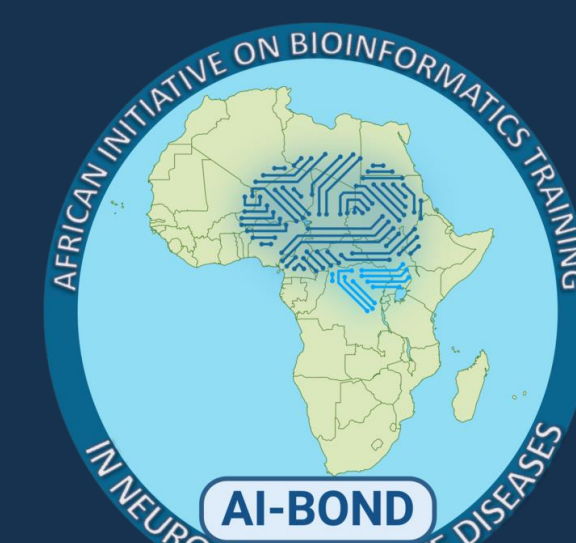


The Gut Microbiome in Preclinical and Clinical Dementia: Insights from Human Cohort Studies

Bernard Fongang, PhD

Glenn Biggs Institute for Alzheimer's & Neurodegenerative Diseases
Department of Biochemistry and Structural Biology
UT Health San Antonio, TX, USA



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INTRODUCTION AND BACKGROUND

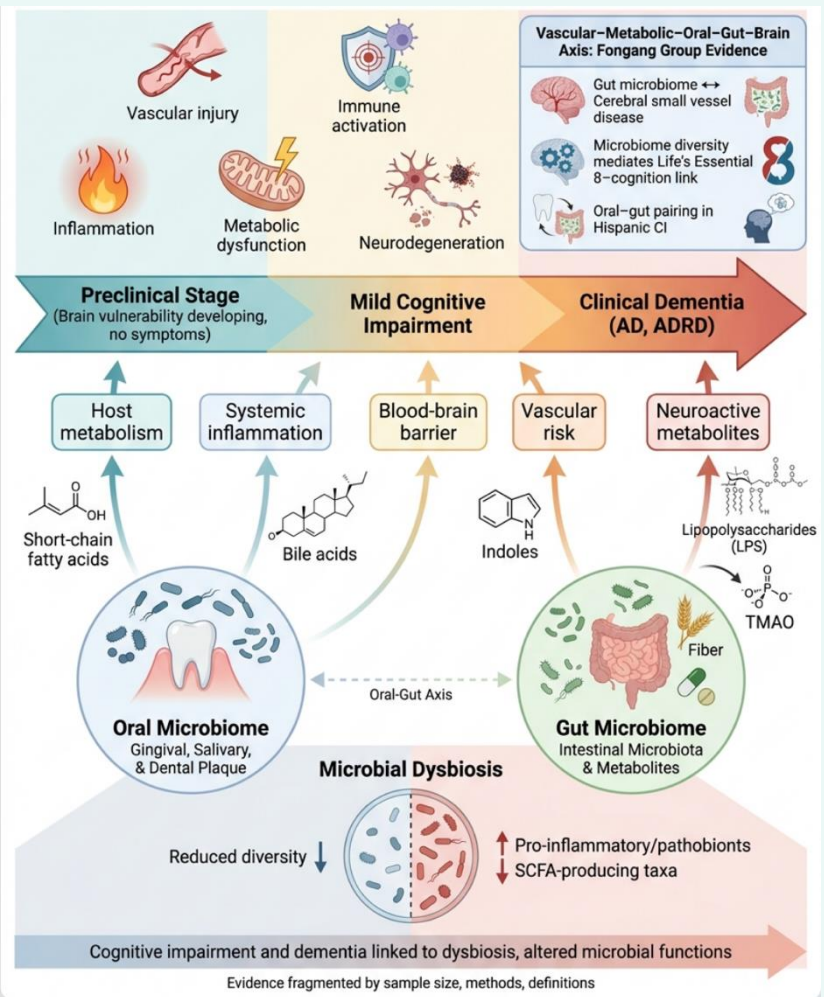
Dementia begins years before clinical symptoms, during a preclinical phase marked by vascular injury, inflammation, metabolic dysfunction, immune activation, and early neurodegeneration.

