The Gut-Brain Axis: A Frontier in Neuroscience and Medicine

The gut-brain axis has emerged as a fascinating frontier in neuroscience and medicine. Mounting evidence suggests that the trillions of microbes residing in our gut can influence brain function and behavior through neural, endocrine, immune, and other biochemical pathways. This gut microbiome-brain communication has been implicated in numerous neurological disorders like depression and Alzheimer's disease. As a result, there is immense interest in exploring ways to modulate the gut microbiome composition and metabolism as a potential therapeutic strategy targeting these conditions.

OniX AI's Unparalleled Access to the Research Landscape

What sets OniX AI apart is its unparalleled access to the research landscape that includes preclinical and clinical data. OniX has one of the most extensive preclinical data in the industry, including proprietary information not readily available in the public domain. By harnessing this wealth of fully standardized global data, OniX AI provides an unmatched window into the current and ongoing research landscape. This real-time intelligence can significantly impact strategic decision-making, R&D prioritization, partnership opportunities, go/no-go evaluations, and investment decisions – empowering each company to stay ahead of the curve in an ever-evolving industry.

Mechanisms of Action for Gut Microbiota-Brain Axis for Neurological Disorders

In this draft white paper, we highlight assets in several key Mechanisms of action (MoA) that could be targeted within the gut microbiota-brain axis to treat neurological disorders such as depression or Alzheimer's disease:

1. **Probiotics/Prebiotics:** Introducing beneficial bacteria or substrates that promote the growth of beneficial bacteria in the gut to modulate the gut microbiota composition and improve brain health.
2. **Microbial Metabolite Modulation:** Targeting specific microbial metabolites, such as short-chain fatty acids (SCFAs) or neurotransmitter precursors, to regulate neurotransmitter levels and neurotransmission pathways in the brain.
3. **Mucosal Barrier Enhancement:** Strengthening the intestinal barrier function to prevent the translocation of harmful bacteria or their byproducts into systemic circulation, thereby reducing neuroinflammation and neuronal damage.
4. **Immune Regulation:** Modulating the immune response in the gut to reduce inflammation and cytokine production, which can indirectly affect brain function and alleviate symptoms of neurological disorders.
5. **Neurotransmitter Production/Modulation:** Stimulating the production of neurotransmitters (e.g., serotonin, dopamine) by gut microbes or modulating their activity to regulate mood and cognitive function.

6. **Neurotrophic Factor Stimulation:** Promoting the production of neurotrophic factors (e.g., brain-derived neurotrophic factor, BDNF) by gut microbes or their metabolites to support neuronal survival, growth, and plasticity.

Modulating the Gut-Brain Axis: Unlocking New Therapeutic Approaches

Whether you are a biotech entrepreneur, pharma executive, or academic researcher, our AI-powered reports empower you with authoritative insights and a competitive edge in the quest to modulate the gut-brain axis and unlock new therapeutic approaches for neurological disorders. By leveraging OniX's comprehensive data and analytical capabilities, you can navigate the complex landscape of gut microbiome research and identify the most promising targets, mechanisms of action, and emerging players in this exciting field.

Modulation of the gut microbiota-brain axis to treat neurological disorders such as depression or Alzheimer's disease

Introduction to the gut microbiota-brain axis and its role in neurological disorders

- Overview of the gut microbiota-brain axis and depression
- Overview of the gut microbiota-brain axis and Alzheimer's disease

Mechanisms of action (MoA) that could be targeted within the gut microbiota-brain axis to treat neurological disorders such as depression or Alzheimer's disease:

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Number of Projects/Assets/Companies

Mode of Action	Preclinical	Clinical	Biotech/Pharma
1. **Probiotics/Prebiotics**	400+	300+	30+
2. **Microbial Metabolite Modulation**	10+	10+	15+
3. **Mucosal Barrier Enhancement**	20+	100+	5+
4. **Immune Regulation**	200+	30+	15+
5. **Neurotransmitter Production/Modulation**	20+	25+	10+
6. **Neurotrophic Factor Stimulation**	80+	60+	20+

Probiotics/Prebiotics

Preclinical studies

Examples

Project: Harnessing chemical biology to control pathogenic bacteria and regulate the gut microbiota

Organization: University of British Columbia, Canada
Project Leader: Katherine Ryan
Research Question:
This research has two main goals:
Develop new antibiotics to treat infections caused by antibiotic-resistant bacteria.
Understand how beneficial bacteria survive in the human gut.
Stage:
This is a basic science research proposal, not directly developing drugs or treatments.
Methods:
The research will use a two-pronged approach:
Develop new antibiotics by studying bacterial chemistry to identify targets for drugs.
Investigate the biochemical pathways that allow beneficial bacteria to thrive in the gut.
Drug Development:
While not directly developing drugs, this research aims to provide the foundational knowledge needed for future antibiotic and probiotic development.
New antibiotics could target specific weaknesses in antibiotic-resistant bacteria.
Understanding gut bacteria survival could aid in developing probiotics or nutritional supplements to promote gut health.

