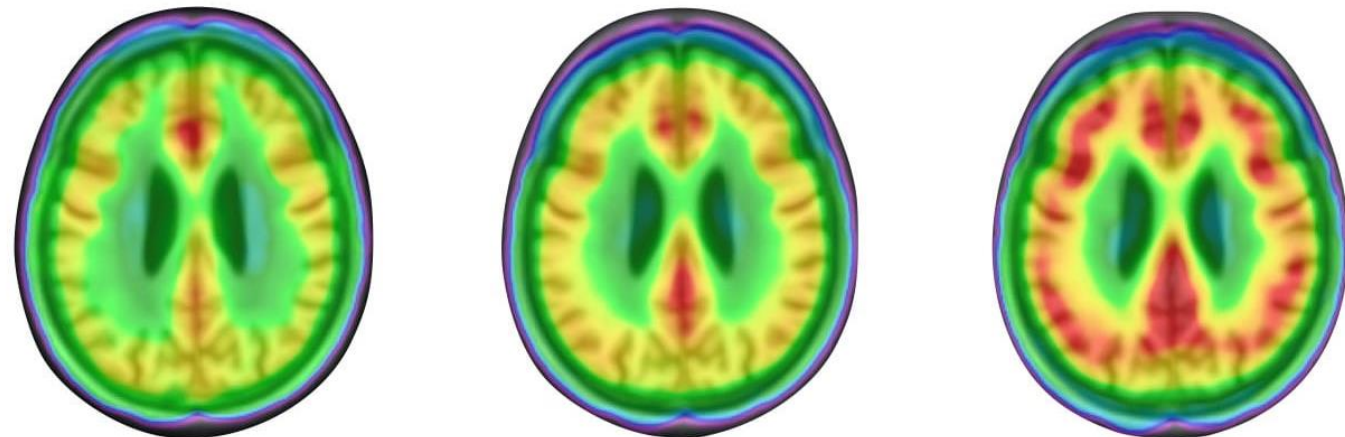
Systemic inflammation during midlife and cognitive change over 20 years

Where this inflammation comes from in aging?

Alden L. Gross, PhD, MHS, Thomas H. Mosley, Jr., PhD, Elizabeth Selvin, PhD, MPH, and B. Gwen Windham, MD, MHS

Dr. Walker
Kwalke26@jhmi.edu

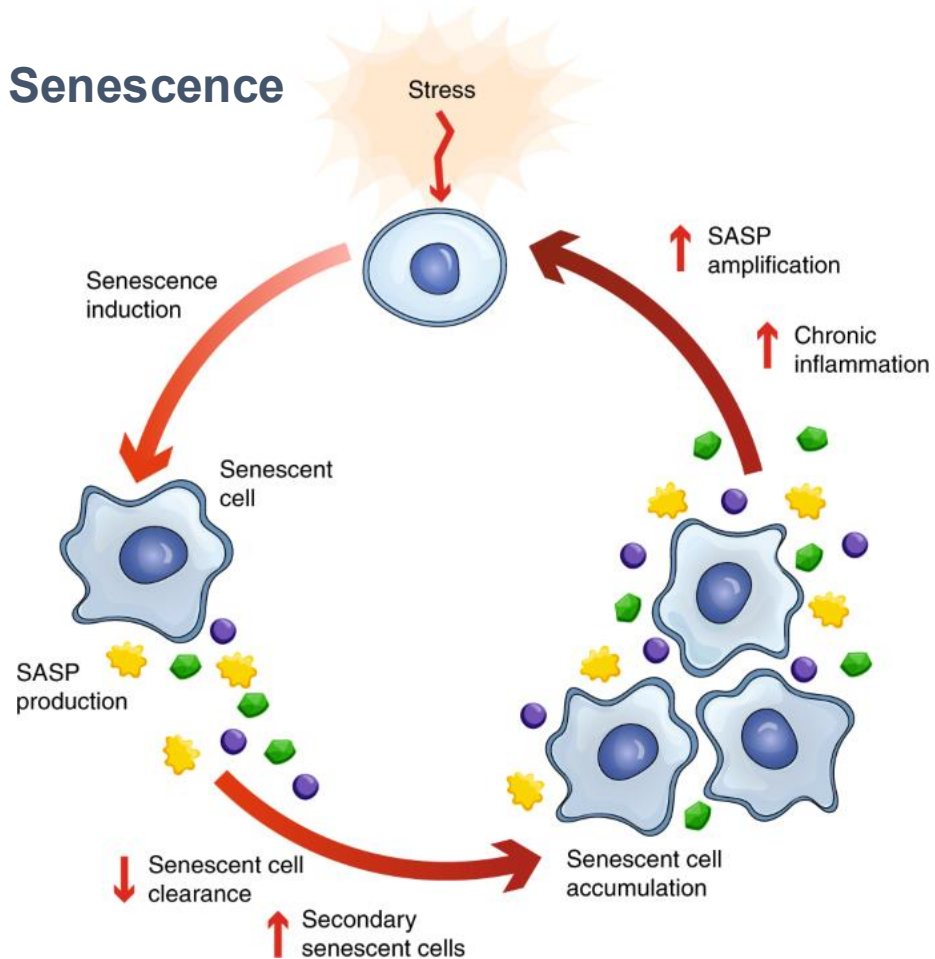
Neurology® 2019;92:e1256-e1267. doi:10.1212/WNL.0000000000007094



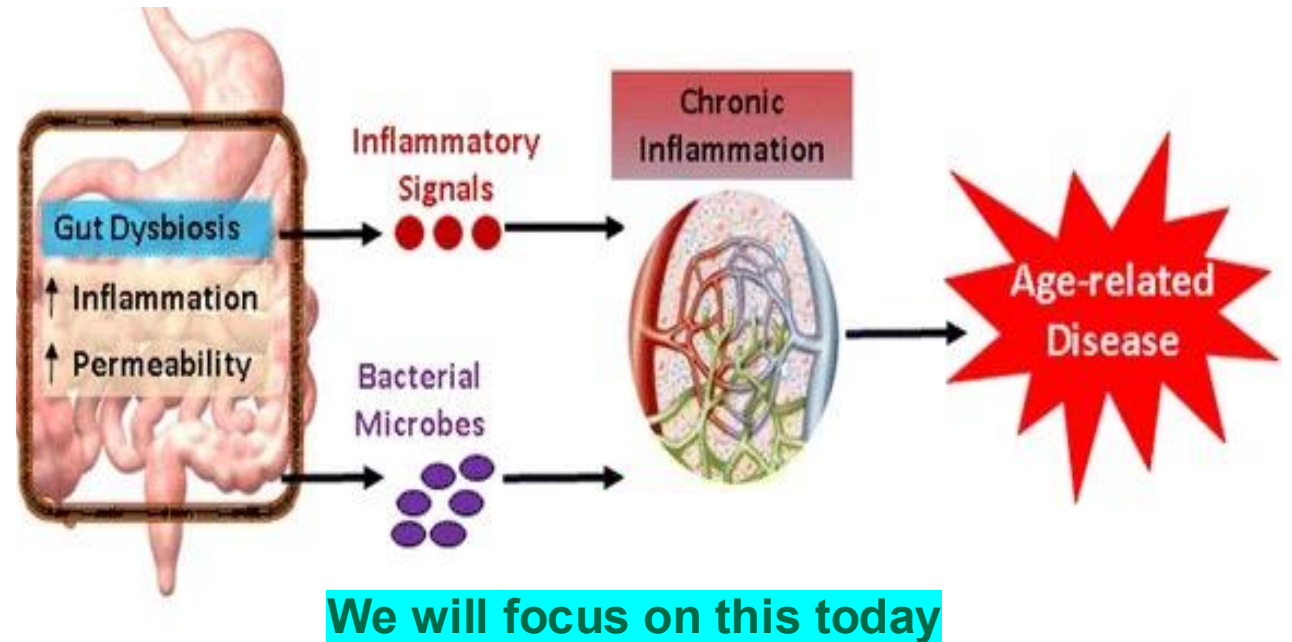
Brain inflammation level
Low High

Two major sources of inflammation in aging

Senescence



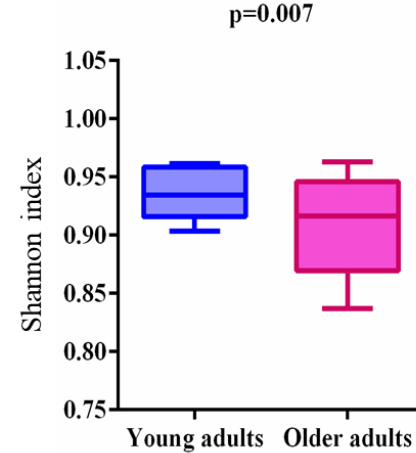
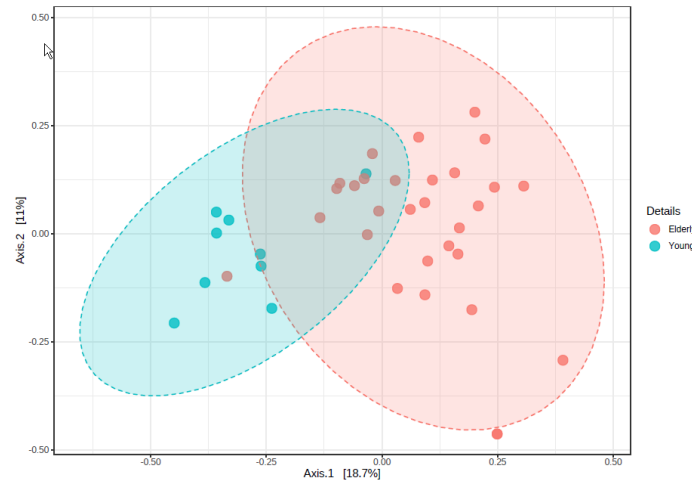
Leaky gut



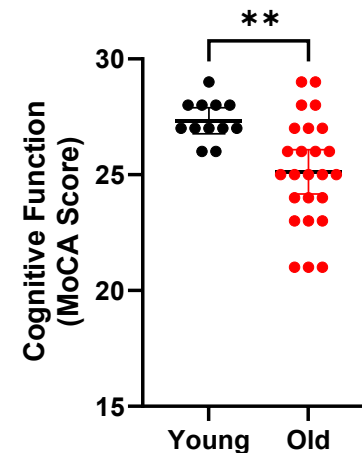
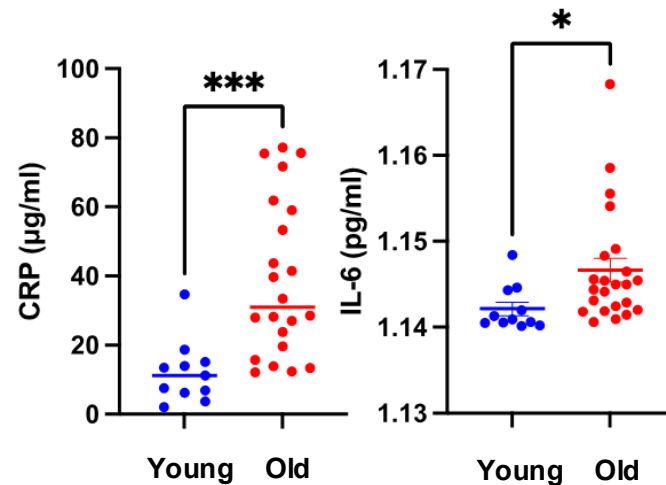
We will focus on this today

Nat Aging 2021;1(10):870-879.
doi: 10.1038/s43587-021-00121-8.