The gut and oral microbiomes may influence these pathways by affecting host metabolism, systemic inflammation, blood-brain barrier integrity, vascular risk, and neuroactive metabolites, including short-chain fatty acids, bile acids, indoles, lipopolysaccharides, and trimethylamine-N-oxide.

Human cohort studies link cognitive impairment and dementia to microbial dysbiosis, including reduced diversity, loss of anti-inflammatory and short-chain-fatty-acid-producing taxa, enrichment of pro-inflammatory/pathobiont organisms, and altered microbial functions.

Work from our group extends this field by connecting the gut microbiome with cerebral small vessel disease, executive function, paired gut/oral microbiome patterns in Hispanic cognitive impairment, and Life's Essential 8-related microbiome diversity and cognition in Framingham. Together, these findings support a vascular-metabolic-oral-gut-brain axis model.

This review synthesizes human cohort evidence across preclinical and clinical dementia to identify consistent microbiome signals for validation, prevention, and therapeutic follow-up.



METHODS

Systematic narrative review of human cohort studies of gut and/or oral microbiome across preclinical and clinical dementia.

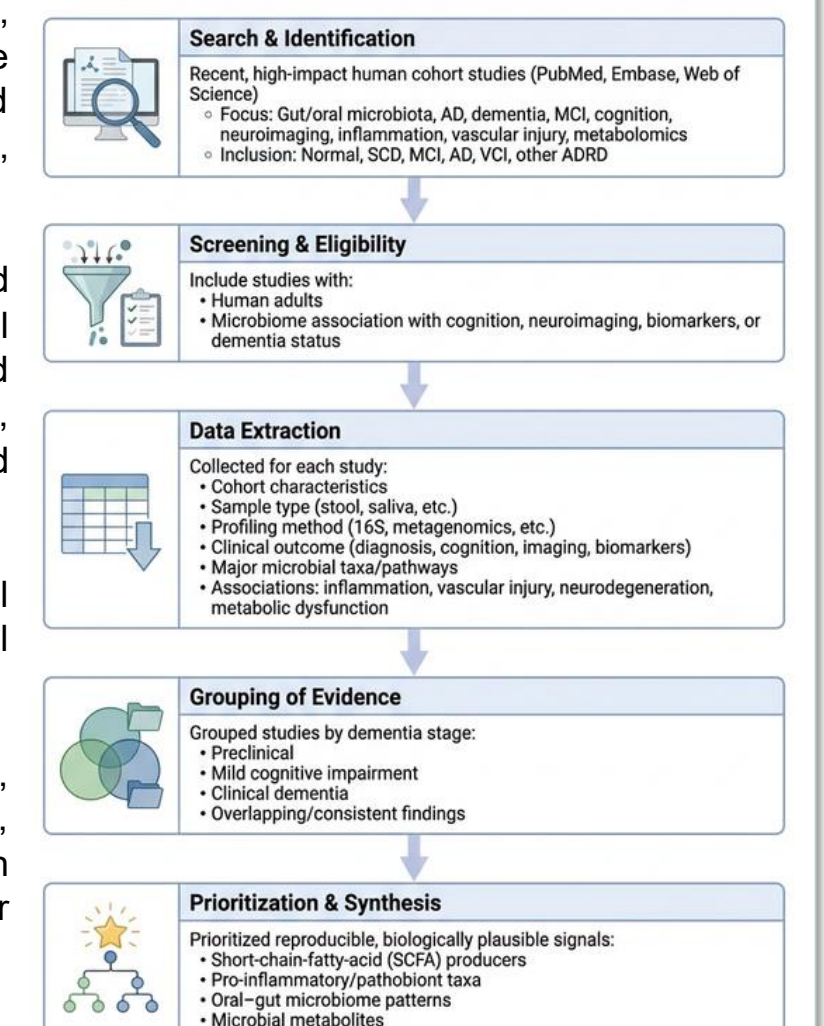
Eligibility: adults with normal cognition, subjective cognitive decline, mild cognitive impairment, AD, VCI, or other ARD; reported microbiome associations with cognition, neuroimaging, biomarkers, or dementia status.

