

Research

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2017

RDPG SYMPOSIUM

GUT MICROBIOME BASICS AND TRANSLATION
INTO CONSUMER PRODUCTS





Dr Gilbert opened the symposium by explaining how unique each individual gut microbiome is and said, "The microbiome is essentially a fingerprint."

GUT MICROBIOME BASICS AND TRANSLATION INTO CONSUMER PRODUCTS

On October 21, 2017, the Research Dietetic Practice Group of the Academy of Nutrition and Dietetics hosted a continuing education symposium sponsored by the Abbott Nutrition Health Institute. The symposium, which was held in Chicago, featured four speakers who study different aspects of the human gut microbiome and how these bacteria affect health throughout the lifespan.

SYMPOSIUM OVERVIEW

Jack Gilbert, PhD, University of Chicago, reviewed basic microbiology and bacterial nomenclature, and introduced the importance of gut bacteria in clinical applications. Bruce Hamaker, PhD, Purdue University, discussed the vast array of fibers that bacteria use as fuel sources. Hannah Holscher, PhD, RD, University of Illinois, focused on science translation and the ways fiber may be used to modulate gut microbes for human health. Finally, Keith Garleb, PhD, Abbott Nutrition, provided a perspective on how industry is applying gut microbiome science to food and product development. Lauri Byerley, PhD, Louisiana State University Health Sciences Center New Orleans organized and moderated the symposium.

LEARNING OBJECTIVES

- Untangle the taxonomy and vast array of bacteria present in the human gut microbiota
- Elucidate the diversity of fiber and its role in fueling human gut microbes
- Establish a connection between human health and the gut microbiota
- Demonstrate how industry is translating the science into consumer products

The goals for the symposium were: 1) to define the role of the gut microbiome and to describe dietary fibers that the bacteria use as fuel sources, and 2) to demonstrate how industry is translating the scientific findings into products. The learning objectives presented the latest scientific findings with clinical applications for patient care. This symposium-focused compendium provides an overview of the presentations, key points, and recommendations for application and translation beyond the walls of the symposium.

2017 marked the 100th anniversary of the Academy of Nutrition and Dietetics at the Food & Nutrition Conference & Expo™ (FNCE®) in Chicago, Illinois from October 21-24, 2017.

AN INTRODUCTION TO THE MICROBIOME

Dr Gilbert opened the symposium by introducing the concept of the human body as a microbial ecosystem. The 40 trillion microbes that live within each human encode for many functions that the body has become reliant on. In fact, bacterial genes, which outnumber human genes by 260:1, help: digest food, provide some amino acids, and produce compounds that humans need to maintain metabolic activity, neuronal health, and immune function.

Although the human gut microbiome is comprised of 500 to 1,000 species encompassing 10,000 strains, the microbial community that resides within every individual is highly unique. Even identical twins have unique microbiomes. Each human microbiome is so diverse that they can be used forensically to track individuals just like a fingerprint. Another implication of this uniqueness is an individual may respond differently to a given medication or food. For example, some people respond very negatively to excessive doses of acetaminophen because they have gut bacteria that can transform this drug into compounds that are toxic to the liver.¹

“OMICS” TOOLS FOR STUDYING THE MICROBIOME

Despite the attention placed on the composition of the gut microbiota, understanding the gut microbiota and their functional (metabolic) capabilities is more important. The tools used to study the microbial genome and its relationship to metabolic activity include various “omics” technologies: metagenomics can be used to understand the functional potential of these microbes; transcriptomics helps researchers understand which genes are turned on or off under different scenarios to learn how functionally active the genes are; and, metabolomics tells researchers which small molecules are being produced and consumed by the microbes (or not) under different scenarios.

A REVIEW OF BACTERIAL SYSTEMATICS

Three domains define all living organisms: Bacteria, Archaea, and Eukaryotes, and the amount of microbial diversity is remarkable. For example, there are approximately 1 trillion bacterial species on earth.² The following are some examples of the diverse bacteria that live in the human gut.

RUMINOCOCCUS

Ruminococcus, members of the genus of bacteria, help digest resistant starches. There are 23 different known species. They are members of the Firmicutes phylum and Clostridia class. Increased abundance of *Blautia torques*, once known as *Ruminococcus torques*, is associated with irritable bowel syndrome (IBS).