Clinical development: Ongoing trials, target indications, key companies involved

Example

Project: Prebiotic and Probiotic Modulation of the Gut Microbiota-gut-brain Axis During Acute Stress

ID: NCT05392556
Phase: N/A
Intervention
This clinical trial (NCT05392556) will investigate the effects of a combination of prebiotics and probiotics on the gut microbiome and brain function during acute stress. Prebiotics are dietary fibers that promote the growth of beneficial gut bacteria, while probiotics are live microorganisms that can improve gut health.
Route of Administration
The specific route of administration for the prebiotics and probiotics is not available in the summary provided. It is likely to be oral, possibly in capsule or drink form.
Mode of Action
The researchers hypothesize that the prebiotics and probiotics will work together to modify the gut microbiome composition. This, in turn, may influence brain function and stress response through the gut-brain axis. The gut-brain axis is a complex communication pathway between the gut microbiome and the central nervous system.
Target
This study is targeting healthy adults between the ages of 17 and 39.
Conditions
The primary focus of the study is on the effects of the intervention on gut microbiome composition and stress response in healthy individuals. It is not targeting any specific disease.
Sponsors
The sponsor information for this trial is United States Army Research Institute of Environmental Medicine.

Publications:

Example

Project: Vitamin B5 supplementation enhances intestinal development and alters microbes in weaned piglets.

Researcher: Wang Xin X
ID: https://www.tandfonline.com/doi/full/10.1080/10495398.2024.2335340

Research Question:

- This study investigated the effects of different dietary vitamin B5 (VB5) levels on gut health and function in weaned piglets.

Stage:

- This is an in vivo animal study using weaned piglets.

Methods:

- The researchers fed piglets three diets with varying levels of vitamin B5 supplementation (0 mg/kg, 10 mg/kg, and 50 mg/kg) for 28 days.
- They then measured various markers of gut health, including:
    - Intestinal weight
    - Villus height and crypt depth (measures of intestinal surface area)
    - Goblet and endocrine cell numbers (involved in mucus production and hormone secretion)
    - Cell proliferation rates in the gut
    - Gut microbiota composition (types and abundance of bacteria)
    - Short-chain fatty acid levels (produced by gut bacteria)

Drug Development:

- This study is not directly developing a drug, but rather investigating the effects of a dietary vitamin on gut health.

Key Findings:

- Higher dietary vitamin B5 supplementation (50 mg/kg) increased:
    - Large intestine weight
    - Villus height and crypt depth in the small intestine
    - Goblet and endocrine cell numbers in the small intestine
    - Cell proliferation rates in the cecum and colon
    - Levels of beneficial gut bacteria
    - Levels of certain short-chain fatty acids (isobutyric and isovaleric acid) were reduced, while butyric acid showed a decreasing trend.
- Lower dietary vitamin B5 supplementation (0 mg/kg) was associated with:
    - Reduced markers of gut health and function
    - Increased levels of harmful gut bacteria

These findings suggest that vitamin B5 supplementation may improve gut health and function in weaned piglets.

Microbial Metabolite Modulation

Preclinical data

Examples

Project: NCS-FO: Developing engineering solutions to investigate microbiome-to-neuron communication

Organization: University of Maryland, College Park

Project Leader: Reza Ghodssi

Research Question:
This research aims to develop an engineering tool to measure and predict communication between the gut microbiome and the brain (gut-microbiome-brain axis).
Stage:
This is an early-stage engineering project to develop a new research tool.
Methods:

- The researchers will design and build a microfluidic device to grow gut epithelial cells, gut microbes, and connected neural tissue together.
- Sensors embedded in the device will measure the release of serotonin (a key signaling molecule) from gut cells in response to gut microbes.
- The researchers will also monitor electrical activity in the neural tissue to understand how serotonin signaling affects the nervous system.
- Machine learning will be used to analyze the data and identify patterns in communication between the gut, microbes, and brain.