Searches focused on studies and reviews using terms related to gut and oral microbiota, Alzheimer's disease, dementia, mild cognitive impairment, cognition, neuroimaging, inflammation, vascular brain injury, and metabolomics.

Evidence was grouped into preclinical dementia, mild cognitive impairment, clinical dementia, and overlapping findings across stages.

We extracted cohort characteristics, sample type, profiling method, clinical outcome, major microbial taxa or pathways, and links with inflammation, vascular injury, neurodegeneration, or metabolic dysfunction.

We prioritized reproducible and biologically plausible signals, including SCFAs producers, pro-inflammatory/pathobiont taxa, oral-gut patterns, and microbial metabolites.



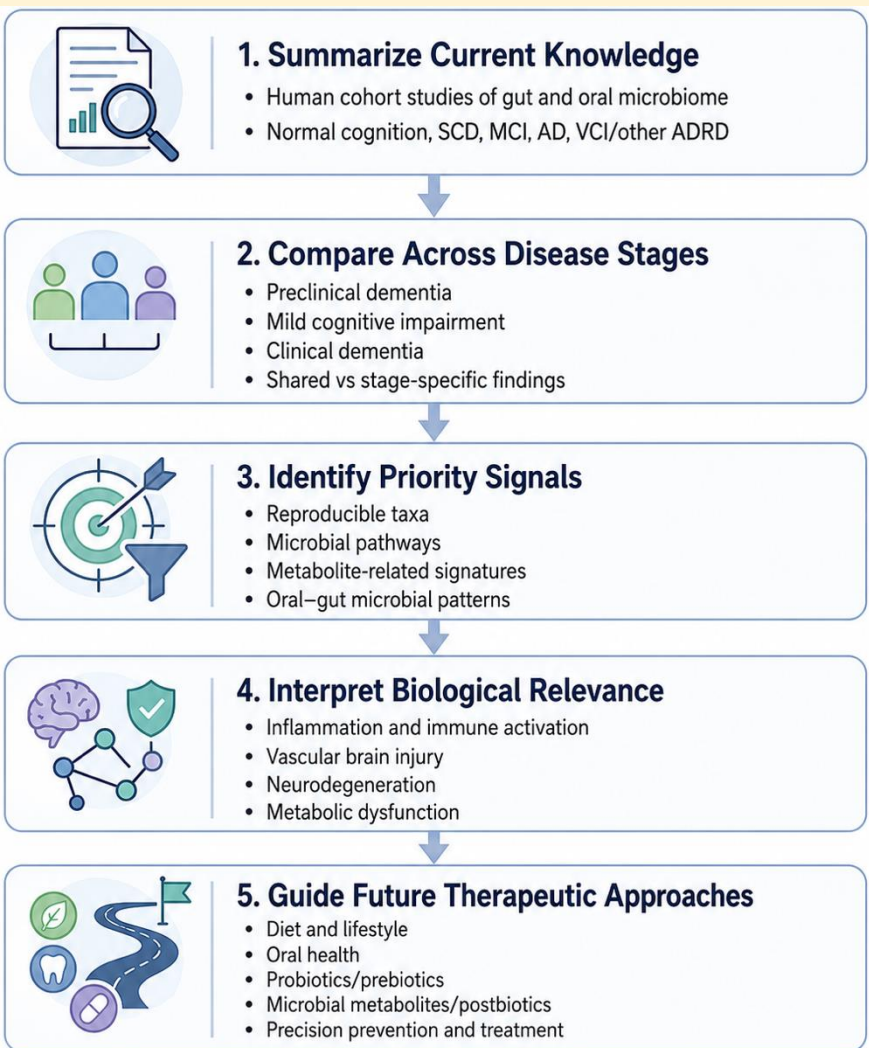
OVERALL OBJECTIVE

The objective of this review is to synthesize current human cohort evidence on the gut and oral microbiome across preclinical dementia, mild cognitive impairment, and clinical dementia.

