



National Institute of Environmental Health Sciences
Your Environment. Your Health.

Impact of Environmental Exposures on Gut-Brain Signaling in Neurological Conditions



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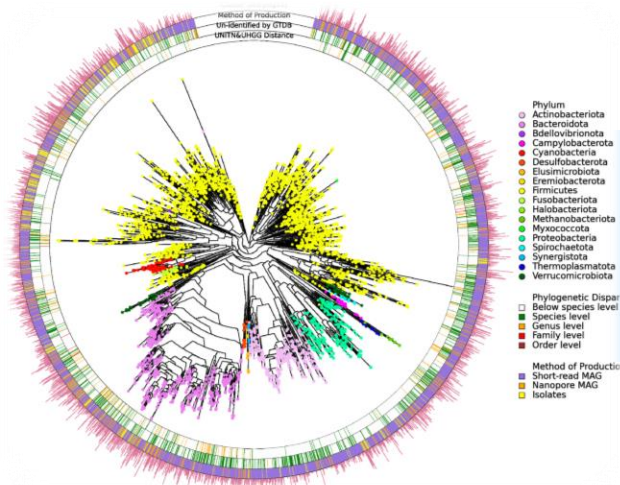
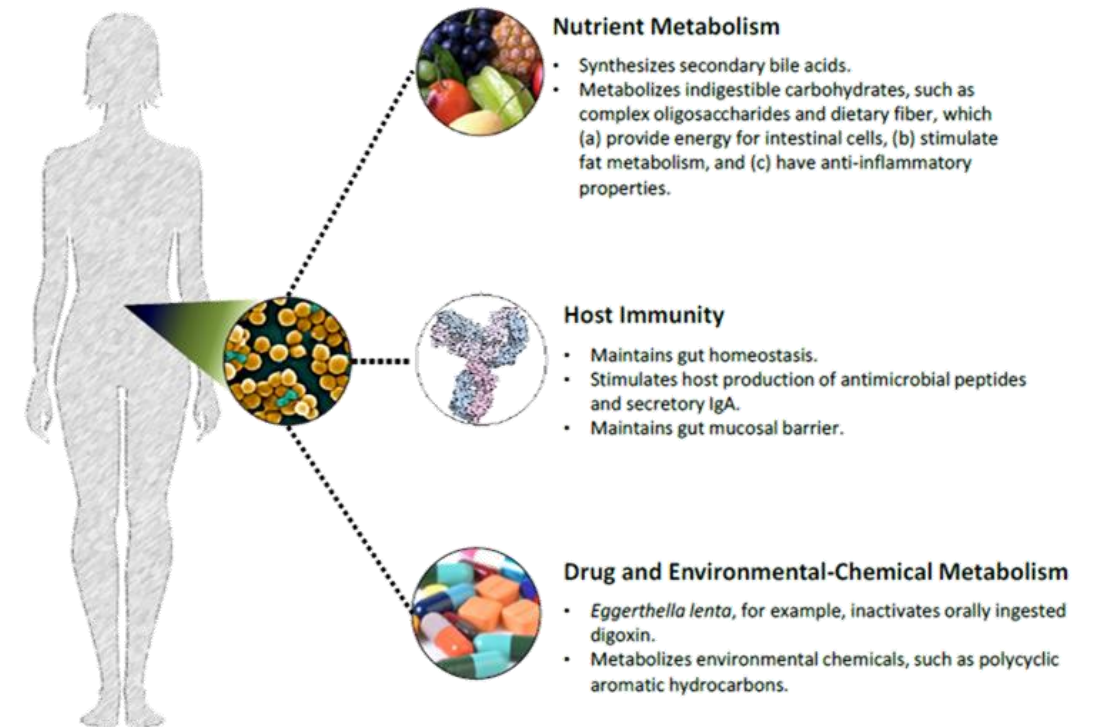
Outline

- Gut microbiome as a mediator of human health and disease
- What is the gut-brain axis?
- An ongoing discussion: retreat and workshops
- Promising case studies
- NOFO objectives