ESCHERICHIA

Escherichia coli are members of the Proteobacteria phylum and Enterobacteriaceae family. Although there are only six recognized species of *Escherichia*, there are about 800 known genomes that may vary from each other by as much as 40%. By comparison, the human genome differs from that of chimpanzees by only 2%. Despite the dissimilarity among *E coli* strains, they have been grouped together in the same species. This example illustrates the dissimilarity between *E coli* species: *E coli* Nissile 1917, that was cultured from a soldier’s gut during World War I, can outcompete pathogenic *Salmonella* in the gut, nullifying the infection. Whereas *E coli* O157:H7 is a highly virulent and potentially deadly pathogen.



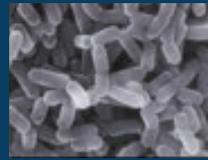
Jack Gilbert, PhD, BSc
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LACTOBACILLUS

The genus, *Lactobacillus*, contains 180 different species and was first isolated in 1901 by Dr Martinus Beijerinck. Consumption of these bacteria, in the form of fermented milk, was promoted by Nobel Prize Laureate, Eli Metchnikoff, during the early 1900s to maintain health. Although evidence is lacking as to whether probiotics maintain health, scientific evidence supports that probiotics may restore health when ill.

BACTEROIDES

Bacteroides species are very abundant in the human gut, making up approximately 20% of bacterial organisms. They are known for their ability to digest sugars (and especially complex host- and plant-derived glycans), and have been associated with diets high in protein, suggesting complex metabolic relationships.



Produce lactic acid from the digestion of glucose

180 different species – highly diverse metabolisms

Used extensively in probiotics – potentially good at stimulating immune responses

LACTOBACILLUS

SCIENTIFIC CLASSIFICATION

Domain:	Bacteria
Phylum:	Firmicutes
Class:	Bacilli
Order:	Lactobacillales
Family:	Lactobacillaceae
Genus:	<i>Lactobacillus</i> Beijerinck 1901

HEALTH IMPLICATIONS AND POTENTIAL THERAPIES

Dr Gilbert described several examples of how the microbiome could potentially be manipulated to improve health in obesity, autoimmune blockade therapy, and surgical infection and sepsis.

OBESITY

Research using animal models show that *Enterobacter cloacae* B29 can increase adipose tissue storage by disturbing the circadian rhythm of organs, which disrupts how the body metabolizes energy.³ The diversity of the gut microbiome may be one reason why weight loss varies, even in controlled settings.

AUTOIMMUNE BLOCKADE THERAPY

Microbiome and diet manipulation may augment autoimmune blockade therapies in cancer. In a 2015 study,⁴ researchers found that a probiotic *Bifidobacterium* strain might actively enhance the efficacy of immunotherapy in preclinical tumor mice models.

SURGICAL INFECTION AND SEPSIS

Researchers are studying whether alterations to the microbiome contribute to surgical site infections or sepsis in the body. Many patients already have disrupted, proinflammatory microbiota prior to gastrointestinal (GI) surgery due to unhealthy diets including high calorie, high fat, and high sugar, and low in fiber. Stress of surgery, 24-hour fasting, oxygen exposure, and antibiotic administration further promote survival of the proinflammatory bacteria, causing them to “panic.” As a result, bacteria attach themselves to the wound site, secrete collagenases that break down the gut wall, and cause the gut contents to spill out into the body cavity, potentially leading to sepsis and death. Researchers have found that the bacterial “panic” response and its resulting adverse effects can be prevented if they pump a caged form of phosphorus into the gut.⁵

Dr Gilbert concluded his presentation with his research on comparing rates of asthma among Amish and Hutterite farming communities.⁶ Amish and Hutterite lifestyles and genetics are similar with factors known to influence asthma risk. However, Amish children have much lower rates of asthma because their families practice traditional farming methods that expose them to microbe-rich environments compared to the industrial farming practices of the Hutterites.

To help explain these findings, researchers intranasally administered house dust to a mouse model of experimental allergic asthma. The mice treated with Hutterite dust extracts had exacerbated eosinophilia and airway hyperreactivity, compared to mice treated with Amish dust extracts. Peripheral blood leukocytes from Amish children had increased proportions of neutrophils, decreased eosinophils, and similar monocytes compared to Hutterite children. Therefore, the dust found in Amish homes was associated with changes to immune cells that seem to lower the risk of asthma in children. These results are fascinating because they suggest that the immune response of an individual can be stimulated by what they are breathing in, what they are exposed to, and what they are doing on a regular basis.