Old gut harbors a dysbiotic microbiome, linked with increased systemic inflammation



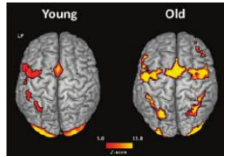
Chaudhari et al, (Geroscience, 2023: PMID: 37213047)



Unpublished

Young FMT reverses leaky gut, neuroinflammation and brain aging

Neuroinflammation



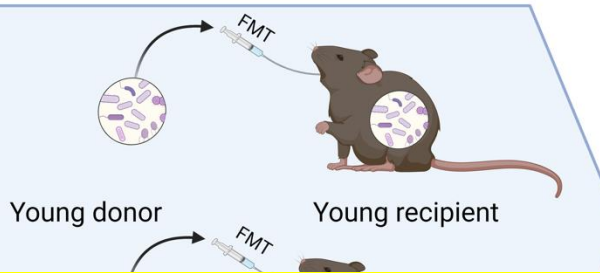
Anxiety



Depression



Dementia



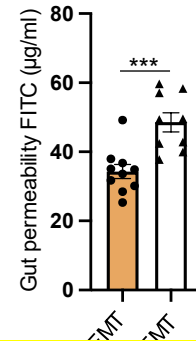
Assays

Gut permeability
FITC-dextran assay
Serum LBP and sCD14

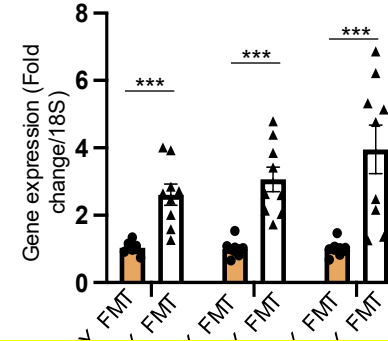
Inflammation
IL-1 β , IL-6, TNF- α in serum and tissues

Gene expression
Tissue histology

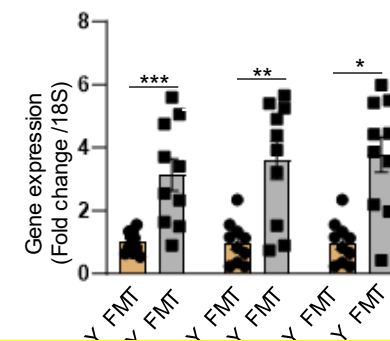
Leaky gut



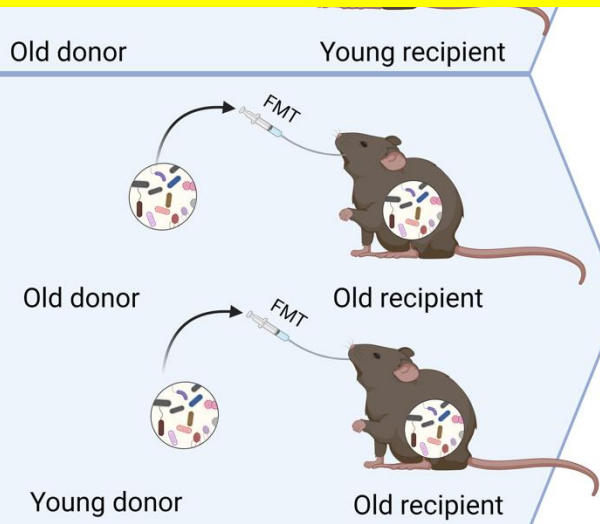
Inflammation in gut



Inflammation in brain



How an aged microbiome induces leaky gut and inflammation?

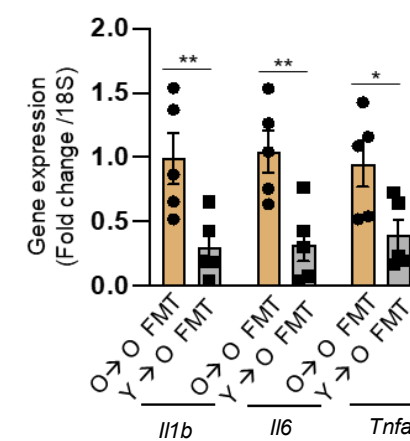
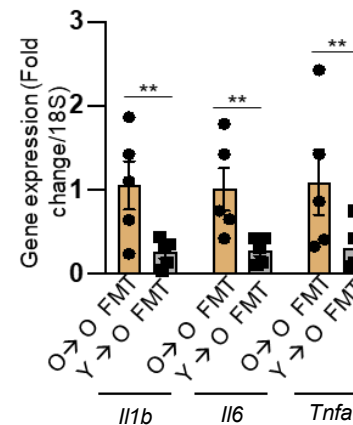
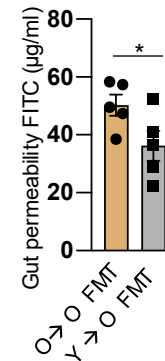


Never edge
Marble burying

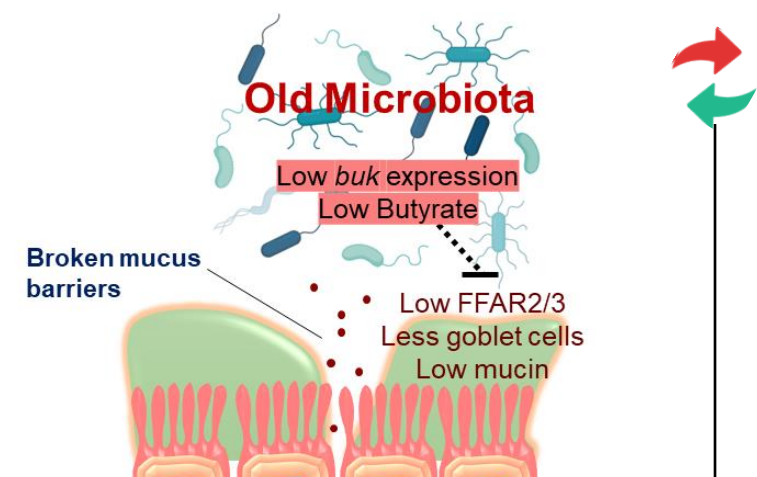
Gut permeability
FITC-dextran assay
Serum LBP and sCD14

Inflammation
IL-1 β , IL-6, TNF- α in serum and tissues

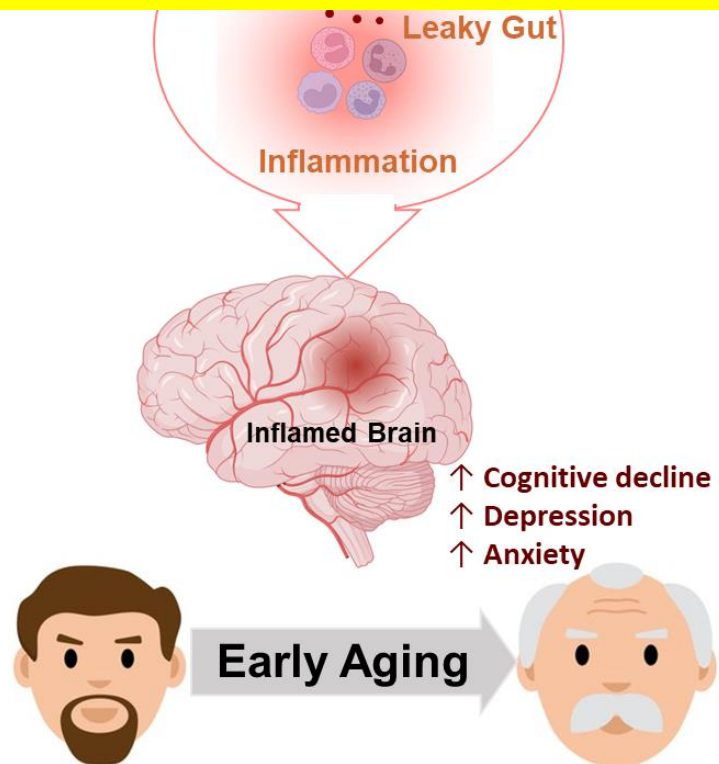
Gene expression
Tissue histology
Behavioral tests
Morris Water Maze
Forced swim
Splash
Novel cage
Marble burying



Summary #1



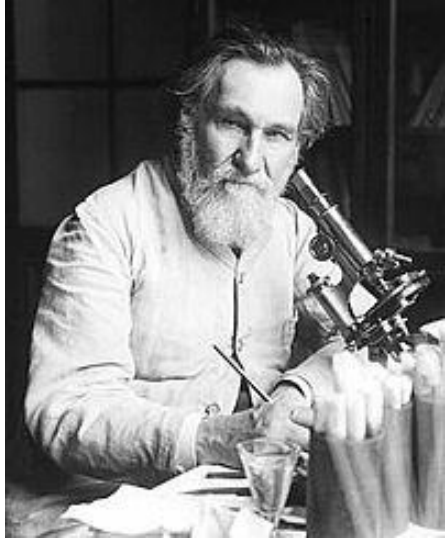
Are there alternatives for reducing age-related leaky gut?



Young FMT
Butyrate

Mishra et al , JCI-Insight; 2024 (PMID: 38329121)

Probiotics, Prebiotics and Postbiotics



Elie Metchnikoff

**20th Century noble prize
winner and Father of
Modern Immunology**

Conceptualize 'probiotics'

Acid producing bacteria in milk products could prevent fouling in large intestine, if consumed regularly, lead to longer and healthier life.

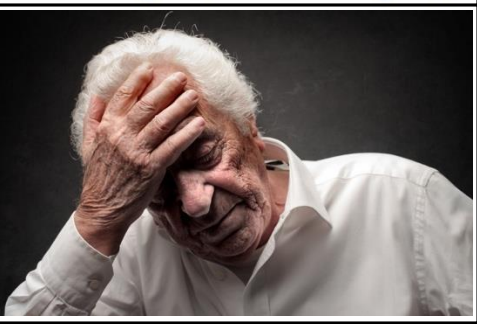
1908: Prolongation of Life (Probiotics)

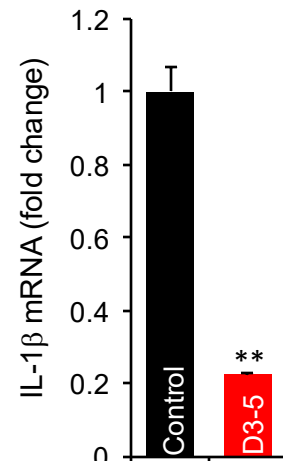
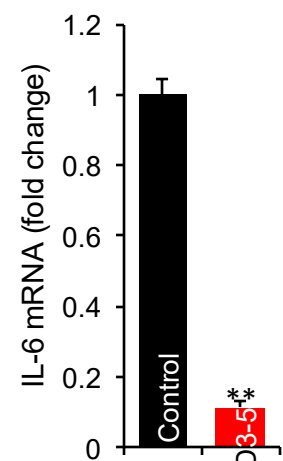
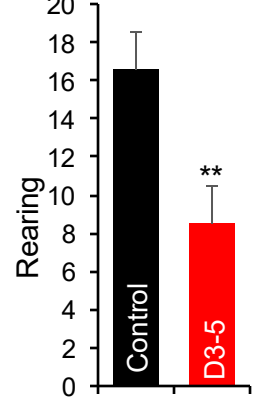
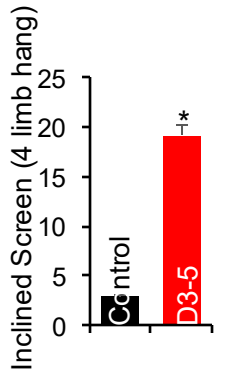
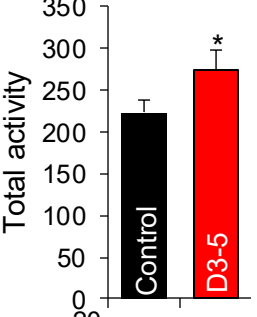
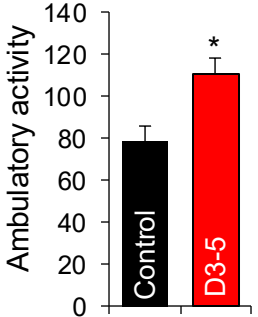
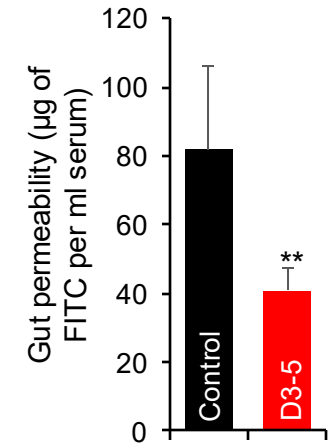
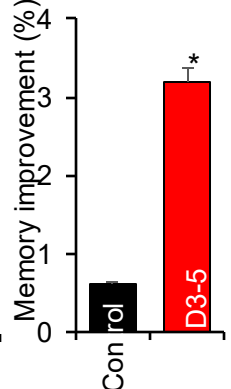
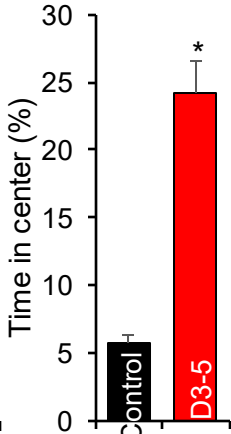
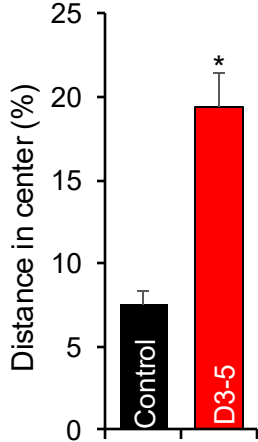
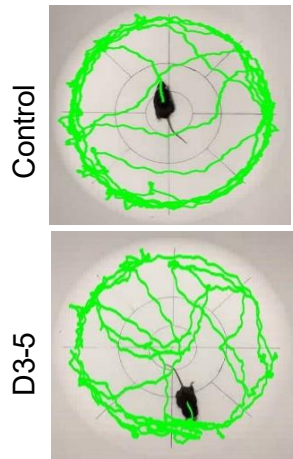
Prebiotics was introduced in 1995 by Gibson and Roberfroid

Prebiotics are nondigestible food ingredients that beneficially affect the host by selectively stimulating the growth or activity of one or a limited number of bacteria in the colon that can improve host health.