Drug development:
This project is not directly developing a drug, but rather a new research tool to investigate the gut-brain axis.
Additional Information:
This project aims to bring together researchers from various disciplines (engineering, biology, neuroscience, etc.) to develop a new approach to studying the gut-brain axis.
The project also promotes diversity in research by including women and undergraduate students.

Clinical development: Ongoing trials, target patient populations, companies involved

Examples

Project:
ID: **Phase**:

Publications:

Example

Project: Short-chain fatty acids in brain neuroinflammation: modulators of immunity and neural stemness
Researcher: TBA
ID:TBA
Research Question:

- How do changes in gut microbiota, and the resulting changes in short-chain fatty acids (SCFAs), contribute to autoimmune diseases like multiple sclerosis (MS)?

Stage:

- This is a preclinical in vitro study, likely using human brain organoids and/or cultured human cells.

Methods:

- Researchers will investigate how different SCFAs, produced by gut microbes, affect various cell types in the central nervous system (CNS).
- This will include studies on:
  - Blood-brain barrier integrity
  - Immune cells
  - Neural stem/precursor cells
  - Mature neurons
  - Glial cells

- They will likely use a multidisciplinary approach including metabolomics, immunology, neuroscience, and bioinformatics.
- Cutting-edge techniques like single-cell RNA sequencing and human brain organoid cultures may be employed.

Drug Development:

- This research is not directly developing a drug, but rather investigating how gut microbiota metabolites influence the CNS in MS.
- Understanding these mechanisms could lead to new therapeutic approaches for MS and potentially other neuroinflammatory/degenerative diseases.

Additional Information:

- This project aims to improve our understanding of the link between gut health, microbiota, and autoimmune diseases in the brain.
- The research will use open-access science and involve public engagement activities.

Mucosal Barrier Enhancement

Preclinical data

Examples

Clinical development: Ongoing trials, target patient populations, companies involved

Examples

Publications:

Example

Project:
Researcher:
ID:

Immune Regulation

Preclinical studies

Examples

Project: The gut brain axis: microbial impact on neural function

Organization: University Of Massachusetts Med Sch Worcester
Project Leader: Mark Alkema
Research Question:
This study investigates the influence of gut microbiota on neural function and migraines. Specifically, it aims to identify how diet and gut bacteria contribute to neurological disorders.

Stage:
The research is in the preclinical development stage, using the nematode C. elegans as an animal model (in vivo).
Methods:

- C. elegans with a mutated calcium channel gene (unc-2/CaV2?(FHM1)) will be used to model migraines.
- The impact of different bacterial diets on the seizure behavior of these C. elegans will be examined.
- Researchers will explore how vitamin B12 produced by gut bacteria affects both gut metabolism and brain function.

Drug Development:
While not the main focus, this research may inform the development of probiotics to improve symptoms of neurological disorders.

Project: Mechanisms underlying regulation of susceptibility to CNS autoimmunity by commensal Lactobacillus species

Organization: University Of Vermont & St Agric College
Project Leader: Theresa Lynn Montgomery
Research Question:
This research investigates the link between gut microbiome and multiple sclerosis (MS). Specifically, it explores how a specific gut bacteria, Lactobacillus reuteri, influences the development of MS-like symptoms.
Stage:
The research is in the preclinical development stage, using a mouse model of MS (in vivo).
Methods:

- The study will analyze how L. reuteri affects immune cells and glial cells in the context of MS.
- Researchers will examine the role of L. reuteri-produced tryptophan metabolites in neuroinflammation.
- This project will involve expertise in:
    - Mouse models of MS with microbiome manipulation
    - Neuroimmunology techniques like flow cytometry and functional assays
    - Studying gut bacteria including culturing, isolation, and metabolic analysis
    - Neuropathology techniques to investigate MS lesions and blood-brain barrier integrity
    - Metabolomics analysis of bacterial metabolites

Drug Development:
While not the main focus, this research may inform the development of probiotic treatments targeting the gut microbiome to potentially prevent or manage MS.