In summary, Dr Gilbert stated the need to understand the environment, the food that an individual is consuming, and the microbiome and its function to help and preserve people’s health and wellness.

BACTERIAL METABOLISM OF CARBOHYDRATES, DIETARY FIBER, AND THE GUT MICROBIOME

Dr Hamaker gave the second presentation of the symposium, shifting the topic to the role of carbohydrates and fiber in the microbiome. He began his presentation by introducing the U.S. Food and Drug Administration's (FDA) new labeling definition for dietary fiber,⁷ which he described as challenging. In 2016, the FDA defined dietary fiber as non-digestible carbohydrates or intact plant lignins. In a second definition, the FDA determined that any isolated and synthetic non-digestible carbohydrates that are added to food and labeled as fiber must be shown to exert a beneficial physiologic effect on human health. For any isolated or synthetic non-digestible carbohydrate that has not been approved by the FDA as meeting this second criterion, the manufacturer of the carbohydrate must submit a petition to the FDA for review and consideration for eligibility as a fiber. The FDA has proposed a compliance date of Jan 1, 2020 for implementation of this new labeling requirement. In addition, the FDA has increased the Daily Value for fiber from 25 g daily to 28 g daily.



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New FDA Dietary Fiber Definition

Dietary fiber is defined as non-digestible soluble and insoluble carbohydrates (with three or more monomeric units), and lignin that are intrinsic and intact in plants; isolated or synthetic non-digestible carbohydrates (with 3 or more monomeric units) determined by FDA to have physiological effects that are beneficial to human health.⁷

Although the Nutrition Facts label describes the amount of fiber in grams, another way to think about fiber is from the point of view of the gut bacteria. Whether the bacteria can use a specific type of fiber depends on whether they have the genes to encode the enzymes that will allow them to take advantage of that form of fiber. Dr Hamaker posed the question: "Are fibers the same from a gut health perspective? There is not one single fiber that is going to make everybody happy," he said. "Even the predominance of a particular fiber may not be beneficial because the gut microbiome is a highly competitive environment and bacteria do not feed fiber equally."

Many fiber structures exist and some of these structures, from a chemical perspective, align to bacteria because the bacteria evolve to utilize fiber. When carbohydrates pass through the small intestine and enter the large intestine, they are fermented by the colonic bacteria. Through this process, major short-chain fatty acids (SCFAs) like acetate, butyrate, and propionate are produced.

A special category of dietary fiber, known as prebiotics, is defined as substrates that are selectively utilized by host microorganisms conferring a health benefit. Prebiotics such as fructooligosaccharides (FOS), inulin, and galactooligosaccharides (GOS) favor the growth of *Bifidobacterium* and *Lactobacillus* spp., and likely other beneficial species in the gut. However, in a broad sense, fermentable fibers that change the gut microbial community structure and provide health benefits may be considered prebiotics.

Dr Hamaker described a hierarchy of fiber functionality for its incorporation into foods. A low aim is that the fiber be tolerable and slowly fermented so people will consume them and that they are fermented in the distal colon where many of inflammatory diseases (eg, ulcerative colitis) and colon cancer are mostly located. A medium aim is that the fiber changes fatty acid profiles such as increasing butyrate due to its anti-inflammatory effects. A higher aim is to alter microbiota composition in a predicted way that creates positive change, such as lowering chronic inflammation and improving gut barrier function.

MAJOR GROUPS OF DIETARY FIBERS*

- Non-starch polysaccharides
 - Cellulose, hemicelluloses (eg, pectin, arabinoxylans, β -glucan, glucomannans, xyloglucans), plant gums/mucilages & hydrocolloids
- Non-digestible oligosaccharides
 - FOS & GOS
- Starch-based material
 - Resistant starch
 - Soluble corn fiber
- Novel carbohydrate compounds
 - Polydextrose, mixed-linked α -glucans
- Lignin

**Not all are confirmed as meeting the new dietary fiber definition by the FDA. The FDA has not yet finalized the list of what qualifies for the new definition of fiber. To date, only a few fibers have been approved by FDA.*

HOW DO THE GUT BACTERIA RESPOND TO DIETARY FIBERS/PREBIOTICS?