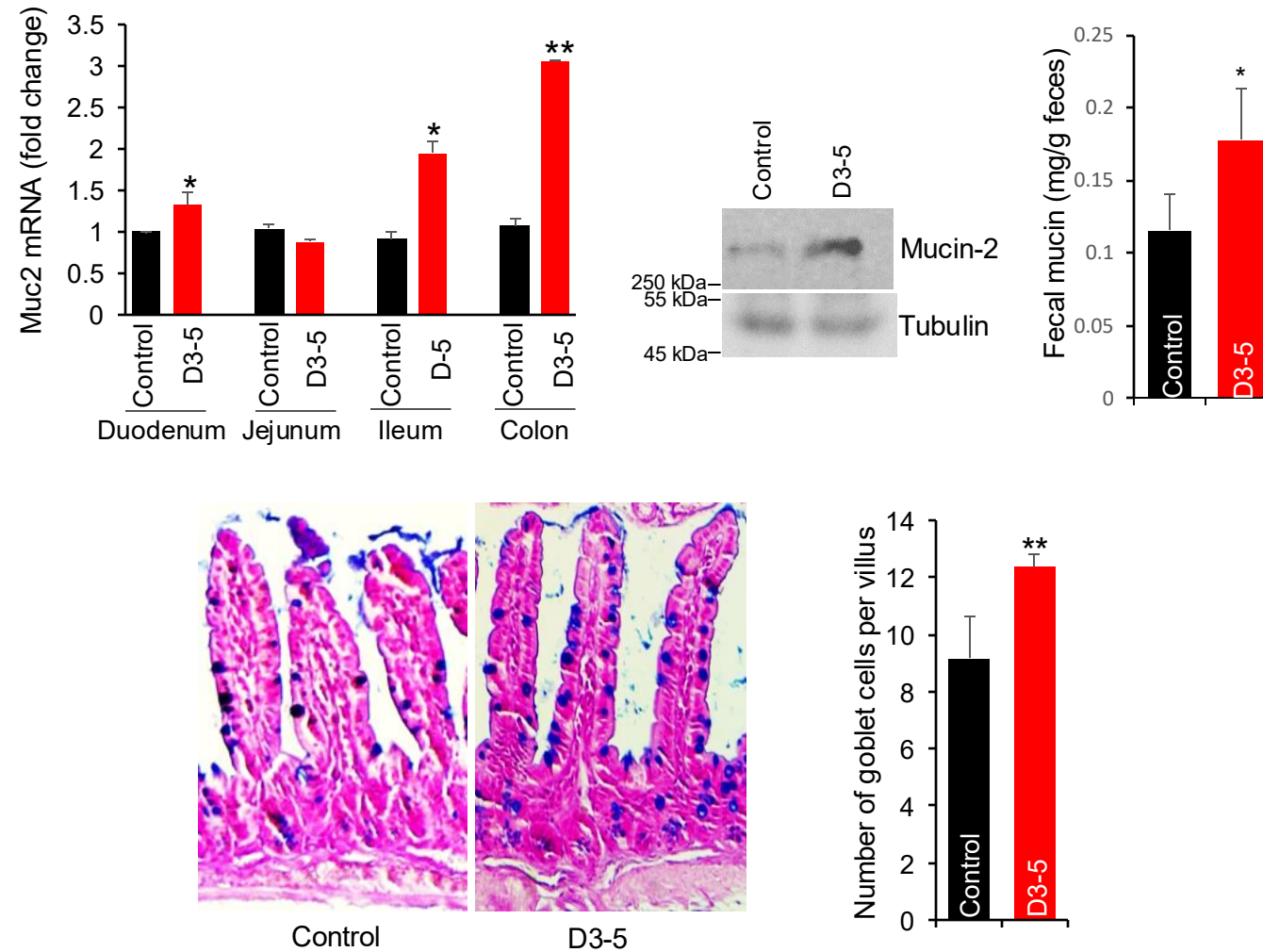
2021, the International Scientific Association of Probiotics and Prebiotics (ISAPP) define postbiotics as preparation of inanimate microorganisms and/or their components that confers a health benefit on the host.

D3-5 reduces aging-related comorbidities in older mice

Depression	
Anxiety	
Physical Function	
Dementia	

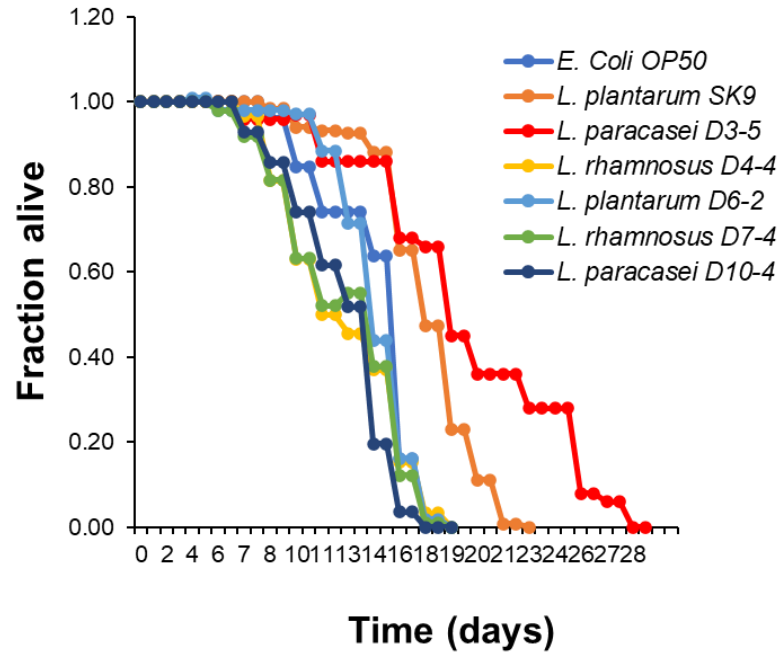


Dead D3-5 stimulates mucin production in the older gut

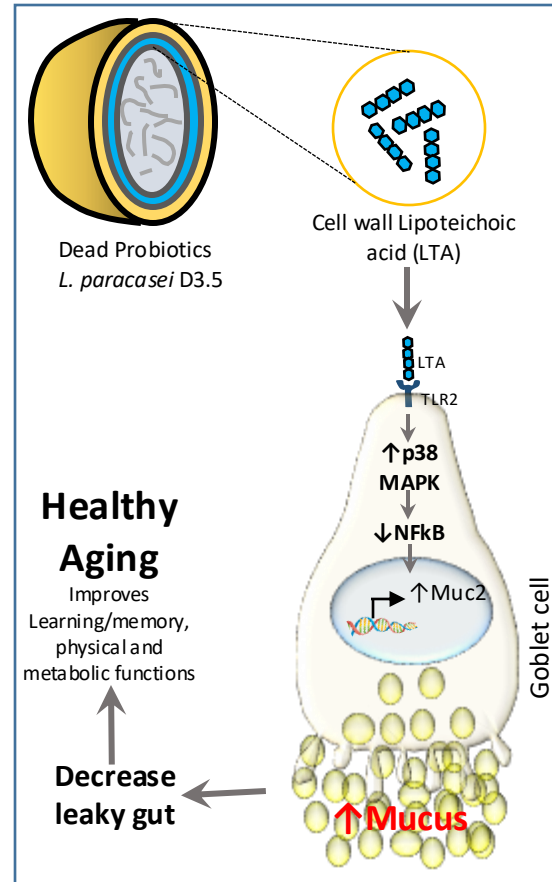


Wang et al, 2019. *Geroscience*, doi:10.1007/s11357-019-00137-4

A newly discovered Postbiotics D3.5 reduces leaky gut



10 days increase equivalent to 50 years of human life



Wang et al, 2019. *Geroscience*, doi:10.1007/s11357-019-00137-4

Postbiotics
INCORPORATED



SCAN ME-PoZibio

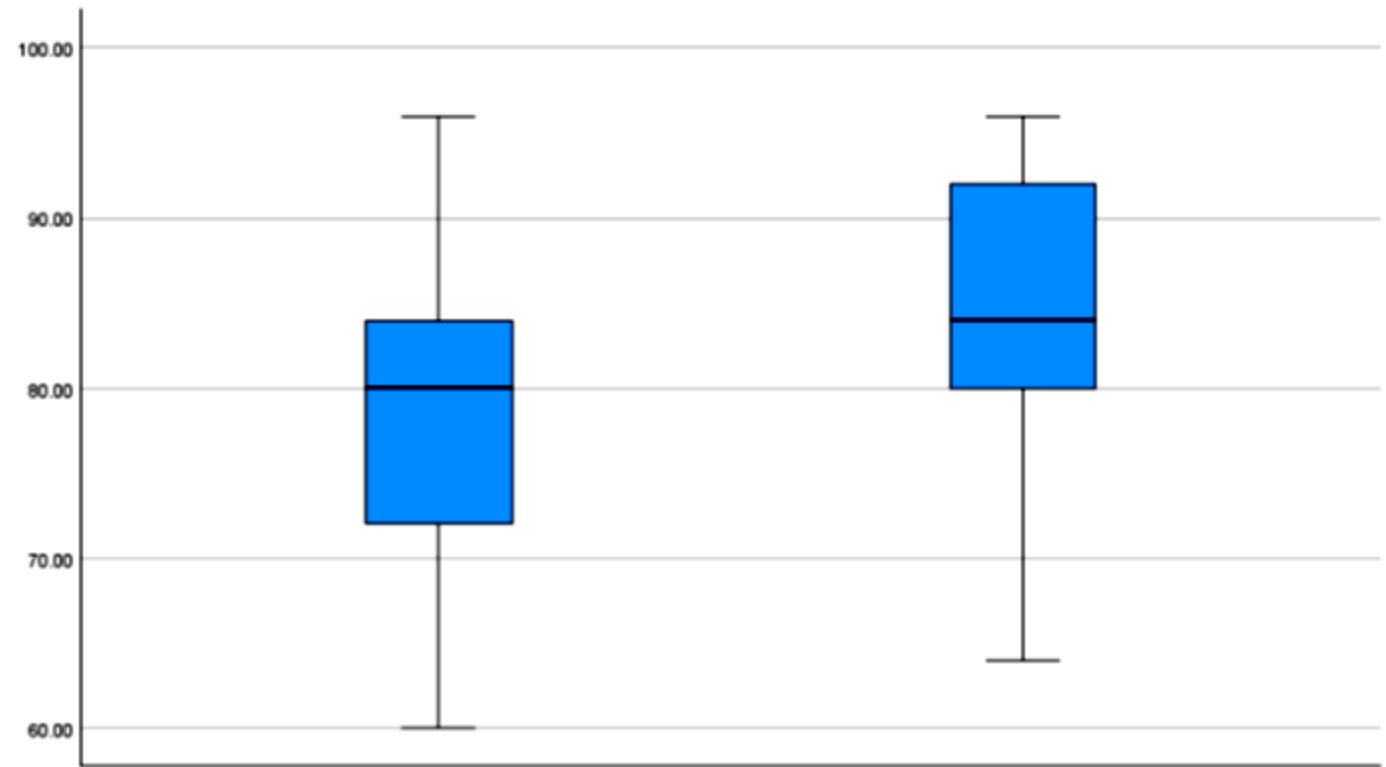
Pilot safety clinical trial: improves mental wellbeing in older adults

4 x PoZibio™ capsules daily (167 mg per capsule) for 30 days, two to be consumed in the morning and two at night

Pre-Post- Open Label trial

Self report questionnaires selected

- Mini Mental State Exam (MMSE)
- Geriatric Depression Scale (GDS)
- Pittsburgh Sleep Quality Index (PSQI)
- Delirium Observation Scale (DOS)
- Patient Health Questionnaire (PHQ-9)
- Generalized **Short Form Health Survey (SF-36)**
- Anxiety Disorder assessment (GAD-7)
- Warwick-Edinburgh Mental Wellbeing Scale (WEMWS)
- Gastrointestinal Symptom Rating Scale (GSRS)