Clinical trials: Current pipeline, trial designs, and early results

Neurotransmitter Production/Modulation

Preclinical research

Examples

Project: A forward chemical genetic screen to illuminate the dark matter of the bioactive microbiota metabolome

Organization: Yale University
Project Leader: Noah Wolcott Palm
Research Question:
This research aims to develop a method to identify biologically relevant metabolites produced by gut bacteria, even when hidden amongst many other chemicals.
Stage:
The research is currently in the development stage of a new technology (in vitro).
Methods:

- The study proposes using G-protein coupled receptors (GPCRs) as a tool to detect bioactive metabolites in complex mixtures from gut bacteria.
- They will develop a high-throughput technology based on next-generation sequencing to rapidly screen large numbers of microbial metabolite samples against GPCRs.
- This will involve analyzing metabolomes from individual bacteria to those from complex human gut communities recreated in mice.
- A bioassay-guided approach will then be used to identify the specific metabolites, the bacteria that produce them, and the receptors they interact with.

Drug Development:
While not the main focus, this research may reveal novel therapeutic targets based on the newly discovered interactions between gut bacteria metabolites and human receptors.

Project: Gut-brain axis interplay via STAT3 pathway: Implications of Helicobacter pylori derived secretome on inflammation and Alzheimer's disease

Organization: Department of Biosciences and Biomedical Engineering, Indian Institute of Technology Indore, Simrol, Indore, India
Project Leader: HC Jha
Research Question:
This study investigates how Helicobacter pylori (H. pylori), a bacterium that causes stomach ulcers, might disrupt the gut-brain axis and contribute to Alzheimer's disease (AD).
Stage:
The research is in the preclinical development stage, using cell cultures (in vitro).
Methods:

- The study examined the effects of H. pylori-derived conditioned media (HPCM) on gastric and neuronal cells.
- They used antimicrobial resistant and susceptible strains of H. pylori.
- Researchers observed increased inflammation and activity of proteins associated with AD (APP and APOE4) in HPCM-treated cells.
- They also found evidence of excessive ROS generation and astrogliosis (activation of glial cells) in these cells.
- Finally, the study investigated the role of STAT3, a signaling molecule, and how its inhibition reduced the effects of HPCM on neuronal cells.

Drug Development:
While not the main focus, this research suggests that inhibiting STAT3 may offer a potential therapeutic target for reducing H. pylori-associated neuroinflammation and AD risk.

Clinical development: Approved and investigational agents, combination strategies

Neurotrophic Factor Stimulation

Preclinical studies

Examples

Project: Gut-brain axis in Alzheimer's disease: translational 7T MRI markers and underlying mechanisms

Organization: University Of Missouri-Columbia
Project Leader: Ai-Ling Lin
Research Question:

- How gut microbiota correlates with Alzheimer's disease (AD) progression and if it can be manipulated to slow or prevent the disease.

Stage:

- This is a translational study involving both human participants and preclinical animal experiments (in vivo with animals).

Methods:

- Human participants will undergo PET scans to assess amyloid and tau levels, high-resolution MRI to measure neurodegeneration, and cognitive assessments. Their gut microbiome will also be sequenced.
- Young, healthy mice with triple transgenic AD (3xTg-AD) will receive fecal microbiota transplantation (FMT) from AD patients.
- The researchers will then compare these mice to a control group to assess the impact of the FMT on:
  - Gut microbiome composition
  - Amyloid and tau levels in the brain
  - Neuroinflammation
  - Cognitive function
- Additionally, the researchers will explore the use of:
  - An inhibitor of an enzyme called inducible nitric oxide synthase (iNOS) to reduce brain inflammation
  - A prebiotic supplement (inulin) to promote a healthy gut microbiome
  - A new type of mouse model with iNOS knocked-out to see if it protects against AD pathology even with gut dysbiosis

Drug Development:

- This study is not directly developing a new drug, but rather investigating potential therapeutic targets (iNOS) and preventative measures (inulin) for AD.

Project: BRC-BIO: Interplay Between Intestinal Barrier Function, Aging, and Neurodegeneration

Organization: Christopher Newport University
Project Leader: Anna Salazar
Research Question:

- This research proposes two questions:
  1. Does the decline in gut barrier function with age contribute to aging pathologies observed in the brain and muscle?
  2. Can strengthening the intestinal barrier reverse or delay aging phenotypes?

Stage:

- This is not a specific study but a proposal for future research.

Methods:

- The proposal mentions using cellular and molecular biological methods but doesn't detail the exact experiments.
- One potential future study might involve investigating the effects of manipulating gut barrier function in fruit flies or other models to see if it affects aging and health in the brain and muscles.