Gut microbiota communities respond differently to the same fibers,⁸ and this affects SCFA production. These differences depend on which bacteria are utilizing the fibers and how they metabolize the fiber. Dr Hamaker cited a recent study⁹ where 62 subjects received either the New Nordic Diet (high in fiber/whole grain, fruits and vegetables) or an Average Danish Diet (control diet) for 26 weeks. Researchers found that individuals with a higher *Prevotella to Bacteroides* (P/B) ratio appeared more prone to lose body fat on diets high in fiber and whole grain than subjects with a low P/B ratio.

THINKING IN A DIFFERENT WAY

Dr Hamaker concluded his presentation suggesting that instead of testing dietary fibers to see how they function, scientists should try to understand desirable microbiota individual or group requirements, and align polysaccharides/oligosaccharides (chemical structure/physical forms) for their promotion. He said the same should be done for pairing carbohydrate structure to probiotics, identifying substrates that strains can compete well.

As for the future of prebiotic fibers, Dr Hamaker predicted a broader range of prebiotics would become available. He also foresees a more targeted approach in healthcare in using prebiotics. Targeted approaches may include identification of different prebiotic chemical and physical forms that favor (or disfavor) bacteria or bacterial groups and the location of fermentation in the colon. Lastly, a personalized approach to prebiotics may be the future.

THE GUT MICROBIOME AND HUMAN HEALTH

Dr Holscher began her presentation by defining the following learning objectives: 1) to compare-and-contrast bacteria and fibers interplay with chronic disease, and 2) to discuss the ways fiber can be used to modulate gut microbiota and health. She presented an analogy that the microbiome is a microbial organ that needs to be supported through diet because the microbial byproducts influence the balance between health and disease.

The gut microbiome performs many functions¹⁰⁻¹¹ such as fermenting nondigested food and synthesizing secondary bile acids, vitamins, and neurotransmitters. Protective functions include pathogen displacement, nutrient competition, immune stimulation, and antimicrobial secretion. Although the symposium focused on fiber, microbes can ferment protein and interact with dietary fat. Therefore, any food that escapes digestion from human intestinal secreted enzymes can become available and utilized by microbes if they have the genetic capacity and the enzymes to break the food down. Systemically, the gut microbiome is associated with bone health, cognition and brain development, intestinal disease, obesity and insulin resistance, and nonalcoholic liver disease.¹⁰

FIBER AND ITS FUNCTIONS

Fiber is described by its solubility, viscosity, and fermentability.¹² Insoluble fibers (cellulose, bran) have laxative effects. Soluble, viscous and non-fermented (psyllium) fibers lower cholesterol and improve glycemia, weight loss, and stool normalization. Soluble, viscous, and readily fermented fibers (β -glucan, pectin) lower cholesterol and improve glycemia. The classic prebiotic fibers are soluble, non-viscous, and fermentable, which are fructo- and galacto-oligosaccharides, inulin, polydextrose, soluble corn fiber, and resistant starch. Fermentable fibers result in the production of SCFAs that can, in turn, affect satiety and food intake through the enterohormones peptide YY (PYY) and glucagon-like peptide 1 (GLP-1).¹³



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Low microbiota diversity limits the benefits of an optimal diet because the microbes do not have the tools to break down fibers, thus limiting the production of SCFAs. A complex diet and high microbiota diversity increase access to complex carbohydrates, allowing the microbes to utilize the energy and produce fermentation end products.¹¹ Unfortunately, most Americans have low diet complexity and low microbial diversity because they do not consume the daily recommended intake of fiber.

EXAMPLES OF FIBER-MICROBIOME INTERACTIONS

Specific fibers that can be fermented by gut microbes include β -glucan and inulin.¹⁴ Common sources of inulin include chicory root, onion, artichoke, agave, wheat, bananas, and garlic. Some of the reported positive health effects of inulin intake include reduced inflammation,¹⁵ food intake, body weight, and fat mass.¹⁶

Food sources containing β -glucan include whole grain barley, oats, and rye. Similar health benefits included positive immunomodulation effects.¹⁷ From a metabolic perspective, β -glucan may improve glucose, insulin, and lipid levels following consumption.¹⁸⁻¹⁹ β -glucan may also adhere to bile, improve insulin sensitivity, and slow gastric emptying.²⁰ Microbially, β -glucan may increase SCFAs,¹⁵ increase the abundance of *Lachnospira* and reduce *Enterobacteriaceae*,¹⁵ and increase abundance of beneficial bacteria such as *Bifidobacterium* and butyrate producers such as *Eubacterium* and *Roseburia*.²¹

Dr Holscher concluded her presentation with two key takeaways: 1) dietary fibers and prebiotics differentially affect the human gut microbiome, and 2) the connections between the microbiome and human health include gastrointestinal as well as metabolic and psychological outcomes.