Background: Gut Microbiome

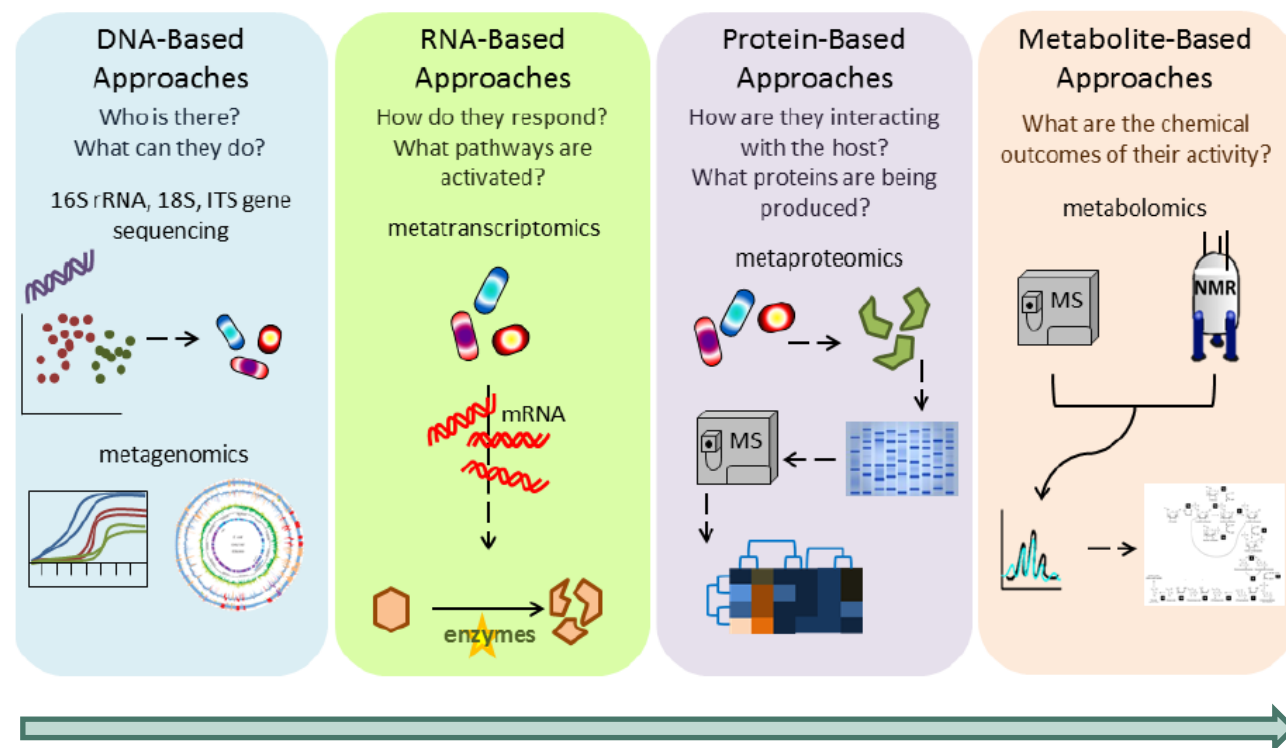
- The **human microbiome** comprises bacteria, archaea, viruses, and eukaryotes which reside within and outside our bodies.
- The **microbiome** is the collection of all **genomic elements** within a distinct community of microorganisms in a distinct environment.



The **gut** is the richest ecosystem of **microbes** in the human body and has **great influence** on our health.

Trends in Microbiome Studies

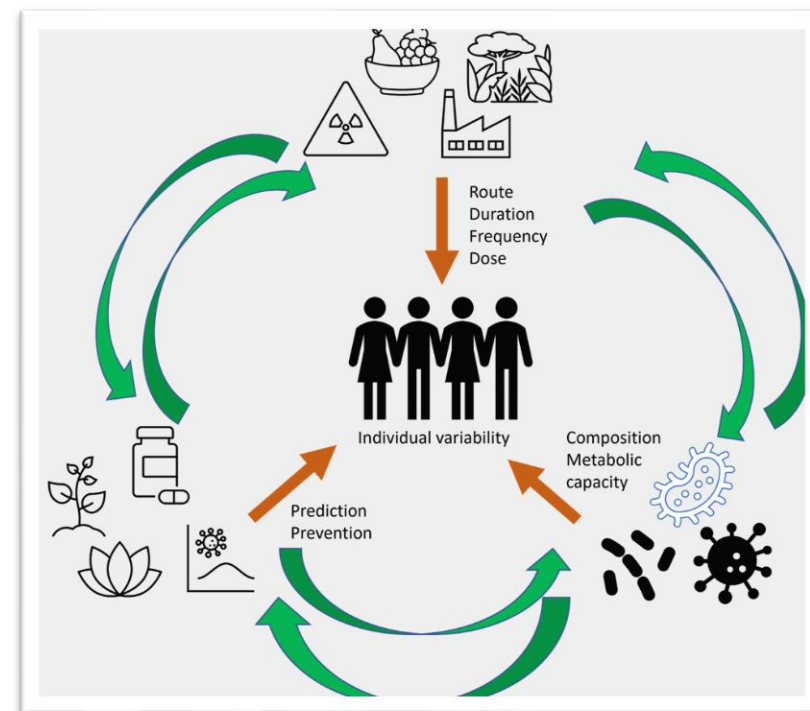
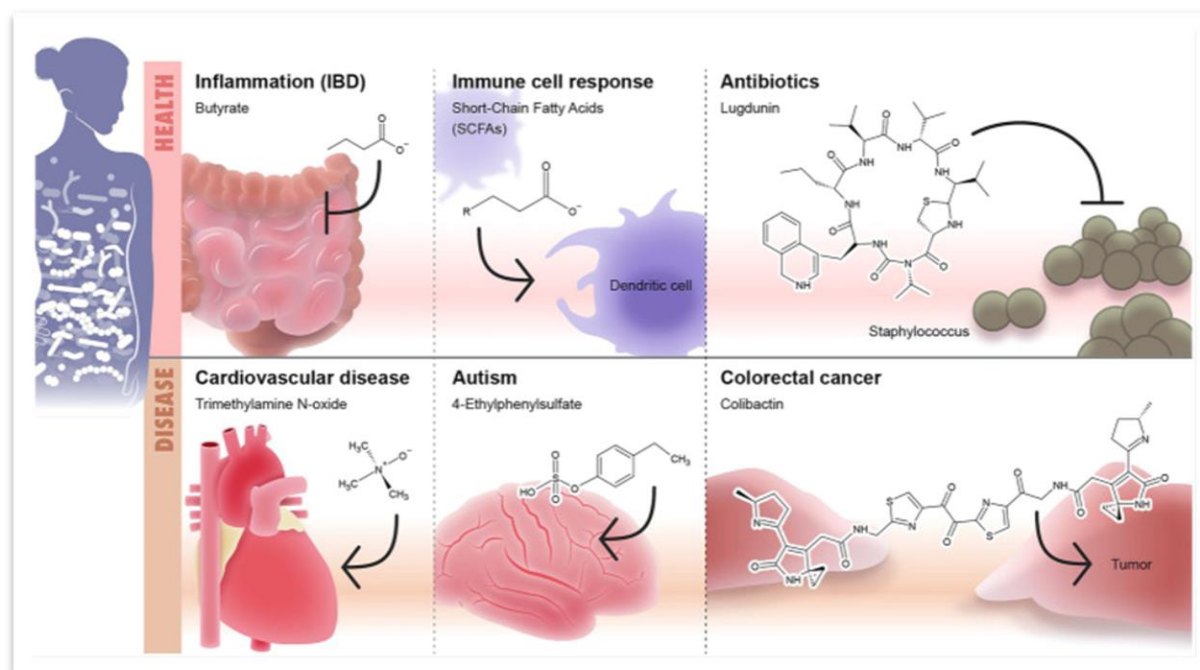
- Development of more accurate predictive models
- A better understanding of factors affecting microbial community structure and function
- New approaches to study microbe-microbe interactions and microbial associations with specific host tissues
- A more comprehensive view of the roles of the microbiome in diseases
- Development of microbiome-based biomarkers for disease risk and detection
- Development of microbiome-based prevention and intervention strategies



