ILSI North America Gut Microbiome Committee
Request for Proposals

Identification of microbially-derived metabolites as biomarkers: What changes (presence and quantity) of which metabolites matter for health?

The International Life Sciences Institute (ILSI) North America is a public, non-profit scientific organization that advances the understanding and application of science related to the nutritional quality and safety of the food supply. The organization carries out its mission by catalyzing relevant research projects, professional education programs and workshops, seminars and publications, as well as providing a neutral forum for government, academic and industry scientists to address scientific issues of common concern for the well-being of the public. ILSI North America’s programs are supported primarily by its industry membership.

The Gut Microbiome Committee advances the science required to substantiate dietary modulation of the gut microbiome in ways that are conducive to health.

ILSI North America adheres to strict procedures to maintain scientific integrity in all work we support. These requirements are described further in the attached TOP Guidelines and 8 Guiding Principles for Scientific Integrity addendums.

Background: Gut microbiota can be modified by diet, medications and other lifestyle factors. Current scientific data show that understanding microbiome composition and diversity may not inform a causal link to health benefits. However, at this time, there exists no valid, noninvasive tool to monitor gut microbe activities in real time. The need to identify microbiome-related biomarkers of health in stool, blood or urine is paramount to understanding what microbiome function means for health. Thus, research on gut microbiome has moved to elucidate gut microbe function, e.g., through examination of metabolite production and change.

Study of microbially-derived metabolites which may be of potential benefit or adverse consequence (locally and in distant organs, such as liver, skeletal muscle, and brain), can enable our understanding of their impact on metabolism, physiology and health. The literature is rife with examples in which microbially-derived metabolites produced from a dietary substrate (see, e.g., Chambers et al. 2019, Mitchell et al. 2019, Hayashi et al. 2018, De Filippis et al. 2016, Urpi-Sarda et al. 2019) or a specific metabotype (Palmnäs et al. 2019, Riedl et al. 2017, Urpi-Sarda et al. 2019) have been linked to a health outcome or a validated marker of benefit or risk.

There is a need to identify metabolites that are physiologically relevant and may serve as biomarkers for health. One way to start linking diet-induced changes in the gut microbiome and
microbially derived metabolites to health is understanding whether a change in presence or quantity is clinically significant, such as short-chain fatty acids from fibers, indole and phenols from proteins, and trimethylamine from choline and creatine. Given individual variability, a review of metabotypes that are linked to indicators of health and diet/food/nutrient could be a start; followed by evaluating the microbial compositions that are linked to those metabotypes.

The ultimate objective of this project is to identify candidate microbially-derived metabolites or metabotypes that may be indicators of a health effect. Through this project, the intention is to: 1) initiate a dialogue on what changes in microbially-produced metabolites are derived from dietary constituents, 2) identify metabolites or metabotypes that show promise for a link to health outcomes/impact, as well as data gaps to achieve this level of knowledge, and 3) identify and describe what is needed to link to a physiological effect (e.g., quantities of a metabolite sustained over a specific time period) and/or ideally, a health outcome.

**Objective:** Document the current level of understanding related to microbially-produced metabolites or metabotypes — derived from the diet or endogenously produced — that show promise as a biomarker for health.

**Suggested approach:** The committee suggests a phased approach toward the objective. Adequacy of the evidence-based to move forward will be assessed at each phase.

**Phase 1:** Preliminary search/evidence review to:¹

a. Identify diet-related and gut-derived metabolites and/or metabotypes that have been linked to specific health outcomes and/or well-accepted markers of those health outcomes.
   i. Health outcomes of focus could include gut, immune, muscle, liver or cardiometabolic health, risk of diabetes, and related well-accepted markers of benefit or risk (the committee is open to applicant suggestions).
   ii. Where possible, literature related to demonstrating a causal link between a diet or dietary intervention and changes in metabolite levels or metabolotype(s) is of specific interest.
   iii. Focus on human studies with animal evidence as secondary or supporting evidence.

