

## IMPACT ON R1 METRICS

### I. Compelling case on funding source possibilities with citation of external funding sources' RFPs.

**I.A. The National Institutes of Health will be announcing in March 2019 a new nutrition research initiative.** The [Strategic Plan for NIH Nutrition Research](#) will focus efforts in “advancing the scientific understanding of interactions between diet, nutritional status, biological processes, and the environment.” Specifically, it will focus on the effect of nutrition across the lifespan with an emphasis on maternal and child health, *which is a focus of my current research*. Multiple initiatives listed in this plan are directly related to this research, as well as, my overarching research focus. The following scientific and training priorities listed in their strategic plan directly align with this research:

- 1-1. Advance Nutritional Biochemistry and the Bioinformatics of Nutrition-Related Pathways
- 1-3. Identify and Leverage Interrelationships between Diet, Host, and the Gut Microbiome to Promote Health
- 2-5. Determine Mechanisms by which Dietary Patterns Affect Health Status and Chronic Disease Susceptibility
- 3-1. Elucidate the Biological Factors Underlying Individual Variation in Response to Dietary Interventions
- 4-1. Identify and Leverage Interactions Among Nutrition, Disease States, and Treatments
- 4-3. Identify Triggers and Endpoints for Nutritional Support in Clinical Settings
- 6-4. Develop and Improve Tools Using Big Data for Systems Science Approaches to Nutrition Research
- 6-5. Develop Sensors for Continuous Monitoring of Nutrients and Metabolites for Personalized Nutrition Research
- 7-1. *Facilitate Training in Host, Gut Microbiome Metabolism, and Diet Interrelationships*
- 7-2. *Enhance Training in the Application of Big Data Approaches to Nutrition Research*

Thus, buying into critical cutting-edge technologies, like the MBRAs, will be paramount in positioning Baylor University to take full advantage of this coming opportunity, and to coordinate research and student training efforts around Baylor to build capacity for this new strategic plan at the NIH. (see **Appendix – NIH Strategic Plan for Nutrition Research and Training Plans**).

The results of this research have far-reaching impacts on:

- 1. Broad basic mechanisms governing host diet-microbe relationships (NSF)
- 2. Development of prebiotic therapy for infection and cancer prevention (NIH/Foundations/Industry)
- 3. Novel precision prebiotics for improvement of cancer therapy and treatment outcomes (NIH/Foundations)

**I.B** Several organizations, both governmental and non-governmental, are key targets for funding of this research. Specifically, one of the National Cancer Institute's (NCI) *Provocative Questions in Cancer* is “**PQ11: Through what mechanisms do diet and nutritional interventions affect the response to cancer treatment?**”, which is addressed by this research. **The following funding mechanisms or RFPs are listed below:**

NCI Provocative Questions (RFAs):

- R01 [RFA-CA-18-019](#)
- R21 [RFA-CA-18-020](#)

Other RFAs or Funding Mechanisms Specifically Aligned with this Research:

- Source: NIH - [R01 Advancing Mechanistic Probiotic/Prebiotic and Human Microbiome Research](#)
- Source: NIH - [Nutrigenetics and Nutrigenomics Approaches for Nutrition Research \(R01 Clinical Trial Optional\)](#)
- Source: NIH - [Early-Stage Preclinical Validation of Therapeutic Leads for Diseases of Interest to the NIDDK \(R01\)](#)
- Source: NIH - [Food Specific Molecular Profiles and Biomarkers of Food and Nutrient Intake, and Dietary Exposure \(R01 Clinical Trial Optional\)](#)

- Source: NIH/NCI - [R01 \(NIH/NCI\) Age-related Microbiota Changes and their Implications in Chronic Disease Prevention, Treatment and Progression](#)
- Source: Dannon Institute - [Dannon Gut Microbiome, Yogurt and Probiotics Fellowship Grant Program](#)
- Source: NIH - [R21 \(NIH\) Mechanisms of Cancer and Treatment-related Symptoms and Toxicities \(PA-16-258\)](#)
- Source: Cancer Prevention Research Institute of Texas - [Multiple RFAs and general funding awards](#)
- Source: NASA - [Translation Research in Space Health \(TRISH\)](#)