We aim to identify microbial taxa, functional pathways, and metabolite-related signatures that are consistently associated with cognitive decline, Alzheimer's disease, vascular brain injury, inflammation, and neurodegeneration.

By comparing findings across disease stages, this work seeks to distinguish early microbiome signals that may contribute to dementia risk from later dysbiosis associated with established disease.

The ultimate goal is to define priority microbiome targets for future validation, risk prediction, and therapeutic development, including strategies focused on diet, lifestyle, oral health, probiotics/prebiotics, microbial metabolites, and modulation of inflammatory and vascular pathways relevant to dementia prevention and care.

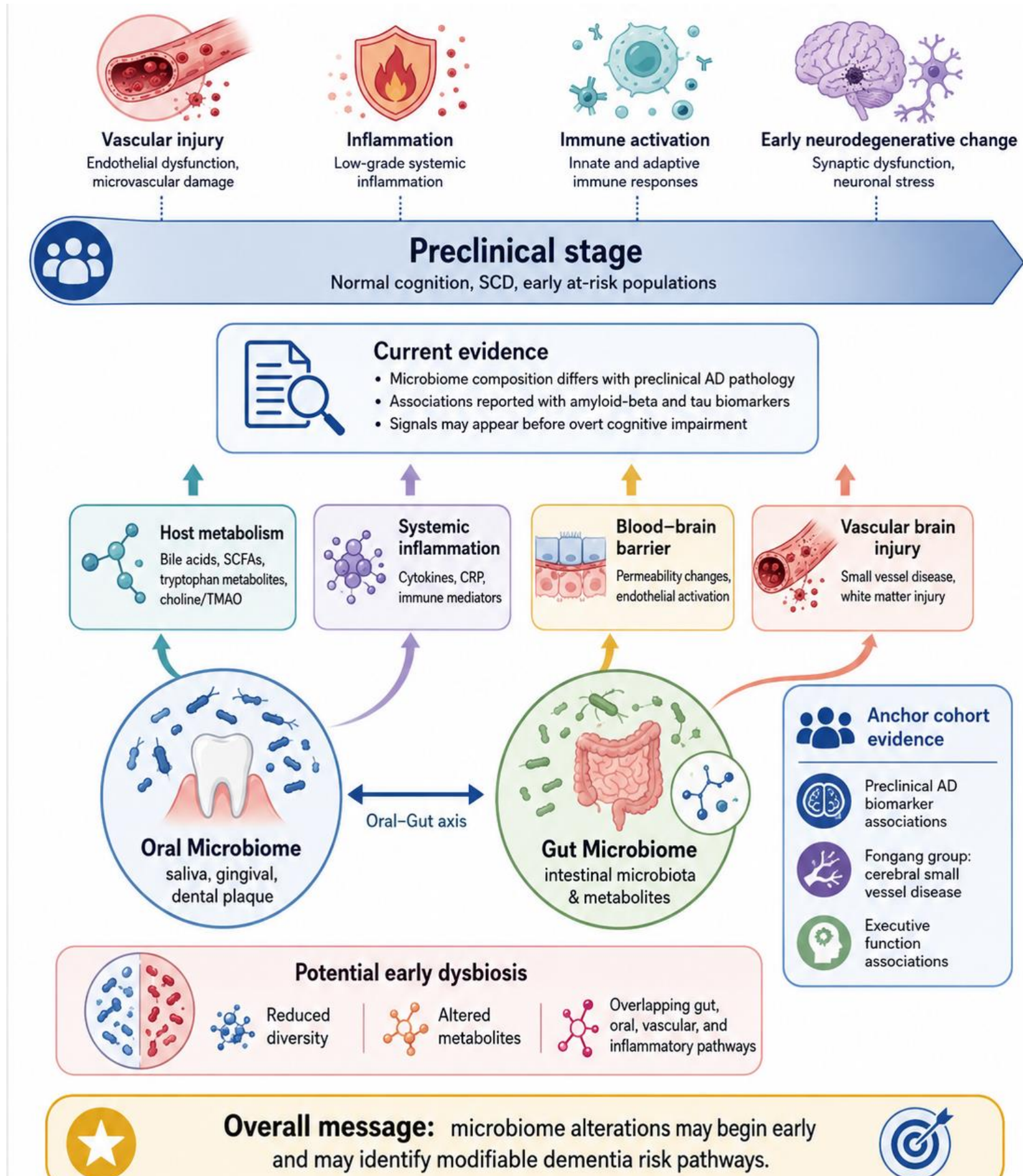


RESULTS: PRECLINICAL DEMENTIA

Human evidence suggests that microbiome alterations may appear before overt cognitive impairment. In cognitively normal older adults with preclinical