LEVERAGING MICROBIOME SCIENCE IN THE FOOD INDUSTRY

Dr Garleb gave the final presentation from an industry perspective. To preface the talk, he agreed that the microbiome field “holds a lot of promise,” but cautioned against “outrunning the science.” His presentation focused on the factors that need to be accounted for when companies develop products to address the microbiome. These include scientific rationale, commercial claims and regulatory considerations, and user experience. He then followed with an overview of commercially available products containing fiber or probiotics, and discussion of benefits of next generation products.

SCIENTIFIC RATIONALE

Before developing a product, the following basic scientific questions need to be addressed.

- What are the benefits of a healthy microbiome?
- What does a healthy microbiome look like and are there individual “hero” organisms?
- What dietary constituents can modify the composition and/or activity of the microbiota, and can these be added to food?
- Do we understand the mechanism of action?
- Does the entire microbiome need to be added, or can we stimulate the microbiota by adding only a prebiotic?

PREBIOTIC HEALTH EFFECTS

Fructooligosaccharide (FOS)

- Satiety
- Calcium and other mineral absorption, bone health

Galactooligosaccharide (GOS)

- Stimulation of neurochemical-producing bacteria in the gut
- Urogenital health
- Decreased symptoms of Irritable Bowel Syndrome (IBS)
- Skin health, improved water retention and reduced erythema
- Decreased incidence of Traveler’s diarrhea

FOS & GOS

- Decreased risk of allergy
- Metabolic health: improved glycemia; decreased incidence of dyslipidemia, inflammation
- Bowel habit and general gut health in infants
- Decreased risk of necrotizing enterocolitis in preterm infants

Adapted from Table 1: Health end points targeted in human trials of orally administered prebiotics from the International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics²²



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COMMERCIAL CLAIMS AND REGULATORY CONSIDERATIONS

Commercial product considerations include benefits, what the product does; and claims, what manufacturers can say the product does. To claim a health benefit of a product, the claim must be substantiated by scientific (clinical) evidence, and the claim must follow government regulations, which differ across the globe. Because of this, food companies must carefully plan what type of clinical endpoints to measure and how large of a sample size will be needed for clinical trials knowing that they cannot make drug claims.

Dr Garleb also noted that the believability of claims is very important. As an example, even though interest in the potential effects of nutrition on cognition is high, believability of its effects on the adult population is low. These factors influence both research strategy and consumer choice. The lower the believability, often the greater, and more enduring the challenge to sufficiently do the science.

USER EXPERIENCE

The consumer's experience using a product is important to consider as explained by Dr Garleb: "Having the product in the marketplace is important, but so is keeping the product in the marketplace." Consumers must like the taste of the product, easily obtain and keep the product fresh, and be tolerant of potential side effects.

Maintaining probiotic viability is especially challenging because they cannot be made into a retorted shelf-stable liquid. Although probiotics can be incorporated into powder products, their stability varies depending on the moisture content of the powder and the complexities of distribution. Finally, GI tolerance to fiber may be difficult to gauge due to the variable effects it has between different individuals.

Lastly, Dr Garleb discussed the value of the product, which is the cost-benefit. Another element is whether the consumer realizes the benefit and how long the benefit takes to occur. Consumers want to know that the product is working.

CURRENT FOOD OPTIONS

The marketplace currently offers various microbiome modulators. Probiotics and prebiotics could theoretically alter the microbiome. Some of the many commercial probiotics include members from the following genera: *Lactobacillus*, *Bifidobacterium*, *Lactococcus*, *Streptococcus*, *Bacillus*, and *Saccharomyces*. All, except for *Bacillus coagulans*, which is a spore-former, are prone to temperature inactivation.