### **I.C. Plans to communicate with external funding sources that will increase the likelihood of your proposal to the them being accepted**

Once this proposal is funded, myself and our team will begin to immediately reach out to program officers from the organizations listed, as well as, those organizations with which our colleagues have favorable connections or previous funding success. Most of the scientists on this team have previous funding from DoD, NIH, CPRIT and Industry. Thus, we have established success in communicating with and obtaining external funding sources. Specifically, I have two contacts at the NCI that are Program Officers, and they are highly interested in this work; Phil Daschle and Roberto Flores. In addition, Dr. Britton has already been successful in obtaining grant funding using this technology, as well as, producing high impact factor publications in *Nature* using this technology. This support and prior success in funding and publications indicates a clear desire from multiple funding agencies for conducting this research once preliminary data is obtained showing feasibility.

### **II. Return on Investment to Baylor University for this project**

- Increased national recognition in research scholarship** – This research is highly regarded by those in the nutrition, cancer, and microbiome fields as a top priority as indicated by the NIH Strategic Plan for Nutrition Research. In consideration of the dramatic increase in spending on pre- and probiotics (>\$1 billion/year) there is a critical need for prebiotic research, which could be met in part through this research initiative. Unfortunately, very few investigators have the skills, team, and resources with which to conduct this type of research. Setting up the MBRA system will be an important first step to launching a much larger multi-phase research project, which will involve multiple investigators/teams and stool donors to test potential prebiotic therapies. Having this type **cutting-edge scientific tool** (e.g. MBRAs) is the key to **a) discovering new mechanisms and potentially new treatment modalities for infection and cancer prevention, b) unlocking federal funding opportunities, and c) impacting consumers and patients' lives to promote wellness. This research will significantly impact nutrition, infectious disease, and microbial research on multiple fronts, from basic mechanisms to treatment, which will lead to high-impact publications and subsequent funding opportunities.** Further, this tool and new research area will allow Baylor to attract highly-research active and successful scientists as faculty. All of these factors together will propel Baylor University to R1 status.
- Improved quality of education and research training** – Access to high-quality research and training is key to preparing students for success in the STEM field, as well as, for career success beyond STEM fields. This research will provide **1) access to experts in the fields of microbial ecology and pre/probiotics (Dr. Britton/Dr. Greathouse), 2) training in use of the MBRA system (Dr. Britton), 3) skills in Data Science (Dr. Greathouse/Dr. Chia), 4) project management and leadership skills (Dr. Greathouse), and 5) exposure to Artificial Intelligence methodology during development of metabolic modeling (e.g. machine learning) (Dr. Chia/Dr. Greathouse).** Further, with the NIH's Strategic Plan on Nutrition Research focused on methods to *Facilitate Training in Host, Gut Microbiome Metabolism, and Diet Interrelationships*, the research outlined in this proposal will dramatically increase our ability to compete for training funding opportunities that align with this objective. In combination, these experiences will dramatically enhance the educational and research training, which will also increase the competitiveness for advanced training opportunities at other R1 institutes, as well as, training fellowships or postdoctoral awards.
- Production and recruitment of high-quality graduate and postdoctoral trainees** – Exposure to the research outlined in this proposal will lead to retainment of high-quality postdoctoral fellows and

production of highly-trained and competitive doctoral students. Among the fields of infectious disease, microbial ecology, and cancer research, all continue to garner significant interest from potential graduate and postdoctoral trainees. Currently, I have 2 doctoral students (Biology/Statistics) and 5 undergraduate research students in my laboratory working on various aspects of microbe-host interactions. To conduct future research, however, I would also require additional top-quality postdoctoral fellows. With my previously established connections at the NCI and other research institutions in the cancer and microbiome fields, I have no doubt I or my team would be able to recruit multiple highly successful and productive individuals for this position. Further, the production of highly trained graduate students is a significant need in our field currently, and would likely garner **support for training grant** funding from the NIH for both undergraduate and graduate students.