Increased “applicability” to health intervention

Microbiome as a Mediator of Health and Disease

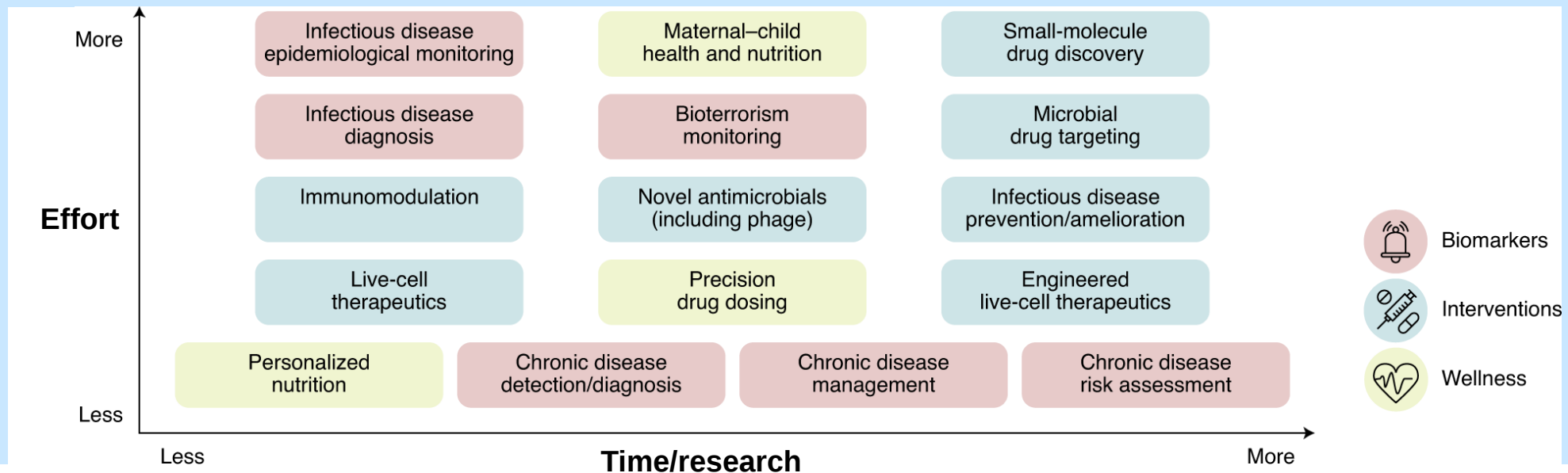
- Microbiome-secreted molecules maintain host health and have been implicated in disease pathogenesis.
- Gut microbiome may mediate the adverse outcomes of toxicants or be a direct target of toxicity.
- Gut microbes may metabolize toxicants, thus conferring a layer of interindividual variability in host response.