LpD3.5 Intervention in Inflammatory Bowel Disease(LIBD) Study

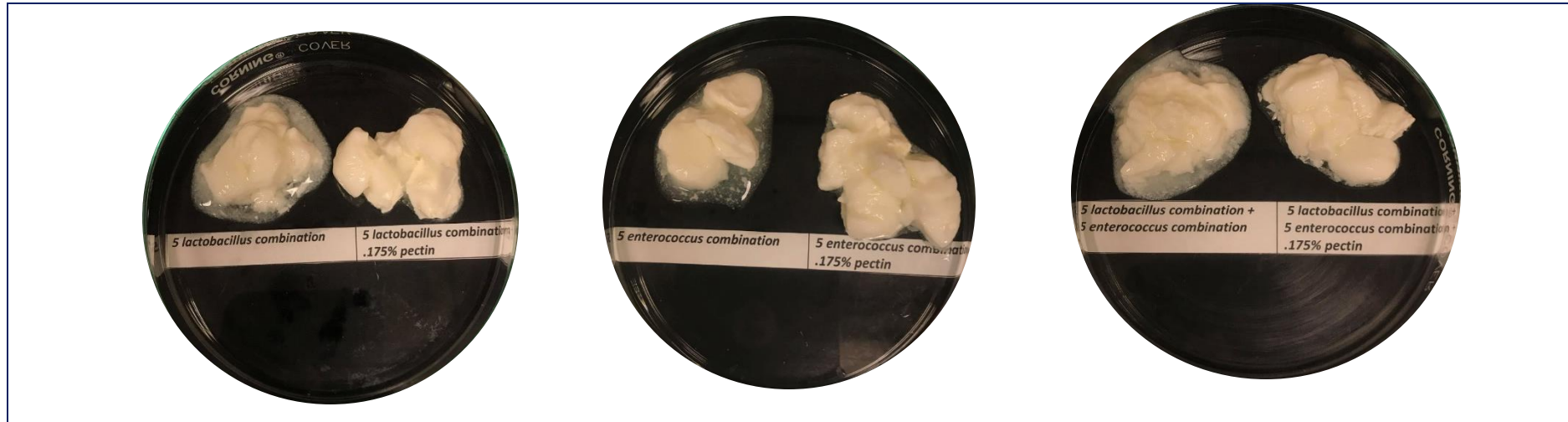


SCAN ME-PoZibio

PoZibio® Improves Quality of Life in Older Adults

A synbiotic yogurt reduces leaky gut

Developed a synbiotics (probiotics + prebiotics) yogurt



Different Versions

Proven in reducing diabetes progression, anti-aging, and cognitive decline in cancer models by modulating gut-brain axis

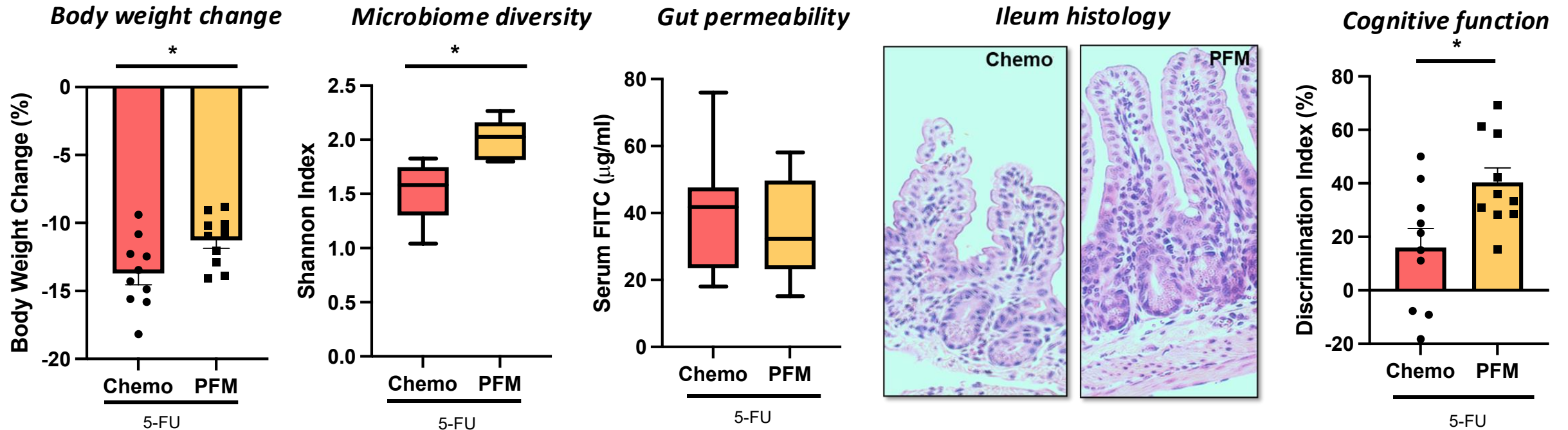


By **MusB** LLC



Brandi Miller
PhD. Candidate

Probiotic fermented milk protects from 5-FU-induced abnormalities



Data are presented as mean $\pm$ SEM or mean (min, max). Unpaired t-tests were performed for all analyses. Histology images were taken at 20x magnification. *P<0.05

Microbiome in CAncer treatment-related Side Effects (MiCASE) Study

The gut of adult breast cancer survivors with higher rate of gut and brain distress will exhibit higher leaky gut and inflammation with unique microbiome signatures than their controls.

Outcomes:

- Microbiome
- Leaky gut
- Inflammation
- Gut distress
- Brain distress
- Quality of life

Another study in food insecure adults will start soon.



The flyer is a colorful recruitment tool for the MiCASE study. It features a teal and pink color scheme with decorative concentric circle patterns. The top right corner displays the University of South Florida logo and the text 'BREAST CANCER SURVIVORS: ARE YOU EXPERIENCING GUT AND BRAIN DISTRESS FROM CANCER TREATMENT?'. Below this, three illustrations of women are shown. The center section includes the website 'https://micasestudy.com/', a QR code, and contact information for Dr. Shalini Jain, Principal Investigator. The bottom left section, titled 'Microbiome and its modulators in Cancer treatment Side Effects (MiCASE) study', describes the study's purpose and lists eligibility criteria. The bottom right section, titled 'PARTICIPATION INVOLVES', lists the study procedures. The bottom center section, titled 'WE ASSURE YOU', lists participant guarantees. The bottom right corner features the University of South Florida logo.

<https://micasestudy.com/>

BREAST CANCER SURVIVORS: ARE YOU EXPERIENCING GUT AND BRAIN DISTRESS FROM CANCER TREATMENT?

IF INTERESTED AND FOR MORE INFORMATION, PLEASE CONTACT US AT:

Dr. Shalini Jain, Principal Investigator
USF Center for Microbiome Research
Department of Neurosurgery and Brain Repair
University of South Florida – Tampa campus
Email: MCOM-MiCASE@usf.edu
Phone: 813-974-8222; 240-899-5684 (USF-IRB protocol no. 002586)

SCAN FOR MORE INFO

WE would like to hear from you!

Dr. Shalini Jain
USF Center for Microbiome Research
Neurosurgery and Brain Repair
Center of Excellence for Aging and Brain Repair
USF Health Morsani College of Medicine
3515 E. Fletcher Ave., MDC 1570
Tampa, FL 33612
Email: MCOM-MiCASE@usf.edu
Phone: 813-974-8222

PARTICIPATION INVOLVES

Microbiome and its modulators in Cancer treatment Side Effects (MiCASE) study
(USF-IRB protocol no. 002586)

Cancer treatments have multiple side effects by inducing distress in the gut and brain, which ultimately reduces the quality of life in cancer survivors.

You are invited to participate in the MiCASE study if:

- You are at least 40 years older
- You have previously been diagnosed with breast cancer
- You have undergone cancer treatment at least 6 months ago

- Visiting the USF-Tampa Campus to meet with a study team member to sign the consent form
- Completing questionnaires for medical history, cognitive function, gut health, dietary recall, and quality of life
- Donating saliva, stool, urine, and blood samples
- Measuring of vitals and physical function testing
- All of the questionnaires, measurements, and testing will be completed within 120 minutes

WE ASSURE YOU

- Participants have the option of receiving a free personal gut microbiome profile
- Participation is completely voluntary and confidential
- Your data/information is confidential and will be used for research purposes only
- Your visit will be scheduled per your convenience