Alzheimer's disease pathology, gut microbiome composition differed from controls and correlated with amyloid- β and tau biomarkers, but not with neurodegeneration markers, supporting a possible early microbiome signal in the AD continuum.

In parallel, work from our group extends this evidence to vascular brain aging by showing that gut microbiome profiles are associated with cerebral small vessel disease burden and executive function in stroke- and dementia-free Framingham participants.

Emerging oral microbiome studies also suggest associations between oral microbial composition and cognitive performance. Together, preclinical findings support early gut-oral-vascular-inflammatory pathways that may precede clinical dementia.



RESULTS: CLINICAL DEMENTIA AND MCI

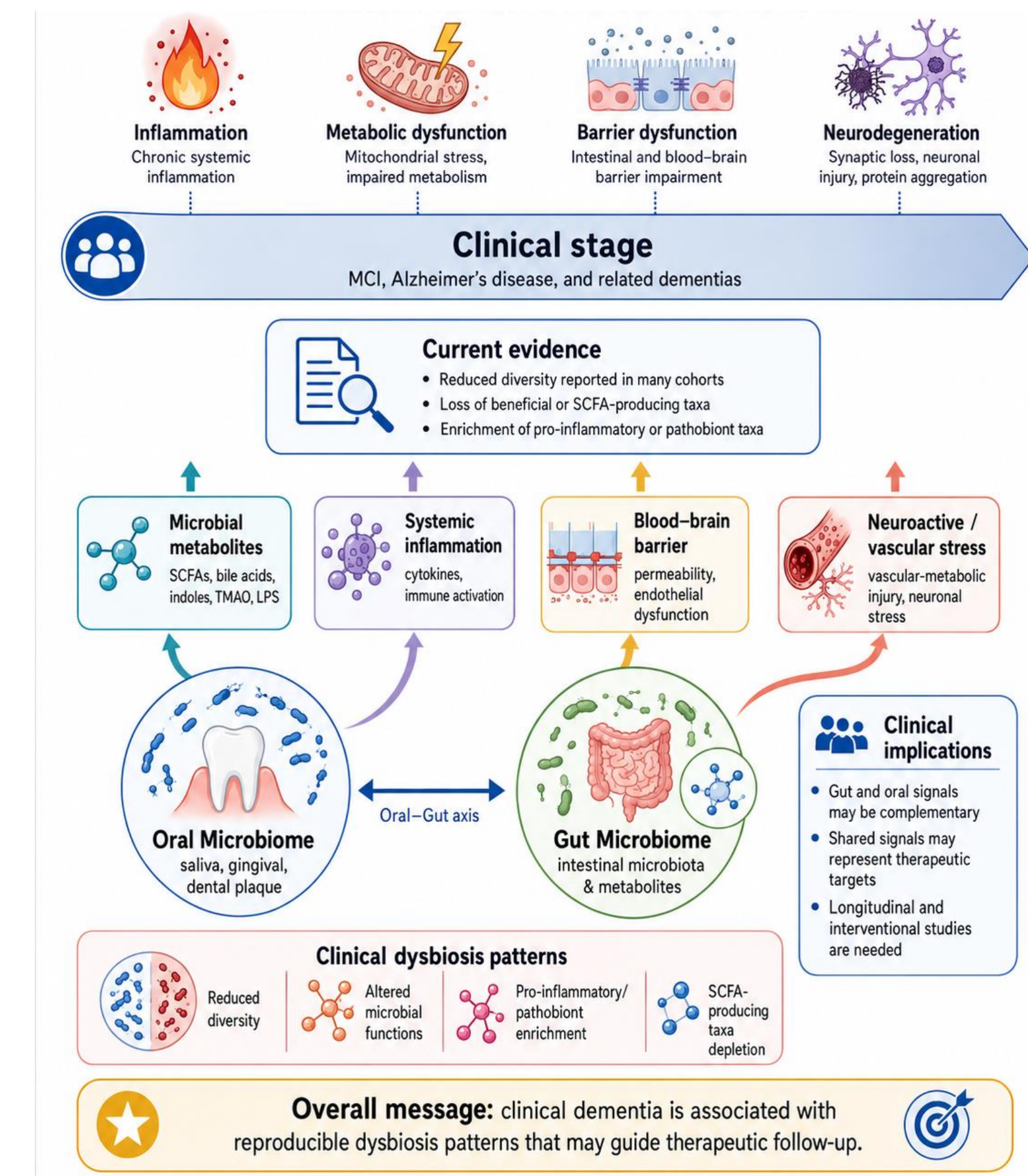
In mild cognitive impairment and clinical dementia, studies more consistently report microbial dysbiosis, although results remain heterogeneous across cohorts and methods.