Precision Environmental Health

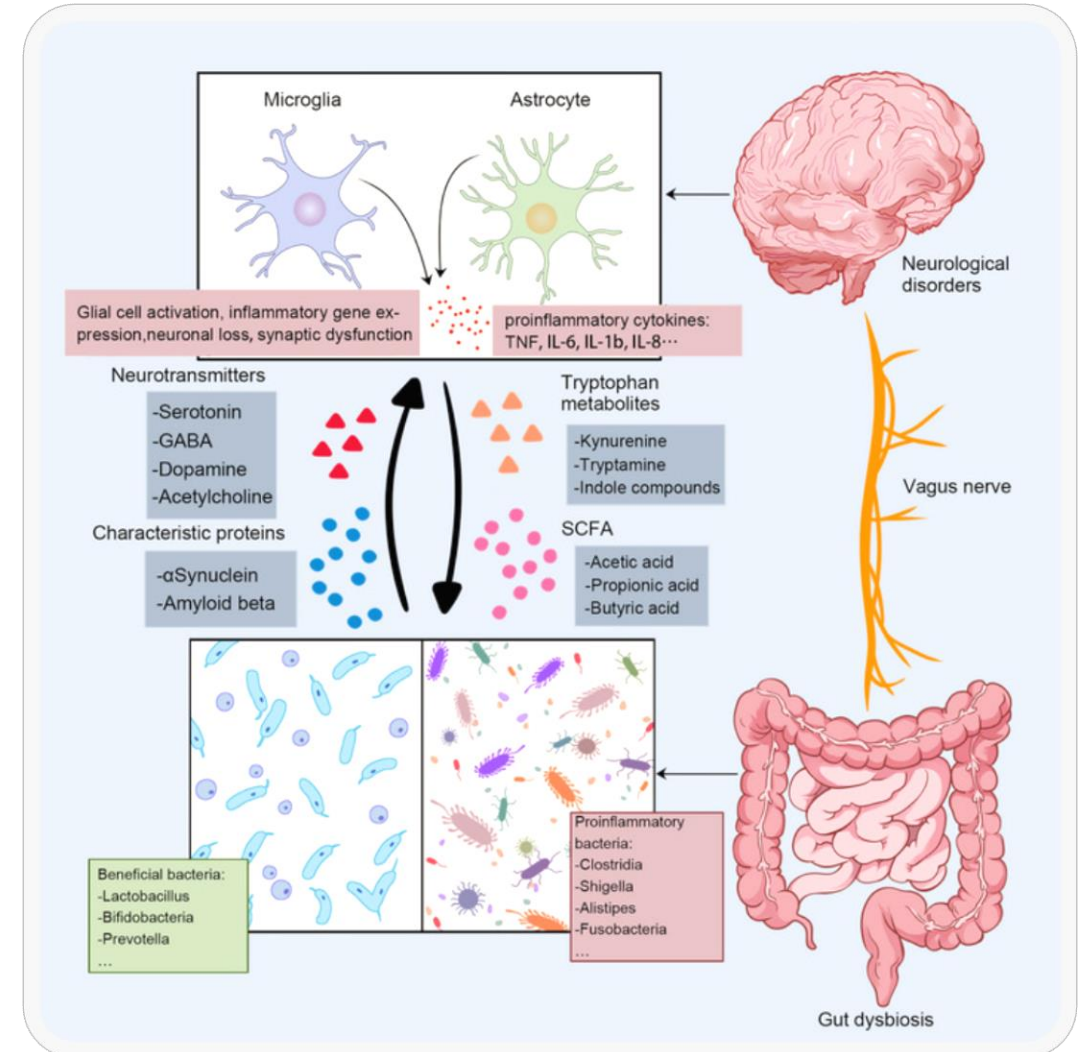
Identification of personalized exposure-response relationships characterized by multi-systems approaches (with multi-levels: molecular, cellular, organism, and multi-omics) to **predict risk** for: disease or exacerbation of disease, and individualized **prevention/intervention** for public health benefit

Microbiome as a Molecular Signature or Therapeutic Target



Background: Gut-Brain Connection

- The **gut-brain axis** is a bi-directional pathway linking the gut (and gut microbiome) to the central nervous system.
- **Facilitates communication** through vagus nerve, immune system, and microbial metabolites.
- **Neuroinflammation is a major mechanism** by which microbial dysbiosis affects the brain.
- Studies in germ-free mice indicate that **absence of a microbiome** confers **differences in brain** physiology and expression of neurotransmitters
 - Suggests a crucial role for gut and microbiome signaling in neurodevelopment and pathophysiology.





NIEHS Workshops

Microbiome workshop dives deep into expanding field

More than 500 researchers — from senior scientists to undergraduate students — participated in a virtual NIEHS workshop.

BY JOHN YEWELL

NIEHS played virtual host to a wide-ranging look at the latest research on the microbiome and environmental health during a Feb. 23-24 workshop. Some 500 participants joined over 70 speakers, ranging from lab heads to undergraduate students.

Scientists from across the institute who are interested in how the microbiome influences environmental health collaborated to organize the workshop. (Image courtesy of NIEHS)



The Impact of Environmental Exposures on the Microbiome and Human Health Workshop

Goals:

- Understand the relationship between environmental agents, the microbiome, and human health
- Build a network of environmental health microbiome researchers
- Determine if best practices can be developed by assessing environmental contaminants and the microbiome

At the Crossroads of Exposures, Microbiome, and the Nervous System Workshop

Topics explored:

- The developing microbiome
- Aging
- Novel technologies
- Strategies for intervention
- Role of nutrition
- Importance of considering environmental exposures

Environmental Factor

Your Online Source for NIEHS News

OCTOBER 2021

Home Science Highlights Community Impact Papers Published

Scientists explore exposures, microbiome, and nervous system

Seventeen experts examined the gut-brain connection and its role in environmental health during two-day NIEHS workshop.

Multi-NIH IC Workshop



Publication



Gastroenterology
Volume 162, Issue 6, May 2022, Pages 1574-1582



Meeting Summary

2021 Workshop: Neurodegenerative Diseases in the Gut-Brain Axis—Parkinson's Disease

Gary M. Mawe¹  , Kirsteen N. Browning², Fredric P. Manfredsson³,
Michael Camilleri⁴, Frank A. Hamilton⁵, Jonathan A. Hollander⁶,
Beth-Anne Sieber⁷, Patricia Greenwel⁵, Terez Shea-Donohue⁵, John W. Wiley⁸



Workshop Goals:

- Evaluate gut-brain communication in neurodegenerative disorders (NDs)
- Coordinate care of motor symptoms and nonmotor GI dysfunction in patients with Parkinson's disease (PD)
- Assess potential of GI tract as a source of biomarkers and novel therapeutic targets for NDs
- Facilitate cross-talk among brain-gut investigators to identify collaborative opportunities

Workshops Highlighted Enticing Opportunities

Environmental exposures may perturb communication between the gut and brain. Future research may inform ways to leverage the gut-brain axis to benefit public health:

Mechanisms

Delineate which microbial metabolites, signaling pathways, and modes of communication between the gut and brain are most heavily implicated in neurological disorders.