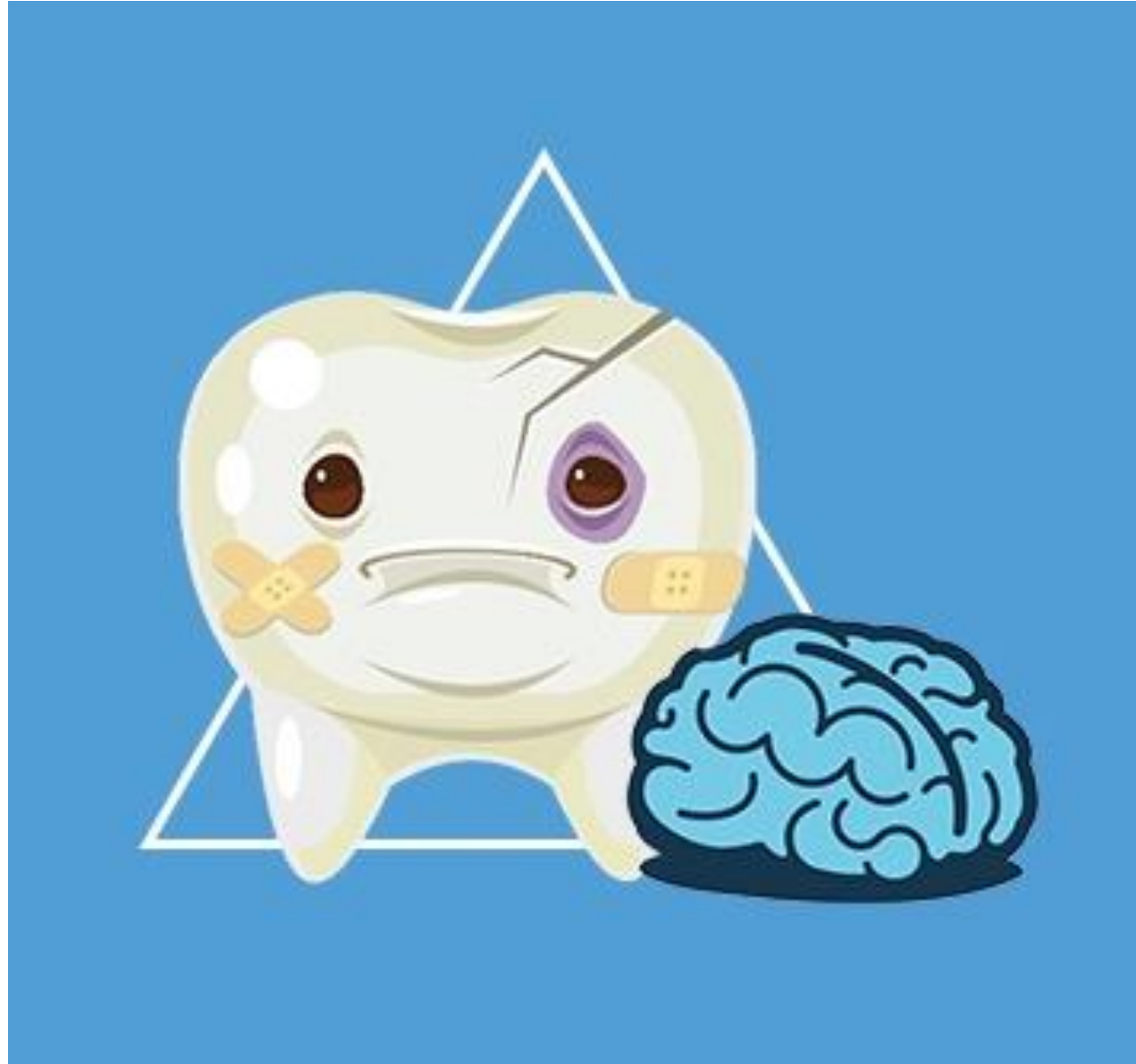
<https://micasestudy.com/>

UNIVERSITY of SOUTH FLORIDA

Summary #2

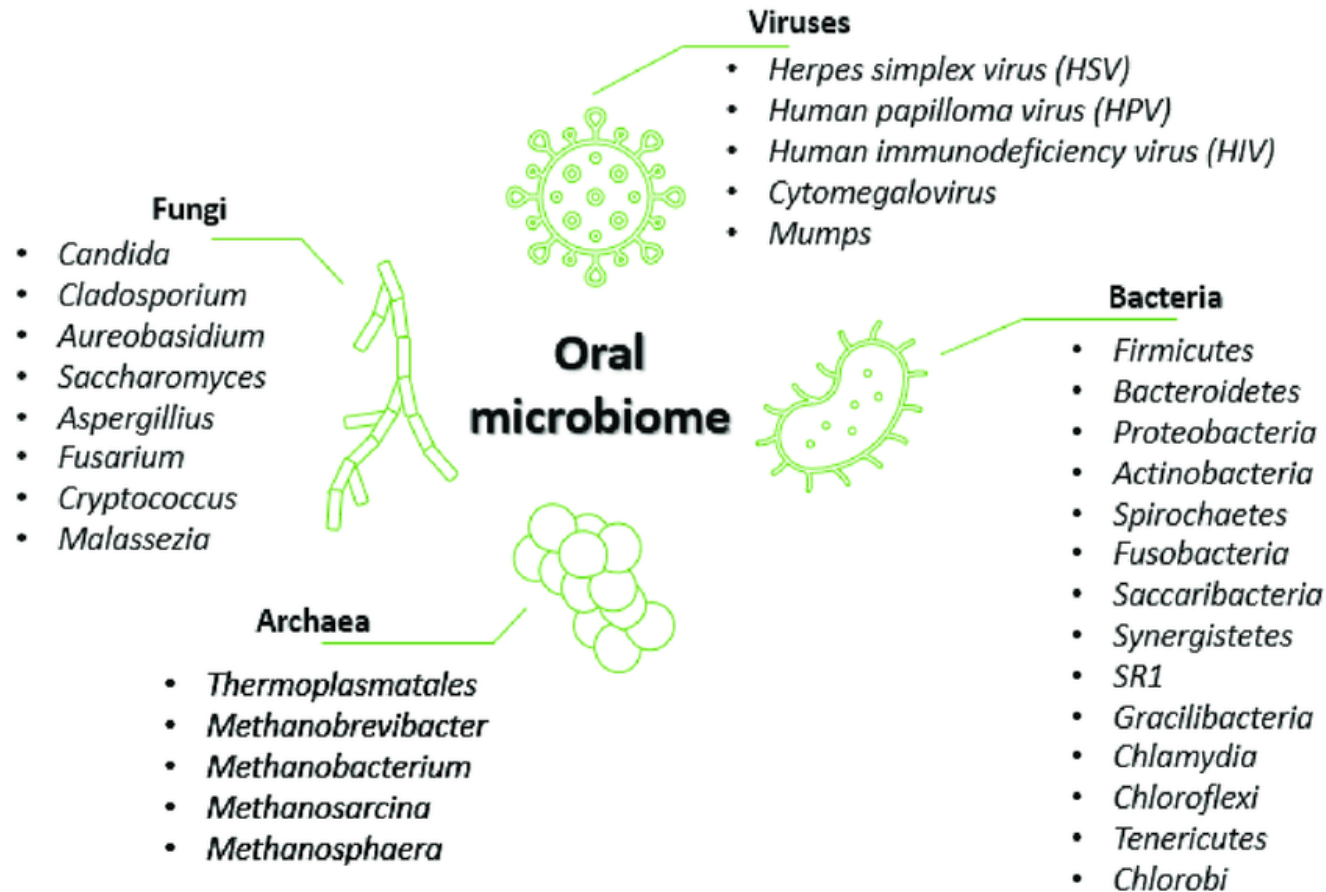
- Postbiotic D3.5 reduces leaky gut and inflammation and enhances cognition in a mouse model, and improves quality of life in older adults.
- PFM intervention protected against 5-FU-induced gut abnormalities by improving microbial diversity, reducing gut permeability, and enhancing cognitive function in mice.
- Clinical intervention of PFM to reduce these abnormalities in older breast cancer survivors is planned.

Oral microbiome and Cognitive function

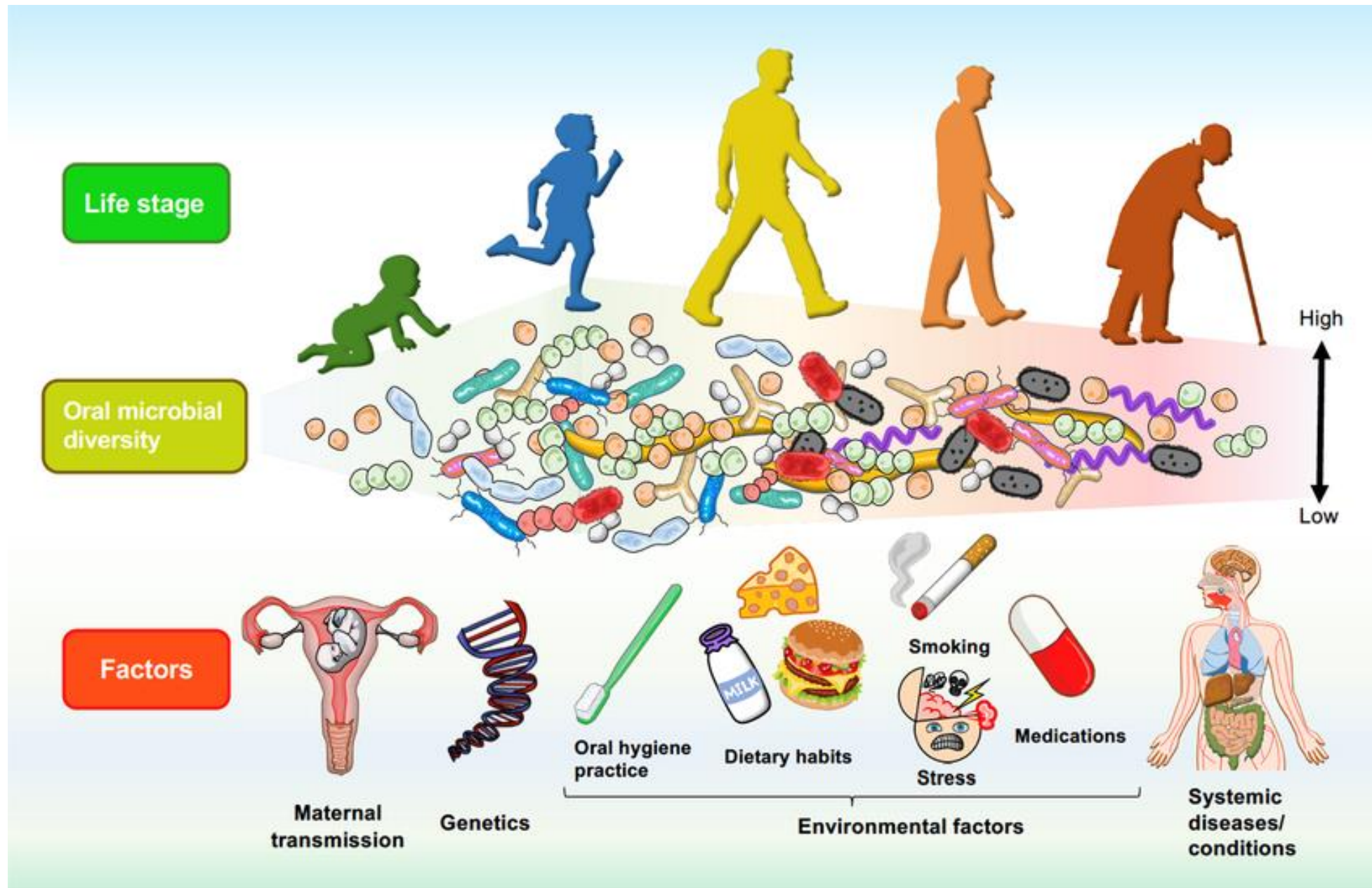


Oral Microbiome

- Oral cavity is a vital interface for the exchange of substances between the human body and the external environment.
- Harbors over 700 bacterial species adhering to oral mucosa and dental surfaces.
- Maintaining a balanced microbial composition is imperative for oral and systemic health.



Oral Microbiome Changes With Human Aging Dynamics



Oral Health And Cognitive Function

- Poor oral health linked with poor cognition.
- Periodontal disease, dental caries and tooth loss represent the common infections of oral cavity that results to microbial or inflammatory signals translocation to brain impacting cognition.
- TriNetX database shows there was two-fold increase in Alzheimer's disease risk in the poor oral health cohort compared to the normal oral health group.
- Studies have shown oral cavity's salivary system is connected to brain through mucosal, blood and lymphatic circulations.

> J Alzheimers Dis. 2020;75(1):157-172. doi: 10.3233/JAD-200064.

Clinical and Bacterial Markers of Periodontitis and Their Association with Incident All-Cause and Alzheimer's Disease Dementia in a Large National Survey

May A Beydoun ¹, Hind A Beydoun ², Sharmin Hossain ¹, Ziad W El-Hajj ³, Jordan Weiss ⁴, Alan B Zonderman ¹



Brain Sci. 2023, 13, 1555. <https://doi.org/10.3390/brainsci13111555>

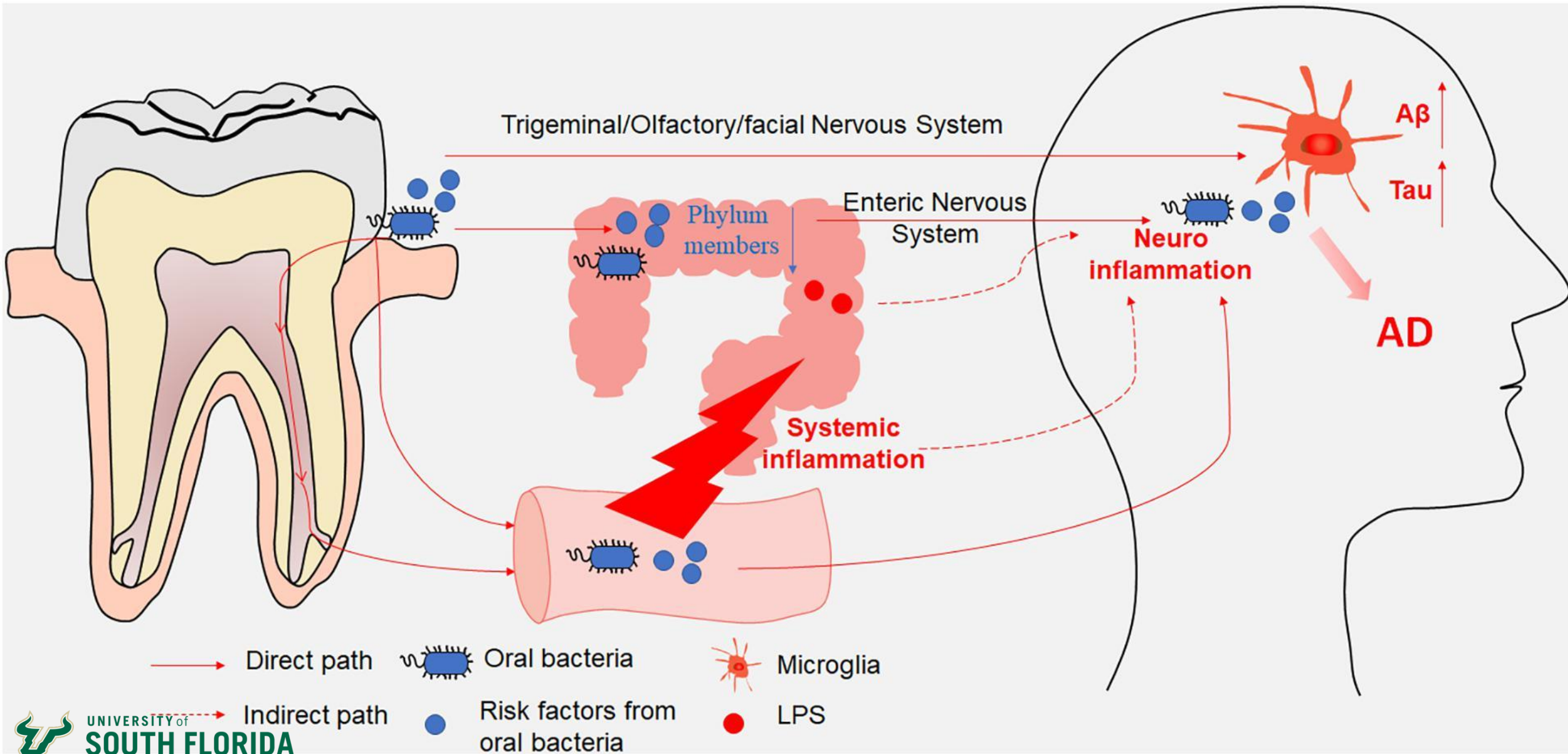


Article

Poor Oral Health Linked with Higher Risk of Alzheimer's Disease

Mihir S. Kulkarni ¹, Brandi C. Miller ^{1,2} , Manan Mahani ¹, Rahul Mhaskar ³, Athanasios Tsalatsanis ⁴, Shalini Jain ¹ and Hariom Yadav ^{1,*}

Saliva is connected to Brain via Oral-gut-Brain axis



Saliva Can Be An Ideal Source of Biomarkers for Dementia

- Early detection of dementia risk is urgently needed.
- The current diagnosis is complex, cumbersome, and not easy to implement.

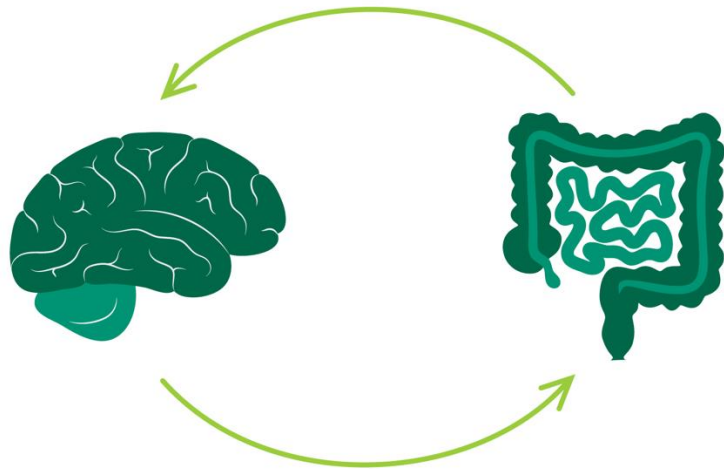
Whether saliva-based microbiome-protein markers can predict cognitive health?