- D. Establishment of long-term collaborations between multiple academic and health care institutes – One of the keys to research success and recognition is establishment of collaborative scientific teams that span multiple disciplines and institutions. Rarely are highly impactful scientific discoveries made by single investigators, but more often take the effort of several independent investigators working together to solve an outstanding problem. For this research to be successful, multiple disciplines are required, including medicine, mathematics, next-generation sequencing, bioinformatics, epidemiology, chemistry, and computer engineering. Bringing together three entities, **Mayo Clinic, Baylor College of Medicine, and Baylor University**, to conduct this research has the potential to lead to long-term powerful collaborations with leverage to obtain multi-site and/or multi-PI program and project grants, including P01 and U01 awards (outlined above). Obtaining these types of awards will continue to propel Baylor to R1 status.
- E. Recognition by Baylor Alumni and Businesses for Targeted Investments to the University – With research success and high-profile discoveries, especially those that impact the lives of loved ones (e.g. infectious disease and cancer), Baylor would be well-positioned to attract significant funding and investments from both Baylor alumni and business or industry partners. The potential impact of this research has the ability to **lead to novel prebiotics that could be patented or developed for clinical use by industry partners**.
- F. Enhance research space and resources for Baylor and Baylor faculty – As we transition to R1, we will initially be confined to current available space. Investment in equipment, like the MBRAs, that can **enhance space already available at Baylor University** will add to the return on investments by: 1) providing a multi-user resource to Baylor Faculty to increase grant funding/publishing, 2) providing opportunity to recruit and train doctoral students, and undergraduates, 3) incentivize new faculty recruits to commit to Baylor, 4) encourage outside collaboration and/or move the MBRAs to a fee-for-service system that would generate income.

### **III. Previous and future proposals planned to advance the larger research agenda**

#### **A. Previous proposals addressing this research agenda:**

##### **Grants Funded**

2019	<i>Baylor University (URSA)</i> Project title: Characterization of Outer Membrane Vesicle RNA During the Phases of Growth of <i>B. fragilis</i> Investigators: Leigh Greathouse Role: PI
2018	<i>Baylor University (URC – mid-range)</i> Project title: A fiber intervention to prevent weight gain and reduce stress levels for physicians in training. Investigators: LesLee Funderburk (PI), Leigh Greathouse (Co-PI), Pete Grandjean (Co-PI) Role: Co-PI