Models

Leverage different models which can provide advantages at different levels of scientific inquiry.

Lifespan

Consider all lifespan factors in study design, including windows of susceptibility for exposure, early life development of the microbiome, and time of disease onset.

Collaboration

Create opportunities for cross-disciplinary collaborations.

Translation

Develop gut-focused detection, prevention and intervention strategies to decrease etiological risk, slow progression or possibly reverse neurological condition(s).



Spotlight - Parkinson's Disease



- First described by James Parkinson (1817)
- Progressive, neurodegenerative disorder
- Afflicts approximately 1 million people in the US
- Typically diagnosed after age 55 (>90%)
- No known treatment to cure/slow disease progression

Pathophysiology:

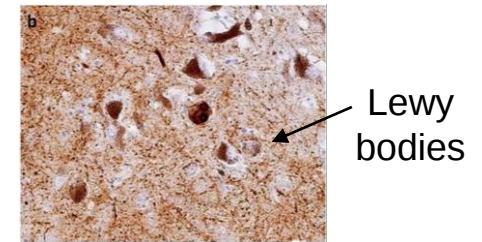
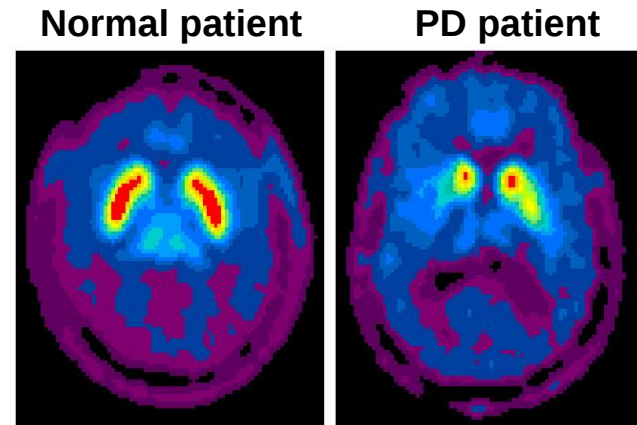
- ↓ Dopamine neurons in the substantia nigra
- ↑ Eosinophilic inclusion bodies (Lewy bodies)

Symptoms:

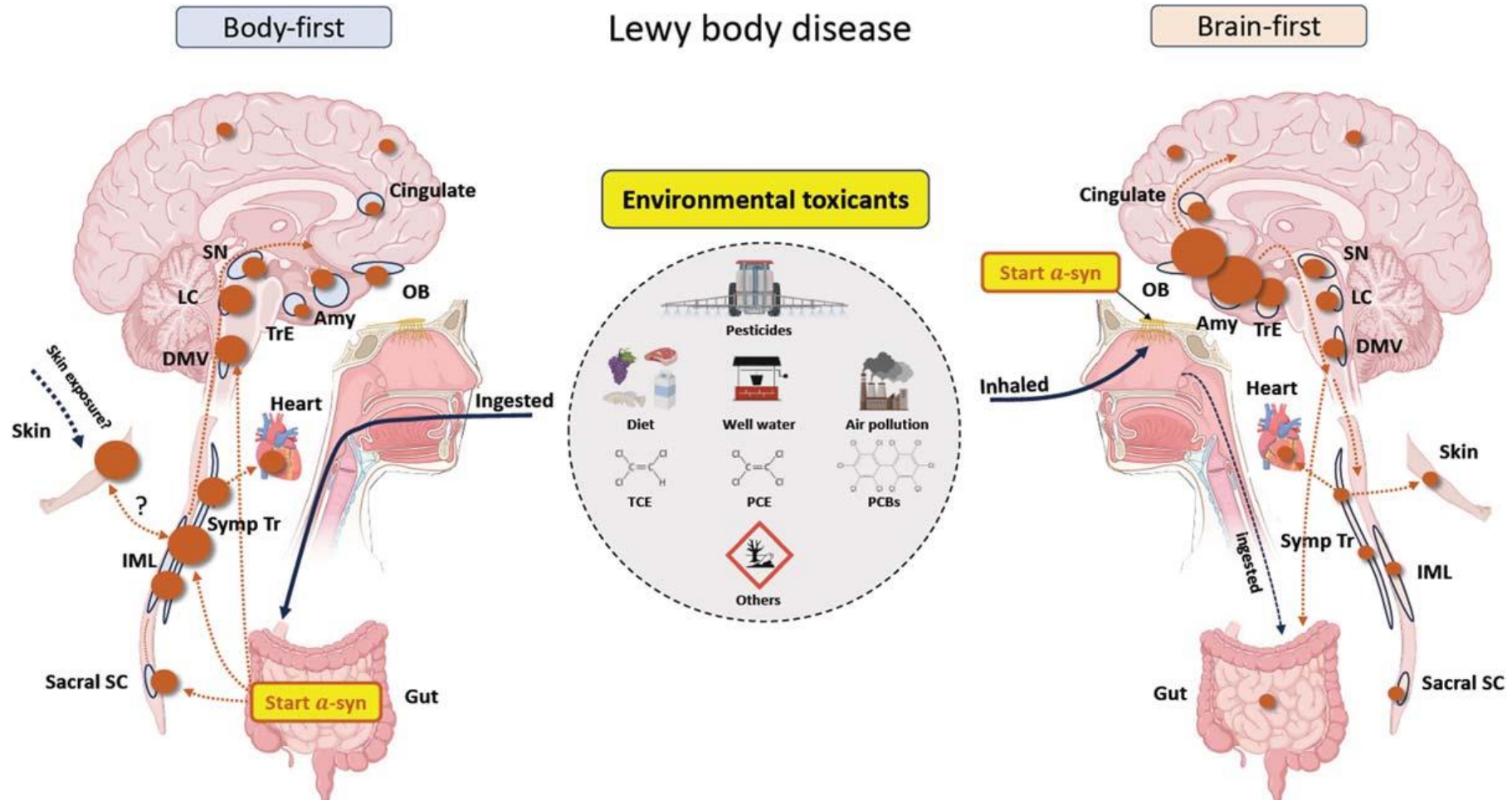
- Involuntary movement
- Resting tremor
- Muscle rigidity
- Gait/postural disturbance
- Autonomic impairment