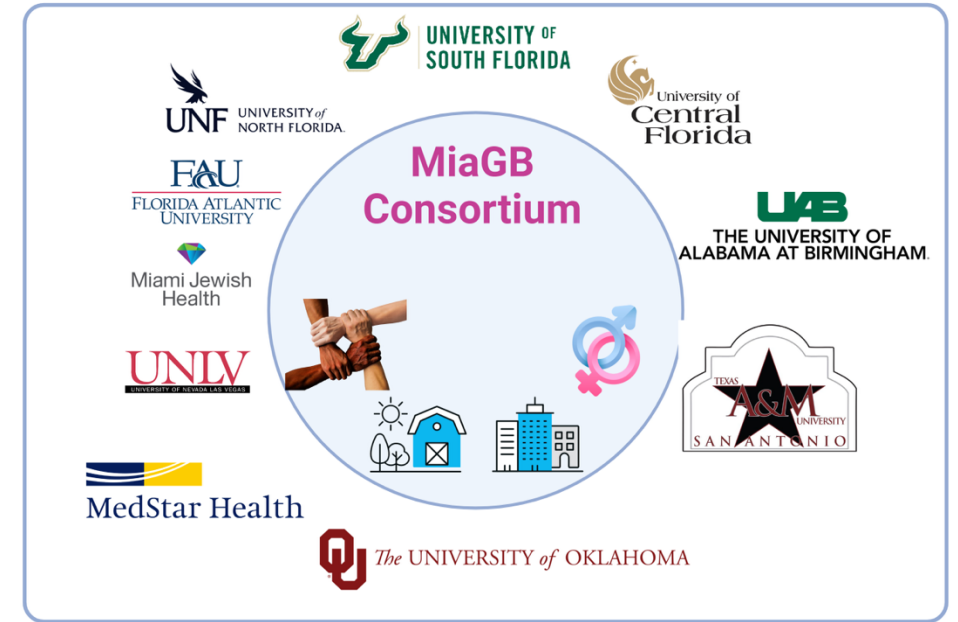
Microbiome in aging Gut and Brain (MiaGB) Consortium

Groups

- Cognitively healthy
- Mild cognitively impairment (MCI)
- Alzheimer's disease related dementia



**MICROBIOME IN
AGING GUT AND BRAIN
(MiaGB) STUDY**



Funded by FL State and NIA



MiaGB study



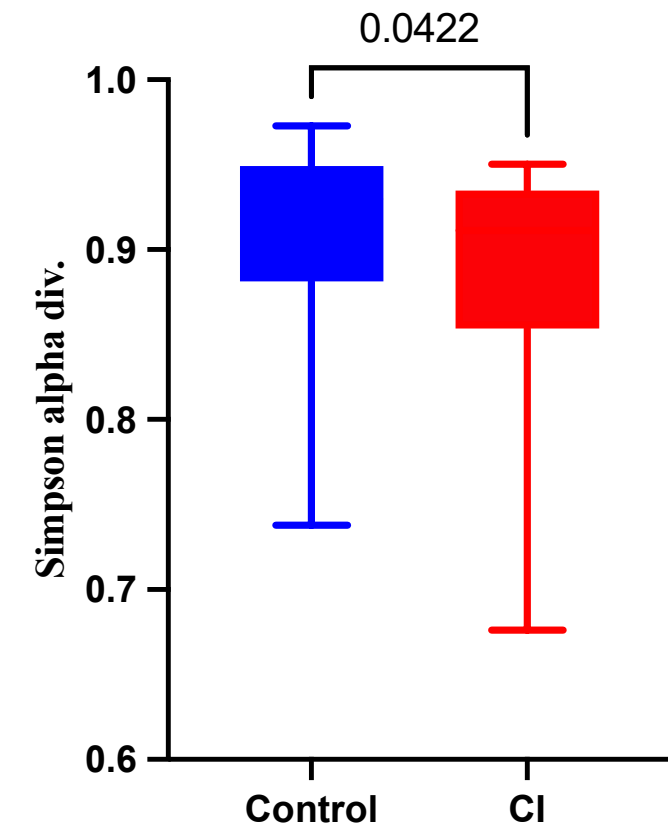
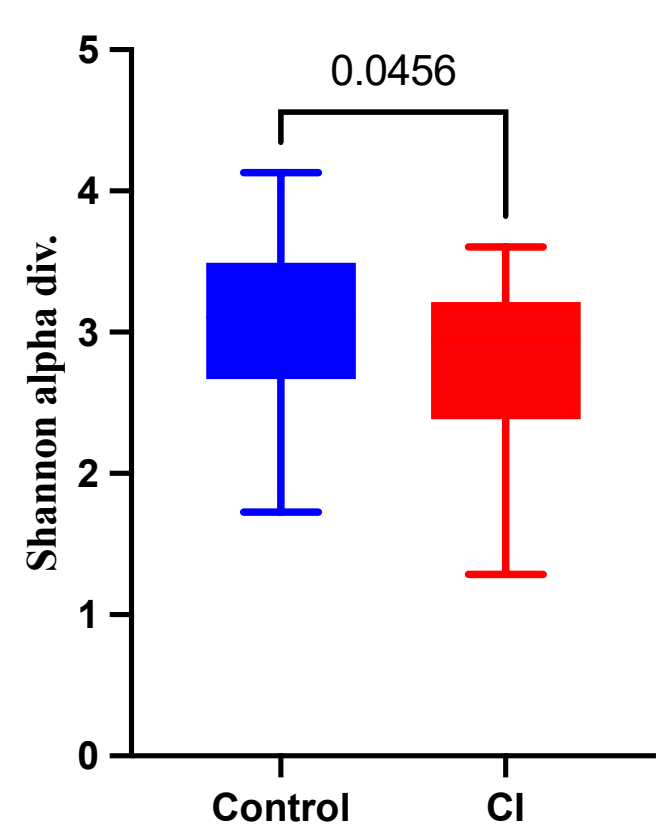
Database

Demographic Information of Pilot Study Samples From MiaGB Cohort

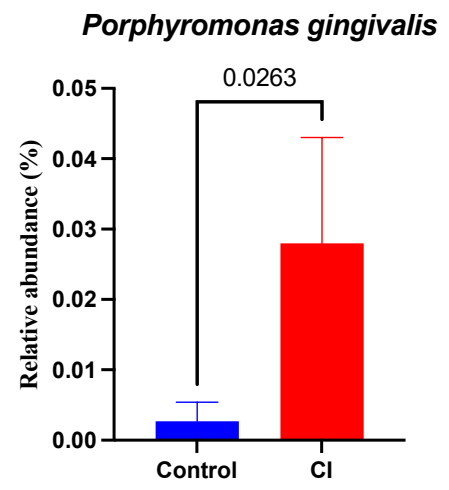
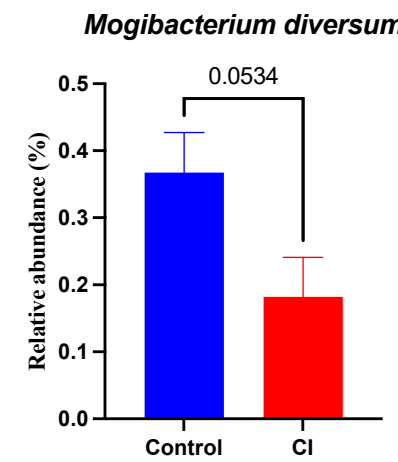
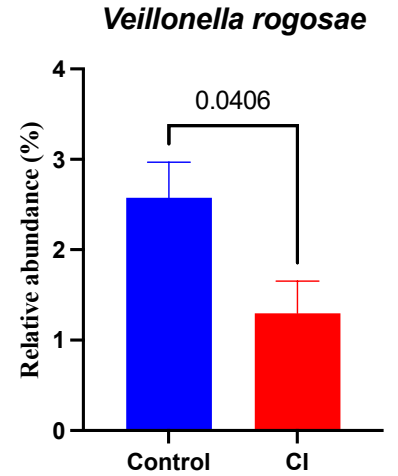
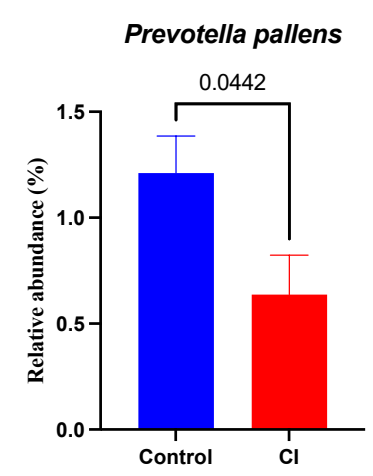
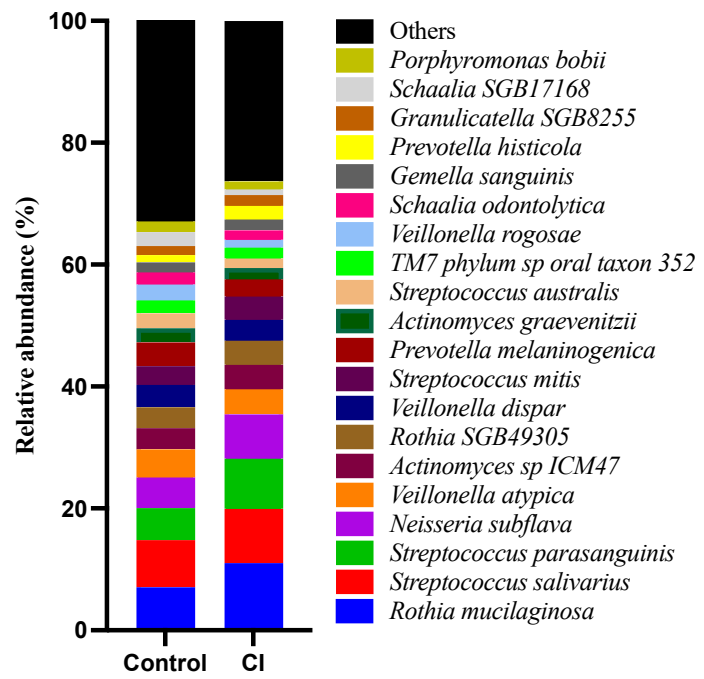
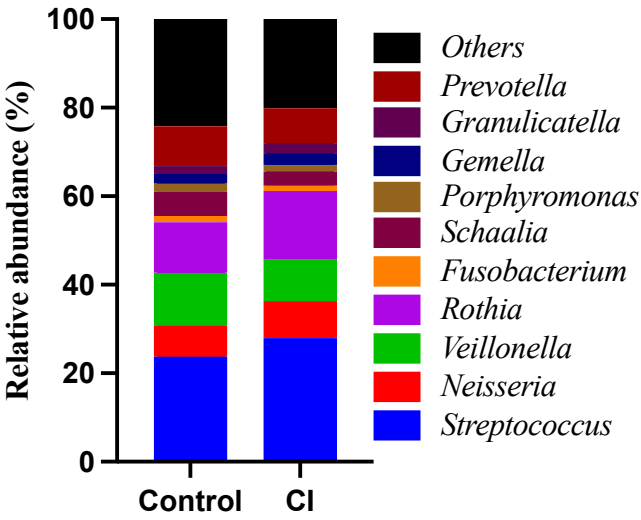
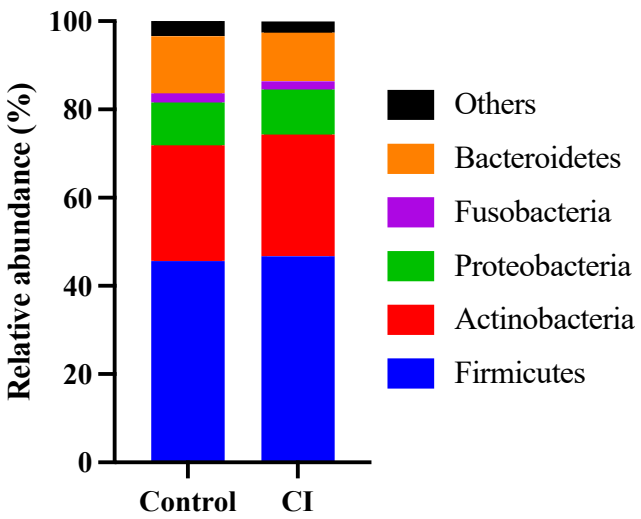
Variables	Control (58)	CI (30)
Male	17	12
Female	41	18
Age	69.7 ± 8.07	75.5 ± 8.06
BMI	27 ± 4.31	26.3 ± 6.01
MoCA	27.5 ± 1.22	21.7 ± 2.82
MiniCog	4.4 ± 0.83	2.9 ± 1.55
MIS	7.1 ± 1.55	5.4 ± 2.51
8 item questionnaires	0.51 ± 0387	2.7 ± 2.64

- A score of MOCA ≥26 considered normal for individuals with 12 or more years of education.
- A score of MOCA ≤25 may indicate cognitive impairment.

