1R34NS126030-01 – Metadata

Project Title: Profiling the human gut microbiome for potential analgesic bacterial therapies
Research Focus Area: Preclinical and Translational Research in Pain Management
Research Program: Development and Optimization of Non-Addictive Therapies to Treat Pain
Administering: NINDS
Institution(s): HOLOBIOME, INC.
Investigator(s): STRANDWITZ, PHILIP PETER (contact); GILBERT, JACK ANTHONY
Location(s): Cambridge, MA
Year Awarded: 2021
NOFO Title: HEAL Initiative: Planning Studies for Initial Analgesic Development Initial Translational Efforts [Small Molecules and Biologics] (R34 Clinical Trial Not Allowed)
NOFO Number: RFA-NS-21-016

NOFO Aims: The goal of this funding opportunity announcement (FOA) is to solicit Initial Analgesic Development R34 applications that propose 2-year exploratory/planning awards that are expected to enable a future application for RFA-NS-21-015 HEAL Initiative: Team Research - for Initial Translational Efforts in Non-addictive Analgesic Development [Small Molecules and Biologics] (U19 Clinical Trial Not Allowed).Thus, the limited scope of aims and approach of these applications are expected to establish a strong research team, feasibility, validity, or other technically qualifying results that support, enable, and/or lay the groundwork for a subsequent Team Research U19 application. These R34 awards will support the building of a research team to collect initial data and recruit additional collaborators. The application must include a plan for developing a strong research team, as well as a strategy to collect preliminary data linking putative therapeutic targets to the proposed pain indication and supporting the hypothesis that altering target activity will produce desirable outcomes for the disease.

Abstract
Disruptions in make-up of the microbiome are associated with disorders characterized by chronic pain and inflammation, such as rheumatoid arthritis and fibromyalgia. The gut microbiome has immune and metabolic effects, and human gut-derived bacteria may be a source of novel, safe, and non-addictive pain treatments. However, connections between gut and pain signals, known as the “gut–pain axis,” are still poorly understood. This study aims to identify human-gut-native bacteria that i) interact with known pain targets in lab studies, ii) test their activity and analgesic/anti-inflammatory potential in an animal model, and iii) develop a computational approach to predict microbial-genetic effects on pain signals.

Introduction
The human gut microbiome is an essential component of host physiology: it modulates immune activity, influences the balance of neurotransmitters both peripherally and centrally, and produces a vast and variable array of small-molecule metabolites which enter circulation to impact distal body sites. It is highly heritable, implying a symbiosis that has developed over evolutionary timescales, but is also susceptible to the influence of diet and other factors such as antibiotic use. Notably, disruptions in microbiome composition are associated with a number of disorders characterized by chronic pain and inflammation, such as rheumatoid arthritis and fibromyalgia. Given the microbiome’s immunomodulatory and metabolic capacities, and its role as a pseudo-endogenous component of human biology, human gut-derived bacteria are a promising potential source of novel, safe, and non-addictive therapeutics for pain management. However, the mechanisms underlying the “gut–pain axis” are still being elucidated, and key functional drivers of the observed connections have yet to be identified. As such, to advance the development of microbiome-derived biotherapeutics for pain management, the goals of this project are: to identify human-gut-native bacteria capable of engaging established pain targets *in vitro*, to

validate their activity and analgesic/anti-inflammatory potential *in vivo*, and to develop a computational tool to predict microbial-genetic drivers of response, which can guide future mechanism validation and therapeutic development. Because the vast majority of human gut bacteria are strictly anaerobic, they cannot be cultivated using typical laboratory equipment and techniques. This has historically presented a roadblock in mechanistic explorations of the gut microbiome's therapeutic potential, resulting in a focus on "culture-independent" methods such as metagenomics—approaches that produce a wealth of correlative data, but little by way of causal validation. Holobiome is uniquely suited to meet this complex challenge, having overcome the difficulties inherent in anaerobic cultivation to build an in-house strain library of nearly ten thousand bacterial isolates from a variety of donors which contains representatives of nearly every major human gut-bacterial taxon cultured to date. This resource, along with an assembled team bringing extensive experience in microbiology, mammalian cell culture and assay development, and computational genomics, will allow a diverse library of human gut bacteria to be individually screened for their capacity to modulate cytokine response, cyclooxygenase expression, TRP channel activity, and other targets with high therapeutic potential for pain. This approach is expected to provide concrete insights on the mechanisms by which the gut microbiome influences nociception and the inflammatory response, with implications for the development of novel non-opioid analgesics. Findings of this research may also have translational potential for the treatment of autoimmune disorders, cancer, and neurodegenerative diseases such as Alzheimer's Disease, which has both autoimmune components and demonstrated links to the microbiome.

Public Health Relevance Statement

While a rapidly growing body of research ties perturbations in the human gut microbiome to countless aspects of health and disease, most of this work is correlative in nature and provides relatively little information regarding the direction of causality and the mechanisms involved. This project, which aims to identify human gut-native bacteria capable of modulating nociception and inflammation, will generate valuable insight on the roles of specific gut taxa and bacterial genes in regulating pain sensitivity. The outcome of this project will represent a major step toward the development of novel non-opioid analgesics with a strong safety profile, which may also help stem the ongoing opioid crisis.

Outcomes

While a rapidly growing body of research ties perturbations in the human gut microbiome to countless aspects of health and disease, most of this work is correlative in nature and provides relatively little information regarding the direction of causality and the mechanisms involved. This project, which aimed to identify human gut-native bacteria capable of modulating nociception and inflammation, generated valuable insight on the roles of specific gut taxa and bacterial genes in regulating pain sensitivity. We believe this is a major step toward the development of novel non-opioid analgesics -- derived from the human gut microbiome -- with a strong safety profile, which may also help stem the ongoing opioid crisis. Key achievements for this project include: - We screened 250 unique strains of human gut bacteria for activity against a wide range of known pain-related targets leveraging *in vitro* cell-based assays. - We identified bacteria with analgesic (and algesic) potential from these screens, as well as built a pipeline to uncover putative mechanisms driving this effect. - Using an *in vivo* model (rodents) of inflammatory pain we found preliminary efficacy with some of our promising analgesic strains. These strains largely reverse brain signatures of a pain response, as measured by fMRI. - We assembled a world-class team of experts in microbiome, sequencing, and pain biology, and now seek to further advance these promising strains preclinically, as well as initiate a broader screening effort for novel pain targets.