TMCity

Investigating the Gut-Brain Axis for Applications to Brain and Mental Health

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Overview

A recent explosion of research has established the pivotal relationship between the gut and a host of metabolic, neurologic, endocrine, and immune functions [1]. One particularly strong linkage is the gut-brain axis, the two-way biochemical communication between the central and enteric nervous system that links emotional and cognitive areas of the brain with intestinal functions [2]. The gut connection to the brain is so extensive that the gut is sometimes called “the second brain” [3]. This connection is especially intriguing given the complexity of the brain and the slow progress in unraveling its mysteries; understanding the human brain remains one of the greatest scientific challenges of our times [4]. Consequently, finding effective treatments and therapies for brain and mental health also remain elusive, despite the overwhelming personal and societal cost of untreated neurological dysfunctions.

In particular, studies have suggested that a critical component to the gut-brain interaction is the gut microbiota [2], a collection of trillions of micro-organisms that live in the gut. Composed of at least a thousand species of bacteria, the gut microbiome has attracted increasing interest over the past decade as study after study has implicated its potential to be part of both the cause and the cure of several issues in cognitive, mental, and behavioral health [5]. This potential is especially compelling given that many diseases in these areas, such as Alzheimer’s disease and depression, have proven to be unusually resistant to prevention and treatment, despite decades of intensive research and billions of dollars of funding. Hence, the gut microbiome presents itself as a compelling and promising line of research into understanding the basis of and addressing the root causes of these neurological dysfunctions. In short, if brain function can be cracked via the gut microbiome, then the potential for increased progress in brain and mental health treatments could be enormous.

Two neurological issues in particular stand out for their prevalence, cost, and personal devastation: Alzheimer's disease (and related dementias) and depression. Alzheimer's disease and related dementias is estimated to affect 6 million Americans at a cost of $355 billion in 2021 [6]. While there are treatments that may temporarily reduce the symptoms of Alzheimer's, there is no known prevention or cure. Depression is a similar challenge, estimated to affect 6-7% of full time US workers and to be the leading cause of disability of those of age 15-44 at a cost of $210 billion a year [7]. Treatments for depression usually involve therapy, which can be cost prohibitive and difficult to find, and antidepressants, which only help 20% of those with moderate to severe depression and may not help those with mild depression at all [8]. Each disease alone represents a major public health burden, and combined present some of the most pressing needs for advancement in medicine and health today.

While research into depression and dementia is unequivocally urgent, they represent only two outstanding issues in brain health; examples of other neurological issues of clear personal and societal importance include autism and post-traumatic stress disorder. This Request for Proposal seeks to address any pressing questions at the nexus of basic gut microbiome/brain science and clinical neuropsychiatric best practices, and urgent public health. TMCity Foundation welcomes proposals that seek to understand and/or utilize the gut microbiome as a path toward improving brain and mental health.

Background

Proof of the gut microbiome's connection to cognitive function has been growing in the past decades, in animal experiments [9], small clinical studies [10], and larger cross-sectional studies [11]. Recent studies have shown that gut diversity was associated with all measures of cognitive function at a statistically significant level with some specific species associated with measures of cognitive function [11]. More specifically, patients with Alzheimer's disease have an altered gut microbiota composition compared to patients without [12]. Furthermore, imbalances in the gut microbiota have been linked to the amyloid plaques in the brain that are characteristics of Alzheimer's disease [13].

Evidence linking the gut microbiota to behavioral and mental health has also been growing. Dysbiosis in the gut leads to increased intestinal permeability that impairs the immune system, a known condition for depression and anxiety [5]. In addition, pro-inflammatory bacteria can trigger a cascading effect leading to inflammatory proteins affecting the hypothalamic-pituitary-adrenal axis (HPA), whose dysregulation is one of the most reliable

biological readouts in major depression and anxiety [5]. Conversely, human and animal studies have shown that probiotics reduce anxiety and depressive symptoms [5], with probiotic use shown to be comparable to antidepressants with respect to reduced cortisol levels and improved self-reported psychological effects [14].

However, although the link between the gut microbiome dysregulation and neuropsychiatric diseases is well established, much remains unknown about both the basic science and the clinical best practices of that relationship. For example, research is lacking in the exact role of the microbiome in the pathogenesis of mental health disorders. Additionally, while a robust wellness industry has embraced probiotic foods and healthy eating as holistic remedies, no form of probiotics is currently regulated by the FDA or is considered standard, reliable therapy for anxiety or depressive disorders as compared to psychiatric medications [14].