- 2017 *Summer Research Sabbatical*  
 Project title: COLON-MD (Pilot): COLon cancer LONGitudinal study of the Microbial metabolites and Dietary factors that influence response to treatment  
 Investigators: K. Leigh Greathouse  
 Role: PI  
**\*preliminary background research from this sabbatical on conducting the pilot study lead to the publication of book chapter describing how to conduct a cancer microbiome study**
- Baylor University (URC – mid-range)*  
 Project title: Mediation of Host-Pathogen Interaction by Bacterial Outer Membrane Vesicle Small RNAs in Colon Cancer  
 Investigators: K. Leigh Greathouse (PI), Joseph Taube (Co-PI)  
 Role: PI
- Grants Submitted, Not Funded**
- 2018 *Career Development Award (PI: Greathouse) \*received 1.7/Excellent (funded at 1.5 or higher)*  
 Project period: 05/01/2019-03/31/2022  
 Source: DoD  
 Funding: \$485,000  
 Project title: Identification of the dietary and microbial factors that predict chemotherapy-induced diarrhea in colon cancer. The goal of this study is to identify the dietary and microbiome factors among colon cancer patients undergoing chemotherapy that predict chemotherapy induced diarrhea.  
 Role: PI
- 2018 *DNA Genotek Innovation Award*  
 RECRUITMENT, LONGITUDINAL RETENTION AND REPRODUCEABLE METHODS FOR COLON CANCER MICROBIOME STUDIES  
 Role: PI  
 Funding: \$30K
- Collaborative Faculty Research Investment Program \*not funded because BSWH withdrew from the CFRIP award mechanism*  
 Project title: "COLON-MD (Pilot): COLon cancer LONGitudinal study of the Microbial and Dietary factors that influence response to treatment"  
 Source of Funding: Baylor University
- 2017 *Cancer Prevention, Control, Behavioral Sciences, and Population Sciences Career Development Award (K07)*  
 Project title: "COLON-MD (Pilot): COLon cancer LONGitudinal study of the Microbial metabolites and Dietary factors that influence response to treatment"  
 Investigators: **K. Leigh Greathouse (PI)**  
 Source of Funding: National Cancer Institute (\$444K, 3 years)
- MRC2 Pilot/Feasibility Grants*  
 Project title: "COLON-MD (Pilot): COLon cancer LONGitudinal study of the Microbial metabolites and Dietary factors that influence response to treatment"  
 Source of Funding: University of Michigan
- 2016 *Collaborative Faculty Research Investment Program*  
 Project title: "COLON-MD (Pilot): COLon cancer LONGitudinal study of the Microbial and Dietary factors that influence response to treatment"  
 Source of Funding: Baylor University

*Department of Defense (Lung Cancer Concept Award)*

Project title: "Investigating the relationship of commensal microbiota and DNA methylation in early stage Lung Cancer"

Investigators: As Co-PI, together with Curt Harris (PI)

Source of Funding: Department of Defense

## **B. Future Proposals Planned:**

<b>Due Date</b>	<b>Funding Mechanism</b>	<b>Title</b>	<b>Collaborators</b>
June 19, 2019	R15 AREA (NIH)	Microbial Response to Specific Dietary Fibers Using Model Gut Communities	Rob Britton/Nick Chia/Jun Chen/Ramon Lavado
October 3, 2019	R35 MIRA (NIH)	Using MBRA to Explore Diet-Microbiome Relationships	Rob Britton/Nick Chia/Jun Chen/Ramon Lavado

## **C. Future Users of the MBRA System:**

**Tamara Adair (BIO)** – The MBRA will enrich multiple undergraduate courses by allowing students to design creative and relevant experiments and to analyze large genomic data sets. The following courses would be enhanced by having the MBRA system: BIO 1406 - Analysis of soil microbial communities for types and concentrations of bacteriophage or specific host organisms related to various locations or conditions; BIO 1106 - Analysis of soil microbial communities and experimental design using additions of different types of ciliates, microbes, or pollutant; Independent undergraduate research projects - This technology will provide the opportunity to have large data sets generated in several research labs and generate a rich repository that could be used for genomics and bioinformatics training and analysis. (see Appendix – Training Plan)

**Erica Bruce (ENV)** – Mini bioreactor arrays are an innovative tool that allow for a complex system of microbes and other constituents to be evaluated over multiple endpoints. Specifically, Dr. Bruce could utilize this system to evaluate metabolites of novel drugs, evaluating changes in the microbiome following single dose and multiple dose drug trials, evaluating changes in efficacy of drugs following incubation with microbes, evaluating relationships between co-cultured cells from the GI tract, and evaluating the resulting effects from transformation products. This proposal will add this valuable system to resources available at Baylor University that can be utilized by several scientists, it stimulates collaborative, interdisciplinary project development and represents a meaningful tool to sustain long term funding.

**Chris Kearney (BIO)** – will be able to use MBRA system to develop and test his antimicrobial peptide engineered bacteria for growth and functionality in a polymicrobial stool model community

**Christie Sayes (ENV)** – will use the model to test the metabolic effects after cellulose nanocrystal exposure to the microbiome. Metabolism of engineered materials is a largely under-studied area and needs data to help establish toxicokinetic profiles of nano-enabled food and drug products.