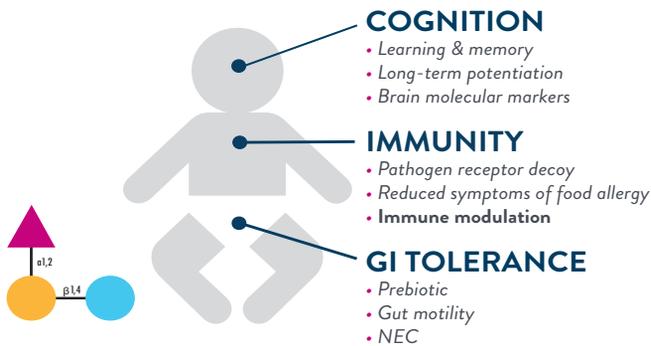
Commercially viable sources of intrinsic fiber include wheat and oat bran. Wheat is a standard product that people are willing to purchase. Dr Garleb noted that wheat and oat bran cereal manufacturers have done a very good job at developing palatable and low cost products that provide health benefits.

Other food products contain isolated or synthetic fiber such as inulin, FOS, and GOS, which were discussed earlier. FOS can be found in infant formula to mimic the natural prebiotic fibers that are found in human milk. An important aspect to remember when incorporating ingredients into processed foods is how their efficacy may change through processing. For instance, some prebiotics are reducing sugars that will react with protein upon heating to form new structures.

NEXT GENERATION OF MICROBIOME MODULATORS

Human milk oligosaccharides (HMOs), which are non-digestible, multifunctional carbohydrates, are the third most abundant macronutrient in human milk. More than 150 different HMO structures have been identified in human milk. Until recently, infant formula manufacturers could not structurally replicate HMOs, so they tried to reproduce the prebiotic functionality of HMOs using other oligosaccharides such as FOS and GOS. However, technology has progressed over the last several years, and some of these HMOs can now be produced through chemical synthesis or fermentation, including 2'-fucosyllactose (2'-FL), the most abundant HMO.

IMPORTANT NOTICE: Breastfeeding is best for babies and is recommended for as long as possible during infancy.



Preclinical italicized
Clinical bolded

CLINICAL BENEFITS

IMMUNITY

Reduced circulating inflammatory markers to be more like breastfed infants

PREBIOTIC

Circulating gut bacterial metabolites more like breastfed infants

POTENTIAL CLINICAL BENEFITS

Reduced abdominal discomfort due to colic or pediatric IBS

Improve feeding tolerance in preterm infants

Alleviate food allergy

Improve cognition

Emerging research indicates the potential multifunctional benefits of 2'-FL. The synthetic form currently is commercially available in some products. Multiple companies are taking advantage of this new technology in formulations that are marketed across the lifespan.²³⁻³⁶

Another emerging area of research supporting the use of prebiotics and probiotics is management of *Clostridium difficile* infection (CDI). *Clostridium difficile* is a gram-positive, spore-forming, toxin-producing bacterium. The infection is the leading cause of nosocomial diarrhea affecting up to 20% of hospitalized patients receiving antibiotics.³⁷ CDI also is responsible for up to 25% of the cases of antibiotic-associated diarrhea, and causes up to 20,000 deaths in the United States annually.³⁷ Disrupted microbiomes are at risk for this infection but a viable, safe, and effective treatment is microbiome restoration through fecal transplant.³⁸

Dr Garleb closed his presentation reviewing that commercial product considerations include benefits (claims), user experience, and value to the customer. Current product options targeting the microbiome are leveraging probiotics and prebiotics. Lastly, as science's understanding of the microbiome and the health benefits it conveys expands, so will the products that target these benefits.

IMPORTANT NOTICE: Breastfeeding is best for babies and is recommended for as long as possible during infancy.

CONCLUSION

The symposium highlighted the interactions between gut bacteria, dietary fiber and our health, and how industry is translating this rapidly expanding body of scientific evidence into consumer products. Up to 1,000 different microbial species reside in our gut. Through the use of prebiotics—particularly dietary fiber—and probiotics, that support colonization of or metabolism within specific species, we may be able to alter the composition and function of our gut microbiome and thus our health.



From left to right: Lauri Byerley, PhD (moderator); Hannah Holscher, PhD, RD (speaker); Jack Gilbert, PhD (speaker); Bruce Hamaker, PhD (speaker); Keith Garleb, PhD (speaker)

GUT MICROBIOME BASICS AND TRANSLATION INTO CONSUMER PRODUCTS

FACULTY AGENDA

THE MICROBIOME AND MICROBIAL SYSTEMATICS

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BACTERIAL METABOLISM OF CARBOHYDRATES, DIETARY FIBER AND THE GUT MICROBIOME

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THE GASTROINTESTINAL MICROBIOME & HUMAN HEALTH

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LEVERAGING MICROBIOME SCIENCE IN THE FOOD INDUSTRY

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