Alpha Diversity Is Significantly Reduced In Older Adults With CI

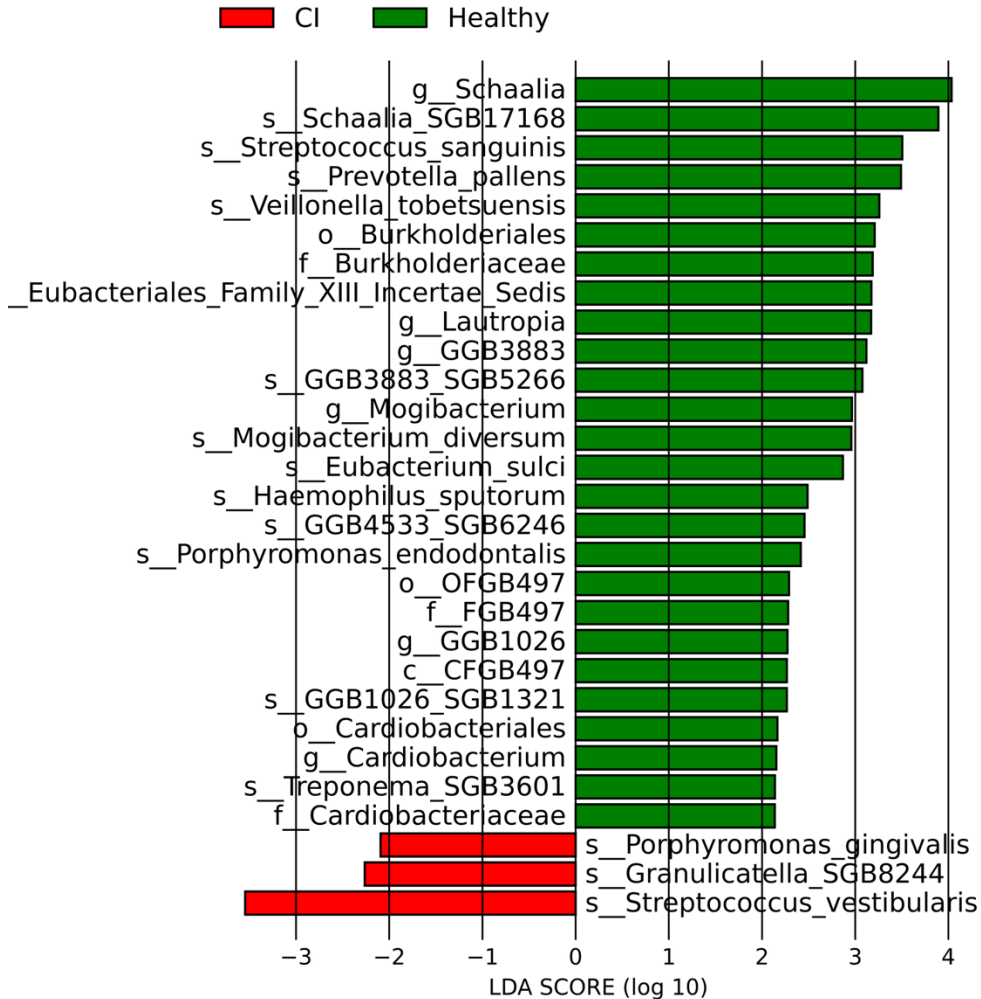


Oral cavity of older adults with CI harbors significantly distinct microbiome than cognitively healthy controls



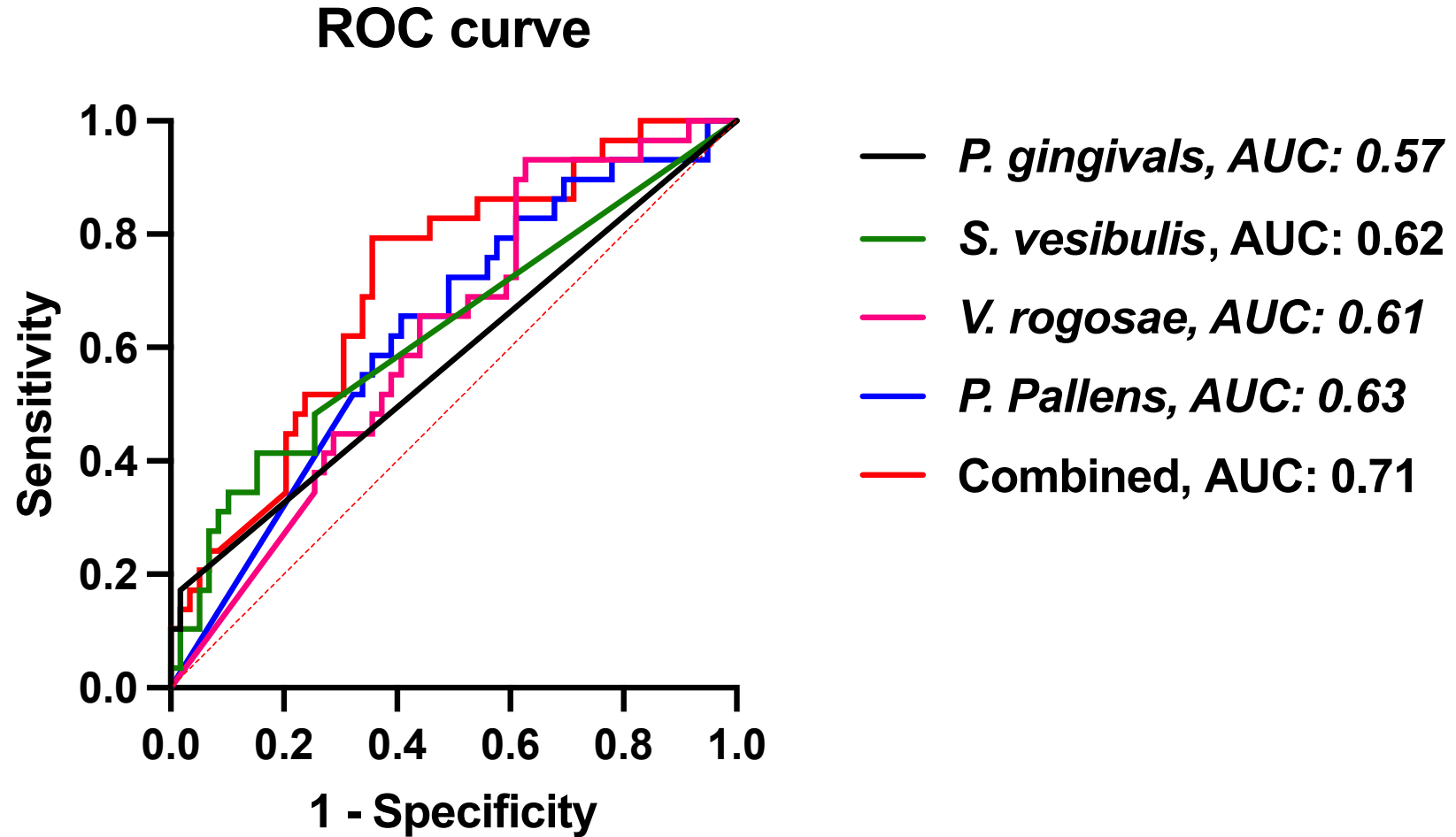
Oral Microbiome To Be Used As Biomarker For Cognitive Decline

LefSe- Microbiome Biomarker Discovery Tool



- **P. gingivalis** –
 - ✓ pro inflammatory pathogenic bacteria associated with Periodontitis,
 - ✓ Gingipains
- **Granulicatella**
 - ✓ Formerly referred as nutritionally variant streptococci (NVS)
 - ✓ opportunistic pathogens
 - ✓ infective endocarditis, bacteremia, and other infections
- **S. vestibularis:**
 - ✓ Induce neurotransmitter alterations in peripheral tissues.
 - ✓ Oral infections, including dental caries and periodontal diseases.

Oral Microbiome Signatures Can Predict The Cognitive Decline



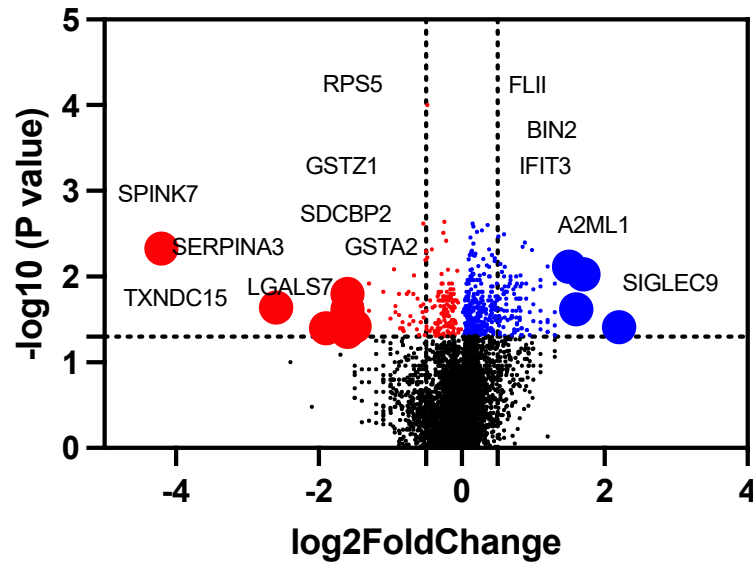
Demographic information of Pilot study samples from MiaGB cohort

Variable	Control (15)	MCI (15)	Dementia (9)
Male	7	7	6
Female	8	8	3
Age (yrs.)	74.2 ± 5.7	73.8 ± 8.37	77.0 ± 6.58
MOCA score	27.8 ± 1.46	23.2 ± 0.81	15.6 ± 2.30
Mini-Cog score	4.4 ± 0.54	3.2 ± 2.16	1.4 ± 0.89
Age	74.93 ± 4.32	73.33 ± 5.56	79.33 ± 9.03
BMI	25.17 ± 3.27	24.56 ± 3.99	28.58 ± 5.67
MoCA	28.2 ± 1.16	23.0 ± 1.59	14.11 ± 3.28
MiniCog	4.46 ± 0.71	3.8 ± 1.51	0.55 ± 0.83
MIS	6.93 ± 2.04	6.33 ± 1.84	2.0 ± 2.49
8 item questionnaires	0.33 ± 0.78	1.26 ± 2.14	3.33 ± 2.86

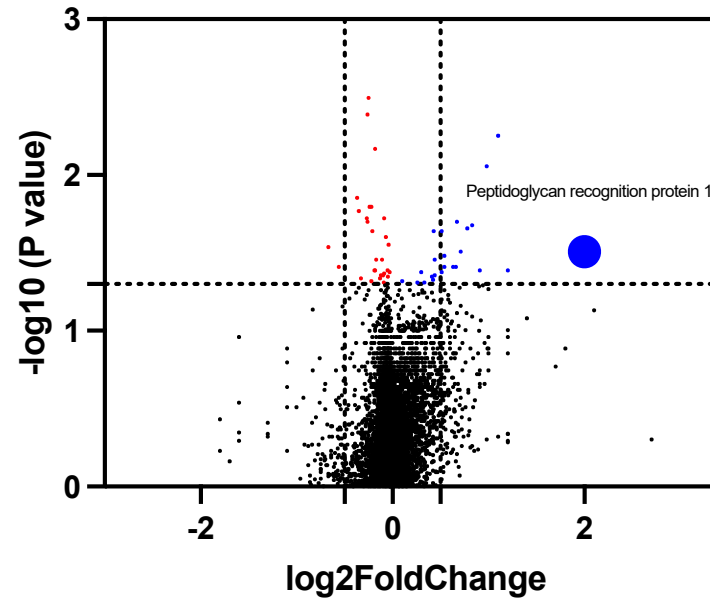
- A score of MOCA ≥26 considered normal for individuals with 12 or more years of education.
- A score of MOCA 18-25 indicate mild cognitive impairment.
- A score of MOCA 17-1 indicate moderate to severe cognitive impairment and dementia.