Drug Development:

- This research is not directly developing a drug, but rather investigating the gut-brain-muscle connection in aging with the goal of potentially identifying new therapeutic targets to improve healthspan and lifespan.

Project: Microbiome Contributions to Age-Associated Cognitive Decline

Organization: University Of Pennsylvania
Project Leader: Timothy Cox
Research Question:

- Does the gut microbiome of older individuals impair cognitive function through a gut-brain connection mediated by the vagus nerve?

Stage:

- This is a proposal for future research, but the applicant has already conducted some initial experiments using in vivo animal models (mice).

Methods:

- The researcher proposes several aims for future studies:
    - Aim 1: Identify specific bacteria in the aged microbiome that cause cognitive decline. This will likely involve bacterial sequencing and cognitive testing in mice.
    - Aim 2: Determine which gut-to-brain signaling pathways are important for learning and memory. This might involve manipulating the vagus nerve in mice and assessing their cognitive function.
    - Aim 3: Investigate how the aged microbiome affects brain activity during memory formation. This could involve brain imaging techniques in mice.

Drug Development:

- This research is not directly developing a drug, but rather investigating the mechanisms by which the gut microbiome might influence cognitive decline. This knowledge could potentially lead to new therapeutic targets in the future.

Project: Modulating Alzheimer's Disease progression by preserving intestinal health.

Organization: BUCK INSTITUTE FOR RESEARCH ON AGING
Project Leader: MARTIN BORCH JENSEN
Research question:

- Can gut inflammation caused by commensal bacteria contribute to Alzheimer's disease (AD) progression by activating signaling pathways in the brain?

Stage:

- This is a proposal for future research using a fruit fly model of AD (in vivo with animals).

Methods:

- The researcher will investigate how gut inflammation caused by bacteria affects the brain in flies with a build-up of amyloid beta (Aβ), a protein associated with AD.

- The study will focus on the role of specific signaling pathways (JAK/STAT) in glial cells (brain cells) and how they might be influenced by gut-derived inflammatory molecules.
- The researcher will use genetic and potentially pharmaceutical interventions to reduce gut inflammation and see if it improves AD phenotypes in the flies.

Drug development:

- This research is not directly developing a new drug, but rather investigating the role of gut inflammation in AD with the goal of potentially identifying new therapeutic targets in the future.

Clinical trials: Current pipeline, trial designs, and early results

Examples

Project: Effect of Fecal Microbiota Transplantation on Aging and the Underlying Mechanism of Gut Microbiome Restoration: a Randomized Clinical Trial

ID: NCT05598112
Phase: Early Phase 1
Intervention
This clinical trial will investigate the effects of fecal microbiota transplantation (FMT) on aging and the mechanisms by which it might restore a healthy gut microbiome.
Route of Administration
The fecal microbiota will be administered through a colonoscopy or enema.
Mode of Action
The researchers hypothesize that FMT will introduce beneficial gut bacteria into the recipient, improving the overall gut microbiome composition and potentially influencing health and aging processes.
Target
This study is targeting adults over 60 years old.
Conditions
The study will focus on the effects of FMT on aging and the gut microbiome, not targeting any specific disease.
Sponsors
The sponsor is Chinese Academy of Medical Sciences, Fuwai Hospital.

Competitive landscape and market potential

Key players in the gut microbiota-brain axis and its role in neurological disorders space (biotech, pharma, and academic institutions)

(1) Biotech/Startup Companies:

- Kallyope Inc. (New York, USA)
- Axial Biotherapeutics (Boston, USA)
- Finch Therapeutics (Massachusetts, USA)
- Seres Therapeutics (Massachusetts, USA)
- Vedanta Biosciences (Massachusetts, USA)

(2) Pharmaceutical Companies:

- Janssen Pharmaceuticals (Johnson & Johnson)

- Takeda Pharmaceutical Company
- Boehringer Ingelheim
- Pfizer Inc.
- AbbVie Inc.

(3) Academic Institutions:

- Harvard Medical School (Massachusetts, USA)
- Massachusetts Institute of Technology (MIT)
- University of California, Los Angeles (UCLA)
- University of Chicago (Illinois, USA)
- Karolinska Institute (Sweden)
- University of Edinburgh (UK)
- INRA (French National Institute for Agricultural Research)

Partnerships, collaborations, and licensing agreements

Market size and growth projections for gut microbiota-brain axis and its role in neurological disorders