Risk Factors:

- **Genetic** (e.g., mutations in parkin, LRRK2)
- **Environmental** factors contribute to risk for and progression of disease (e.g., agrichemicals, metals, head trauma)

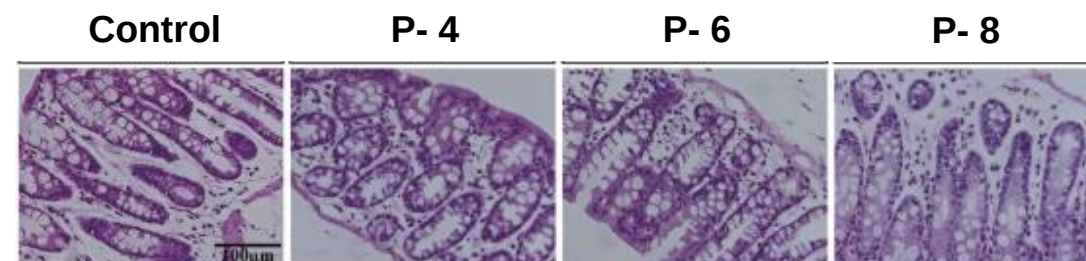


Parkinson's Disease Etiology: A Paradigm Shift!



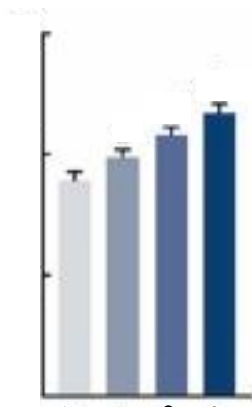
Pesticide Linked with Gut and Brain Pathology in PD Mouse Model

- Injected paraquat (PQ) or saline 2X/week (15 mg/kg) for 4, 6, or 8 weeks
- PQ dose impacted gut microbiota diversity and abundance
- Study shows PQ exposure correlated with gut dysfunction and shared PD pathological indicators in the brain

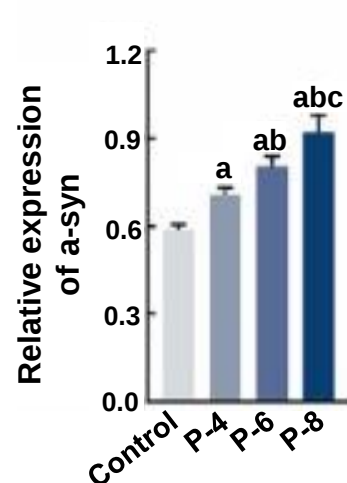


Longer PQ exposure associated with more damage in colon wall

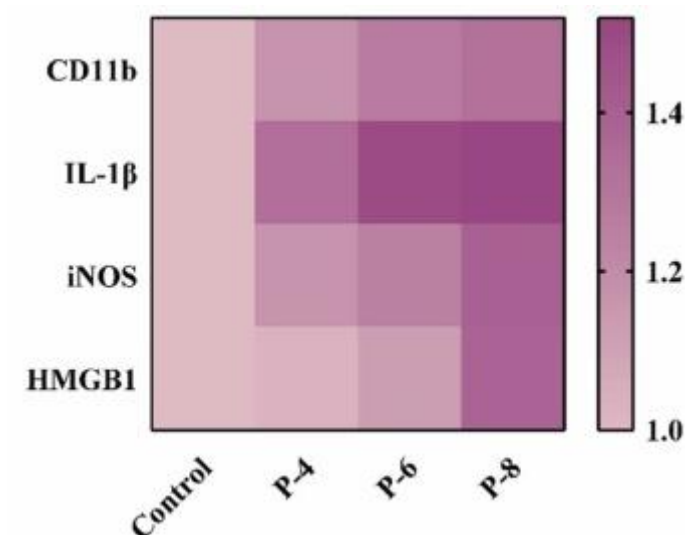
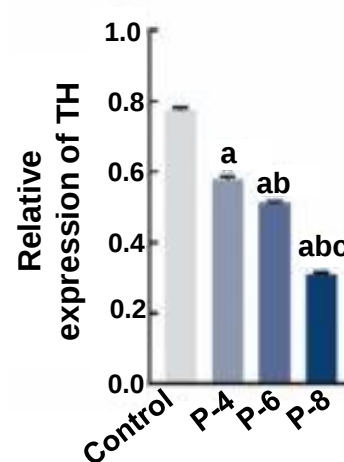
colon