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¹ A systematic review is currently underway in ILSI Europe, which focuses on polyphenols and cardiovascular, cognitive and bone health-related outcomes. Therefore, polyphenols and related metabolites might be excluded from this project. In addition, the CABALA_DIET&HEALTH project funded through the European Joint Programming Initiative aims to examine circulating bile acids as a biomarker of health, as modulated by the gut microbiota and therefore might also be excluded. Applicants could justify their selection using these and other ongoing projects with a similar aim.
b. Provide a summary presentation to the ILSI Gut Microbiome committee with a proposed approach for Phase 2. Through discussion, identify a mutually agreeable set of metabolites or metabotypes on which to focus.

Phase 2: Conduct a scoping review/mapping exercise for the selected metabolite or metabotype — health relationship(s) to document the strength of evidence available.

The scoping review will inform the appropriateness of developing a specific systematic review research question in the future.

Proposal Content:
The Committee requests that applicants address each of the following components below in their proposal:

1. **Background:** Please provide a short description of the project.

2. **Research Approach:** Please provide your approach to the research design elements as described above. Key research questions, primary outcomes and secondary outcomes are to be identified, methodology, and analytic plan. Where appropriate, please reference the validation of the method proposed (e.g., validated scoping review method).

3. **Research Team:** Identify the research team and their individual roles in the project.

4. **Anticipated Challenges:** Describe any anticipated challenges with the approach outlined, e.g., that evidence will be limited or difficult to synthesize due to lack of method harmonization.

5. **Publication Plan:** The Committee wishes the researchers to publish this work in a peer-reviewed journal. Please provide your suggested publication plan.

6. **Investigator Credentials:** Please describe the experiences that make you and your team a candidate for carrying out this project. In addition, the CVs of the principal investigator(s) are required (can be in addition to the 5-page limit).

7. **Resources:** Please describe the resources available to you to allow completion of the project.

8. **Budget, Timeline, and Key Deliverables:** Please provide a budget summary indicating the allocation of the requested funds (including staffing per phase), as well as a corresponding timeline for Phase 1. The timeline for Phase 2 can be outlined pending
results of Phase 1. Please indicate which, if any, additional funding sources will be used for this project. Proposals covering Phases 1 and 2 with a budget in the range of $90-$150K will be considered.
  a. Please note that ILSI North America limits overhead to 10% of project costs.
  b. ILSI North America will directly pay publication fees for open access.

9. **Timeline and Key Deliverables:** Minimally, deliverables should include:
   a. Presentation of results to committee in-person or by webinar
   b. Final manuscript submitted to peer-reviewed journal for publication

10. **Potential Conflicts of Interest:** List any potential conflicts of interests for all investigators, co-investigators, collaborators. We suggest using the Conflict of Interest Guidelines as set forth by the American Society for Nutrition: [https://nutrition.org/publications/guidelines-and-policies/conflict-of-interest/](https://nutrition.org/publications/guidelines-and-policies/conflict-of-interest/)

**Page Limit:** The committee is requesting a proposal of no more than *five pages* in response to the above outlined questions. CVs and other references can be in addition to the five pages.

**Deadline:** Proposals must be received by 12 am ET on July 15, 2020.

**Submission Instructions:** Submit by email to Marie Latulippe at mlatulippe@ilsi.org and cc Char Myers at cmyers@ilsi.org. Questions may also be directed to Marie Latulippe at 202-659-0074 ext. 151.

**Proposal Review Process:** The Committee, which is composed of industry, government and academic scientists, will review proposals and select the grantee. It is possible that the committee will require responses to supplemental questions before a final decision is made. Only projects meeting minimum requested criteria are considered. Proposals are evaluated based on:
  * Demonstrated expertise of the research team
  * Understanding of the research question and relevant nuances
  * Clarity of proposed approach
  * Demonstrated validity of the proposed approach (e.g., application of a previously validated/published method or references that have used this method)
  * Timeline and budget aligned with committee resources

**References:**


Addendum
Adoption of the Center of Open Science’s Transparency and Openness Promotion Guidelines by ILSI North America