Common patterns include reduced microbial diversity, depletion of beneficial or short-chain-fatty-acid-producing taxa, and enrichment of pro-inflammatory/pathobiont organisms, including shifts involving Firmicutes, Bacteroidetes, Proteobacteria, and Bifidobacteria.

Clinical studies also highlight altered microbial metabolic functions related to inflammation, barrier integrity, neuroactive metabolites, and vascular-metabolic dysfunction.

Paired gut/oral microbiome work, including studies in Hispanic older adults with cognitive impairment, suggests that oral and gut communities may provide complementary information.

Overall, clinical-stage evidence supports priority therapeutic targets focused on restoring beneficial taxa, improving oral health, modifying diet, and targeting microbial metabolites and inflammatory pathways.



CONCLUSIONS AND PERSPECTIVES

Human cohort studies support a growing role for the gut and oral microbiome across the dementia continuum, from preclinical brain vulnerability to mild cognitive impairment and clinical dementia.

The most consistent signals include microbial dysbiosis, reduced diversity, depletion of beneficial or short-chain-fatty-acid-producing taxa, enrichment of pro-inflammatory/pathobiont organisms, altered microbial metabolic functions, and emerging oral-gut microbial patterns.

These findings suggest that microbiome changes may reflect vascular, inflammatory, metabolic, and neurodegenerative processes that begin before overt cognitive decline.

Preclinical studies link microbiome composition with amyloid/tau biomarkers, cerebral small vessel disease, executive function, and early cognitive vulnerability.

Clinical studies in MCI and dementia show stronger evidence for dysbiosis, but findings remain heterogeneous because of differences in cohort design, sequencing methods, diagnostic definitions, and analytic pipelines.

Work from our group strengthens a vascular-metabolic-oral-gut-brain axis framework by connecting microbiome features with cerebral small vessel disease, executive function, gut/oral microbial patterns in cognitive impairment, and Life's Essential 8-related microbiome diversity and cognition.