midbrain



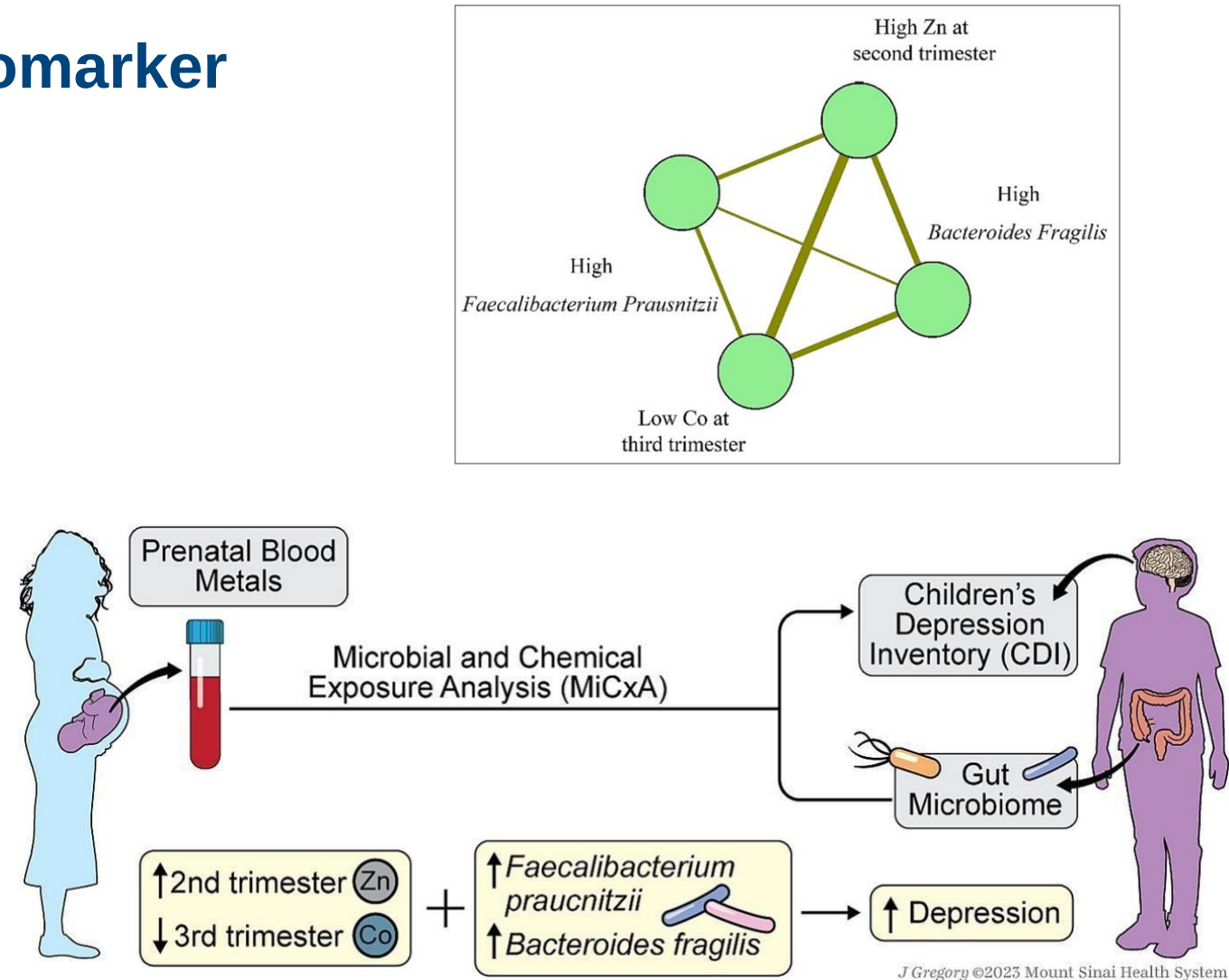
midbrain



Microbiome as a Predictive Biomarker

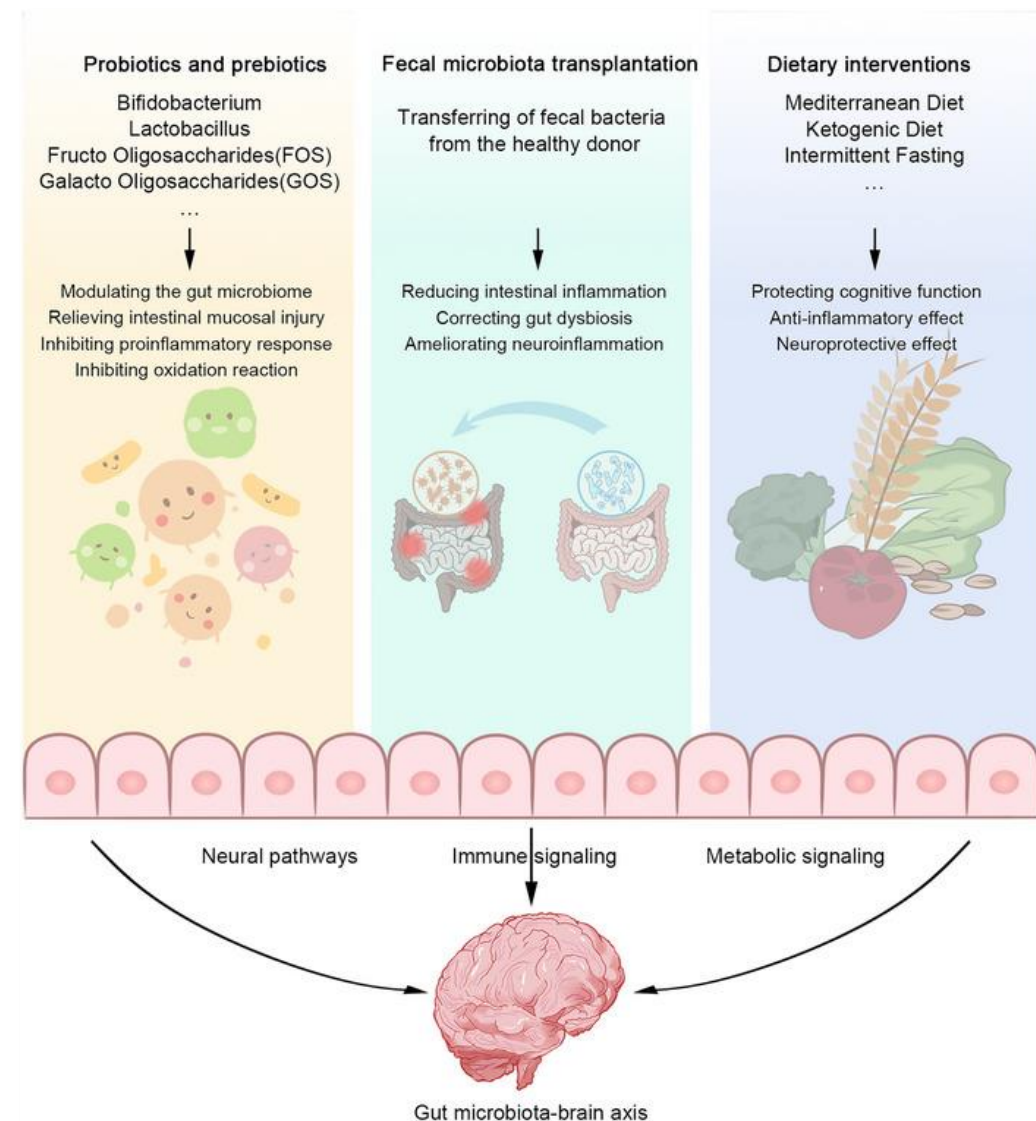
Metals, Microbes, and Depression

- Used a novel machine-learning method to identify **metal-microbial interactions**
- Components of external and internal exposome associated with childhood depression symptoms
- Children with specific gut microbial cliques and prenatal metal exposures have **increased depression symptoms**



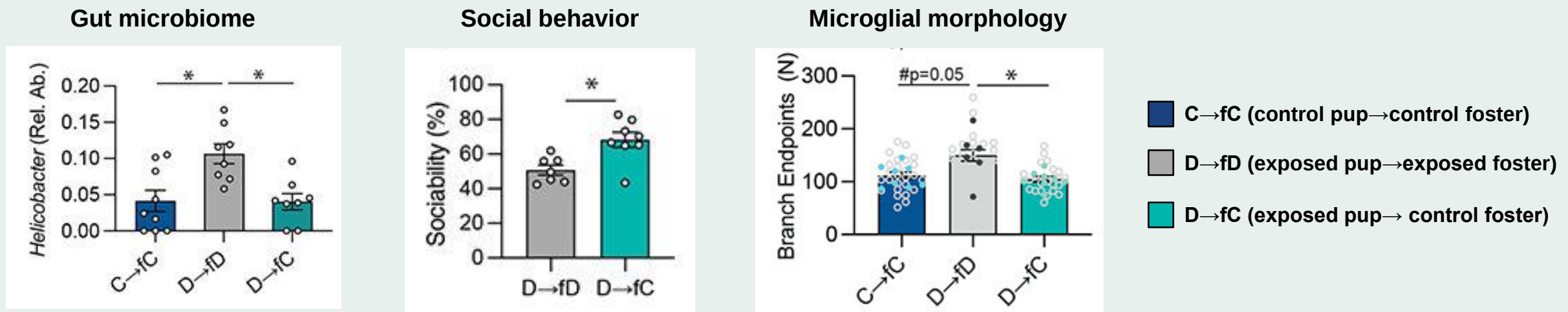
Gut-Brain Interventions

- Therapeutic interventions act through neural, immune, metabolic signaling pathways.
- Common therapeutic interventions:
 - Probiotic and prebiotic supplementation
 - Fecal microbiota transplantation
 - Dietary modification
- Evidence suggests these **interventions can treat or delay neurological disorders by modulating gut microbiota.**



Gut Microbiome Prevents Exposure-Induced Behavior, Brain Changes

- Combined prenatal air pollution and maternal stress exposure altered social behavior and microglial morphology in male pups
- Exposed males had significantly different gut microbiome composition compared to controls
- Cross-fostering shifted the gut microbiome and prevented social deficits and microglial alterations



RFA Proposal: Impact of Environmental Exposures on Gut-Brain Signaling in Neurological Conditions



Purpose: To expand and leverage the role of the gut microbiome-brain axis for improved detection, prevention, and intervention strategies for environmental exposure-induced neurological diseases.



Program Scope

Project Examples:

- Use of applicable model systems to elucidate mechanisms linking gut perturbations and environmental exposures to neurological endpoints
- Characterization of neuroactive microbial metabolites and target receptors in the context of toxicant-induced neurological disease progression
- Identification of gut microbiota signatures that may explain resilience or protection from neurological disease risk following environmental exposures
- Identifying or piloting potential intervention targets and strategies





Discussion

Council Reviewers

Dr. Cathrine Hoyo

Dr. Darryl Hood