Background:
The Center for Open Science's Transparency and Openness Promotion (TOP) Guidelines provide actionable steps for institutions to practice and promote transparent, reproducible, and rigorous research. ILSI North America is a TOP Guidelines signatory. By becoming a signatory, ILSI North America is supporting the principles expressed in the guidelines through their implementation by its funded researchers. The TOP Guidelines include eight modular standards for promoting transparent, reproducible, and rigorous research, each with three levels of increasing stringency. Beginning July 1, 2018, all new research studies moving forward will strive to adhere to the levels of the TOP Guidelines specified below, recognizing that this process will take time and effort to achieve.

TOP Guidelines:

1. **Data Citation Standards (Level 3):** Cite shared data. Don’t publish until it is appropriately cited.

2. **Data Transparency (Level 2):** Data must be shared to the maximal extent allowed by ethical and legal constraints.

3. **Analytic Methods (Code) Transparency (Level 2):** Analytic methods (code) must be shared to the maximal extent allowed by ethical and legal constraints.

4. **Research Materials Transparency Level 2:** Materials must be shared to the maximal extent allowed by ethical and legal constraints.

5. **Design and Analysis Transparency (Level 2):** The researcher must use reporting guidelines when writing up publications. Equator-network website provides a huge choice of standards for research designs. http://www.equator-network.org/ The researcher is asked to select one and register the standard you have selected.

6. **Study Preregistration (Level 2):** When the researcher preregisters his/her study in an independent, institutional registry (e.g., http://osf.io/, https://www.crd.york.ac.uk/prospero/, http://clinicaltrials.gov/), which is encouraged but not required, ILSI North America will request a third party (e.g., Center for Open Science) verify that preregistration adheres to the specifications for preregistration before data collection.

7. **Analysis Plan Preregistration (Level 2):** When the researcher preregisters his/her study analysis plan in an independent, institutional registry (e.g., http://osf.io/, https://www.crd.york.ac.uk/prospero/, http://clinicaltrials.gov/), which is encouraged but not required, ILSI North America will request a third party (e.g., Center for Open Science) verify for adherence to preregistered plan (deviations must be transparently reported) before data collection.
8. **Replication (Level 1):** ILSI North America will occasionally put out a call for replication studies as part of our RFP process.

Learn more about ILSI North America's implementation of the TOP Guidelines [here](#).
ILSI North America’s Guiding Principles for Funding Food Science and Nutrition Research

Background:
The scientific process requires open, transparent examination and honest interpretation of data, regardless of a researcher’s affiliation or source of funding. To address the potential influence of funding source on scientific research, ILSI North America developed 8 Guiding Principles for Funding of Food Science and Nutrition Research. These guidelines were specifically designed to protect the integrity and credibility of the scientific record. All projects supported by ILSI North America must adhere to these principles.

Guiding Principles for Funding Food Science and Nutrition Research:
In the conduct of public/private research relations, all relevant parties shall:

1. Conduct or sponsor research that is factual, transparent, and designed objectively, and, according to accepted principles of scientific inquiry, the research design will generate an appropriately phrased hypothesis and the research will answer the appropriate questions, rather than favor a particular outcome;
2. Require control of both study design and research itself to remain with scientific investigators;
3. Not offer or accept remuneration geared to the outcome of a research project;
4. Ensure, before the commencement of studies, that there is a written agreement that the investigative team has the freedom and obligation to attempt to publish the findings within some specified time frame;
5. Require, in publications and conference presentations, full signed disclosure of all financial interests;
6. Not participate in undisclosed paid authorship arrangements in industry-sponsored publications or presentations;
7. Guarantee accessibility to all data and control of statistical analysis by investigators and appropriate auditors/reviewers;
8. Require that academic researchers, when they work in contract research organizations (CRO) or act as contract researchers, make clear statements of their affiliation; and require that such researchers publish only under the auspices of the CRO.

Learn more about ILSI North America's 8 Guiding Principles for Funding Food Science and Nutrition Research here.

Reference