Goals

This RFP seeks to address the gaps in our knowledge of how the gut affects brain health, with the goal of harnessing that knowledge to bring about measurable improvements to our prevention and treatment of neuropsychiatric diseases. In other words, our aim is to understand and improve brain health by advancing our understanding of the gut and its relationship to the brain. Acceptable proposals include (but are not limited to) any that seek to:

1. Elucidate the key metabolites, biochemical mechanisms, and physiological pathways by which the gut causally affects the brain
2. Demonstrate the gut biome's role in neuropsychiatric disease pathology, especially in its etiology
3. Understand how external factors such as probiotics or lifestyle factors can affect the brain via the gut, and/or how these factors interact with medication to moderate its effect
4. Understand how early life environments and experience shape gut and brain health
5. Quantify the concepts of a healthy versus unhealthy gut with respect to cognitive or mental health, especially with age or sex as a covariate
6. Understand the role of both gut diversity and specific gut composition to healthy functioning of the gut-brain axis

7. Understand the role of genetics to gut and brain health, especially to how an individual's gut responds to both lifestyle factors and to medication and its subsequent impact to brain health
8. Develop tests to quickly, efficiently and/or cheaply measure the state of a patient's gut, e.g., through identifying relevant biomarkers to serve as proxies for gut health
9. Identify gut biomarkers to aid in and help standardize clinical diagnosis of complex neurologic/neuropsychiatric disorders such as dementia, autism, or depression.
10. Standardize clinical practice to maximize gut health at different stages in life as related to brain health, e.g., as related to maternal and neonatal care
11. Replicate relevant previous small studies on a larger basis to confirm findings
12. Replicate relevant previous short studies to longer longitudinal ones to confirm the linkage of gut microbial changes to physiological changes
13. Duplicate relevant previous results in animal models in humans through clinical trials
14. Demonstrate statistically significant changes in cognitive or mental health through use of gut altering techniques (such as fecal transplants) and substances (such as probiotics)

While Alzheimer's disease/dementia and depression have been used as example areas of application in this RFP, any area of brain health is welcome as a focus of a proposal.

Specifications

Requirements and Qualifications

- Applicants must be based at a U.S. academic research organization, a not-for-profit or government body, or a private-sector organization and must be able to accept TMCity Foundation's standard grant conditions.

- Applications should include a proposal, a budget, and a Gantt chart. The proposal should clearly indicate: 1) the problem being addressed, 2) the design of the study, 3) the rationale for the effectiveness of the study to address the problem, and 4) any previous research the study is based upon, both from the literature and from personal ongoing research.

Application Instructions

Budget

TMCity Foundation will make an expected 1-3 grants, up to $250,000. Please refer to the budget template for submitting your project budget. Funds can be combined with other awards to carry out the proposed research.

Timeline/Project Period

Applications must be submitted by July 1, 2022. Final decisions will be announced October 1st, 2022 with the anticipated start date of funding November 1st, 2022. Should these dates be changed, all applications will be notified by email. Individual feedback on submissions will not be possible, and external reviewers may be consulted to evaluate the proposals. Submitted Gantt charts should reflect monthly progress; if enrolling clinical patients with uncertainties related to the pandemic, multiple Gantt charts may be appropriate to reflect alternate scenarios.

Deliverables

- Midterm and final reports
- Quarterly updates by email or teleconference are expected
- Plan for data sharing and algorithm development as relevant

Evaluation Criteria and Review Process

- Impact in terms of long-term goals
- Quality of data collection/analysis/sharing plan of action
- Track record of performance and expertise in the field
- Ability to build upon previous work
- Ability to leverage research done under this grant to secure future funding
- Clarity of research plan and proposal
- Feasibility
- Execution/Risk mitigation measures due to pandemic limitations
- Adherence to best practices
- Proposed costs
- Translational value of specific aims to public benefit/market

Submission Instructions/How to Apply

Proposals with all related materials should be submitted to info@tmcity.org by **July 1, 2022**. Any questions related to this RFP can also be sent to this address.

About TMCity

TMCity is a venture-minded family foundation focused on transforming mental and neurological healthcare by providing catalytic funding for innovative research projects, programs, and companies working at the intersection of technology and mental health. With a focus on diversity of data, we make grants and impact investments with the goal of advancing our understanding of the brain and creating effective, real-world solutions that address mental health and well-being.

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