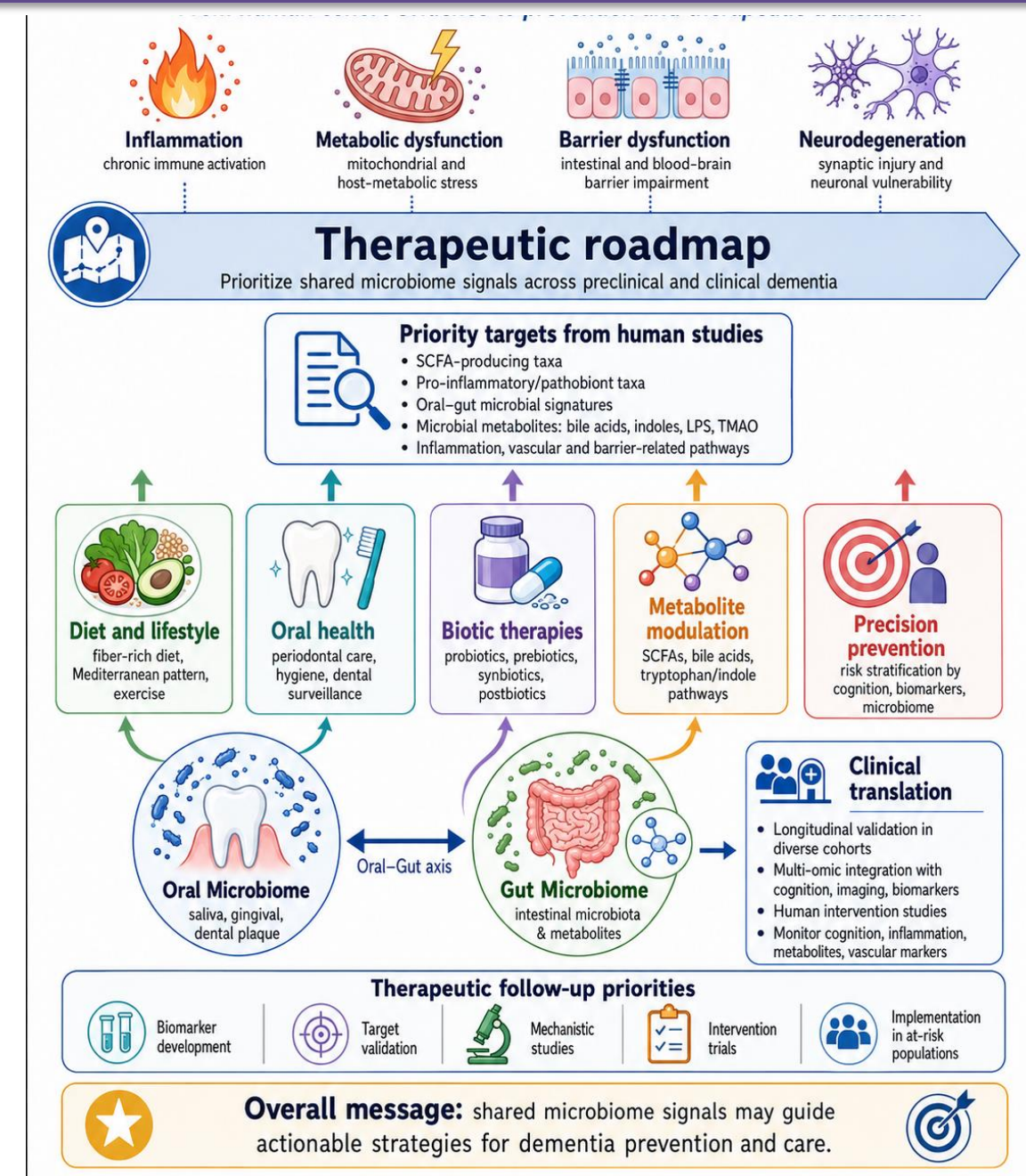
Future studies should prioritize longitudinal, diverse, multi-omic cohorts integrating gut and oral microbiome profiling with metabolomics, inflammatory markers, neuroimaging, vascular brain injury, cognition, and AD biomarkers.

Key targets include SCFA-producing bacteria, pro-inflammatory taxa, oral-gut signatures, bile acids, indoles, LPS, TMAO, and pathways related to inflammation, barrier dysfunction, vascular injury, and neurodegeneration.

Promising therapeutic directions include diet and lifestyle modification, oral health interventions, probiotics, prebiotics, synbiotics, postbiotics, and microbial metabolite modulation.

Overall, consistent microbiome signals may help define actionable targets for dementia risk prediction, prevention, and therapeutic development.

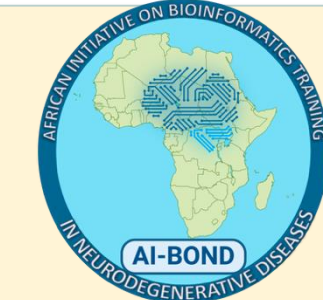
THERAPEUTIC ROADMAP



CONTACT



Bernard Fongang, Ph.D.
Glenn Biggs Institute
UT Health San Antonio
fongang@uthscsa.edu
www.aibond.org



AAIC 26

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