Saliva-based Proteomic Biomarkers To Detect Cognitive Decline

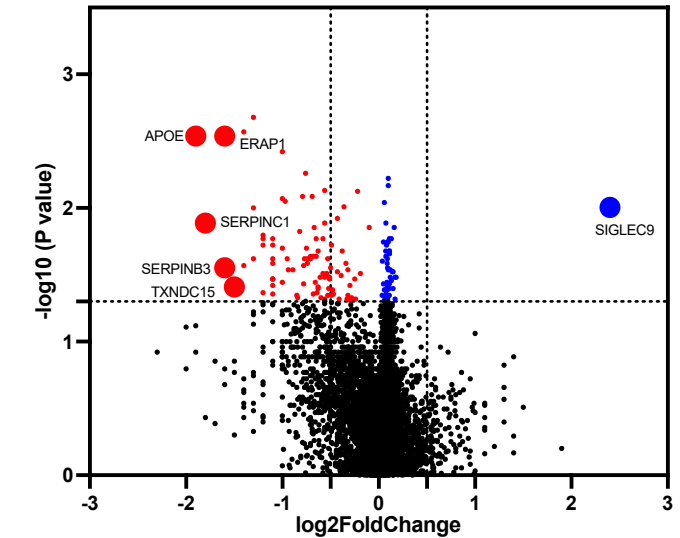
Control vs MCI



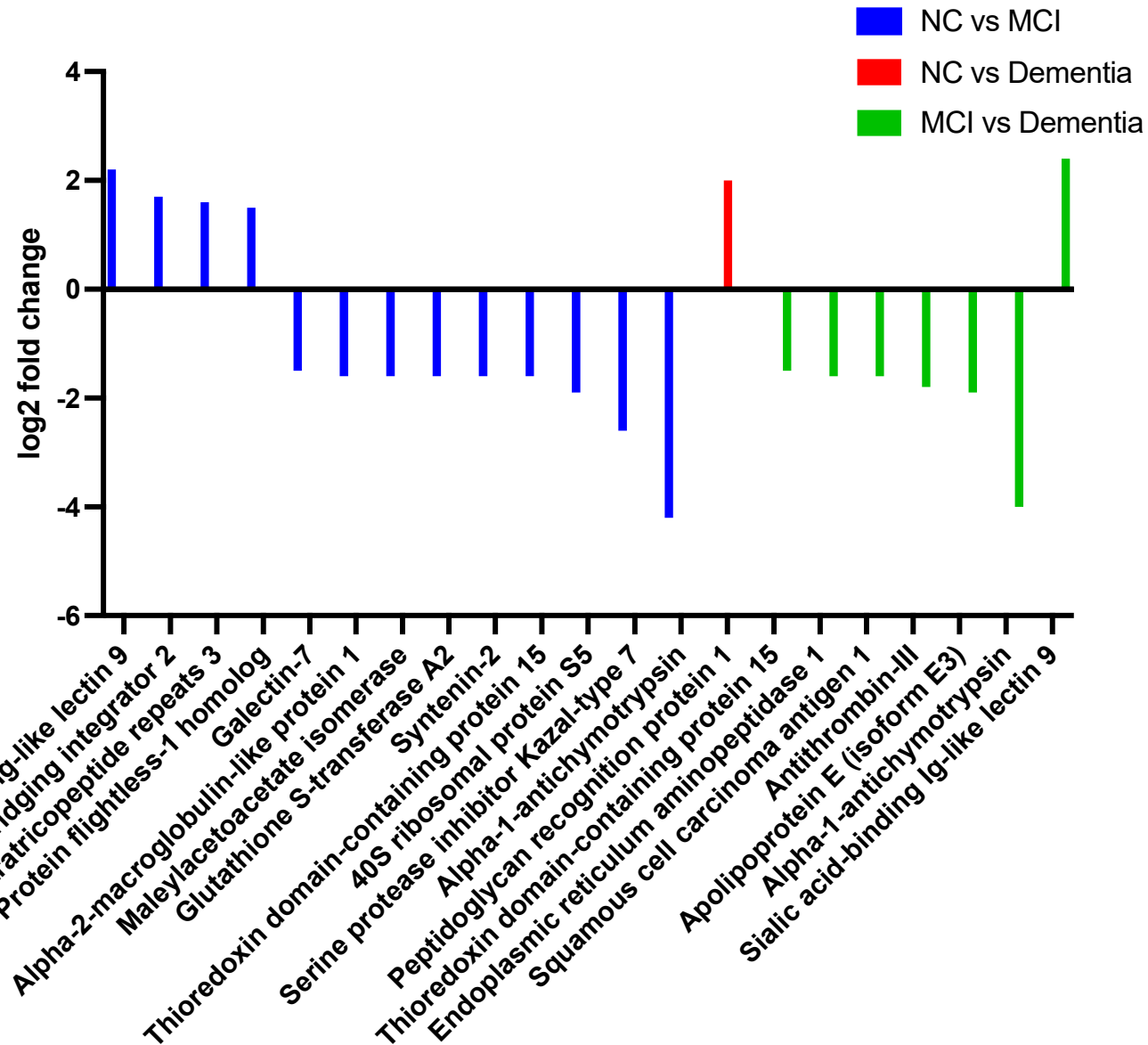
Control vs dementia



MCI vs dementia



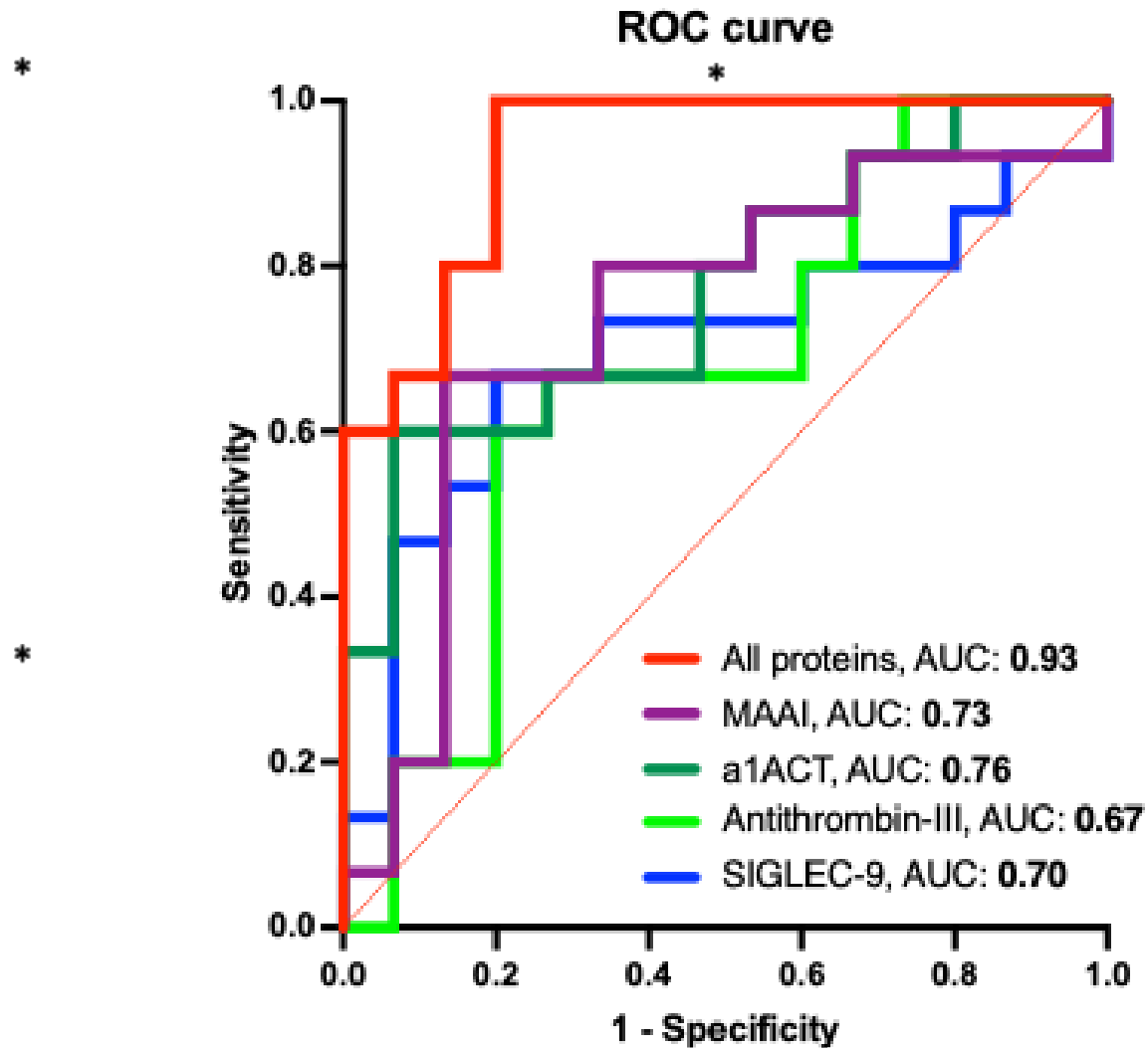
Saliva Based Proteins In Cognitive Impairment



FUNCTIONS

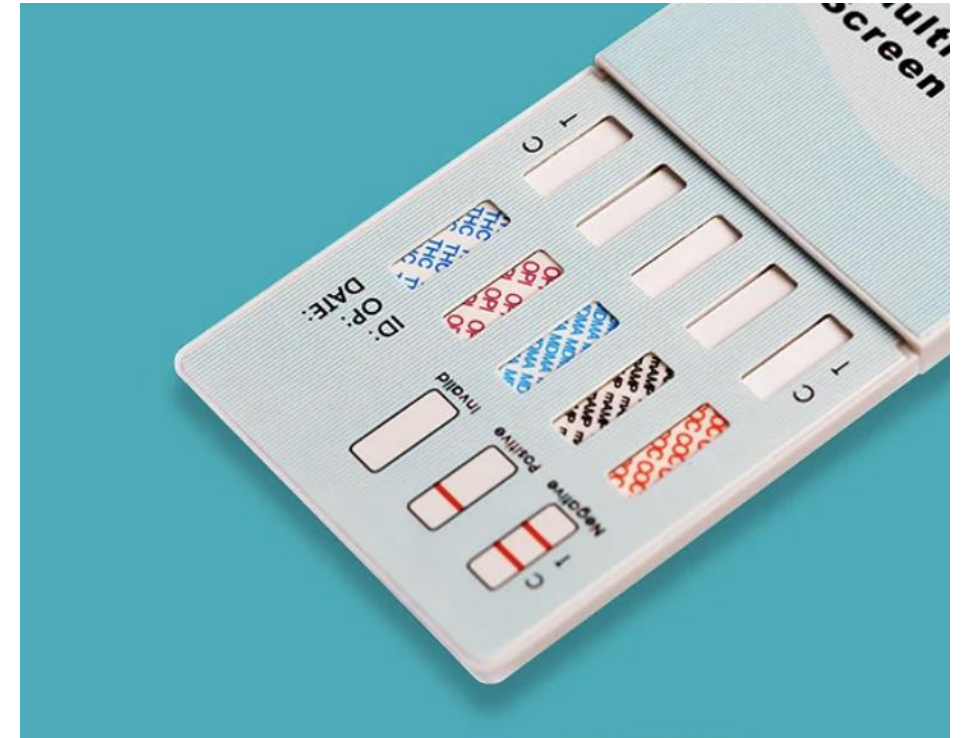
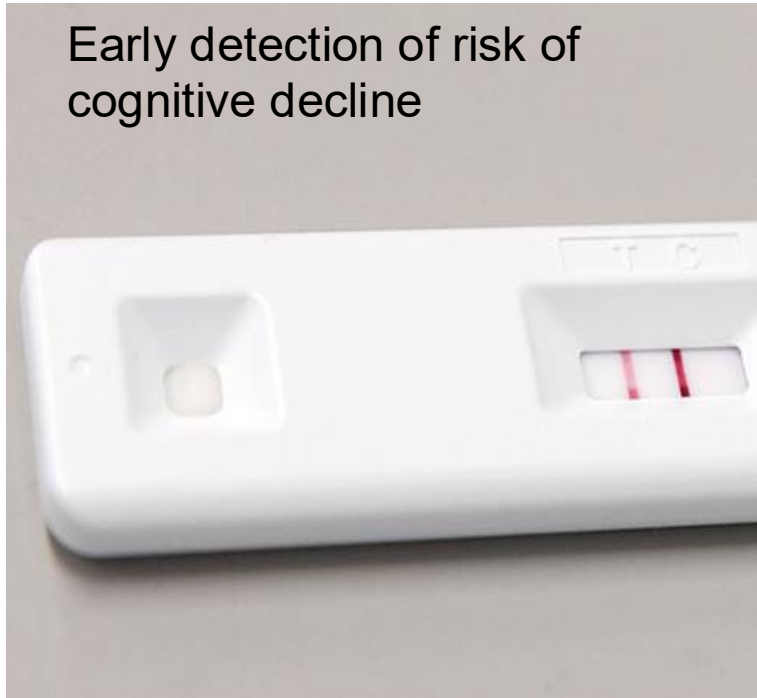
Immune responses
 microglial activation
 the inflammatory response
 Neuroinflammation
 Mediates membrane tubulation
 Modulates membrane curvature
 Inhibiting phagocytosis
 Modulate A β -mediated neurotoxicity
 Neural apoptosis
 Immune defense
 Oxidative stress and neuronal damage
 Cellular defense

Saliva Protein Signatures Can Predict The Cognitive Decline



Saliva based test for early detection of risk of cognitive decline

Early detection of risk of cognitive decline



Summary #3

- CI individuals have significantly distinct oral microbiome signatures than healthy controls, with biomarker capacity but on higher variability.
- Saliva proteomic signatures are significantly distinct in older adults with CI than controls; specifically enrichment of proteins modulating inflammation, oxidative stress and immune cell signaling.
- Saliva based microbiome and protein signatures have potential to detect the risk of the CI.

Overall Summary

- Aged microbiome can promote leaky gut and inflammation due to deficiency of butyrate-producing capacity, which in turn suppresses mucin formation.
- Postbiotics D3-5 and Probiotic fermented milk reduce leaky gut and inflammation and improved cognitive function.
- Saliva based microbiome and proteomic markers may be another way to predict the risk of cognitive decline/ dementia in older adults

Acknowledgements

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Questions!