

14th – 15th October 2015
The Nittany Lion Inn, State College, Pennsylvania



PROGRAM AND ABSTRACTS

Organized by



PennState
College of Agricultural Sciences

Welcome Message from the Conference Chair

Dear Colleagues,

On behalf of the organizing committee, I am honored and delighted to welcome you to participate in this transdisciplinary conference: **The Food Systems Approach to Gut Health**. The Department of Food Science, College of Agricultural Sciences – Penn State University, Penn State Hershey Medical Center, The Children's Hospital of Philadelphia (CHOP), The Seattle Children's Hospital, industries (Agilent and Waters), and the USDA have joined forces to organize a strong interdisciplinary meeting of researchers from plant science, food science, nutrition, biomedical sciences, and medicine focused on development of food-based approaches to chronic disease prevention. During the 20th century, we learned a great deal about the importance of macro- and micronutrients in human health and disease. In the last few decades we learned the critical role saturated fat, cholesterol, and phytonutrients have in the promotion and prevention of chronic diseases. Despite these advances in our understanding of food, effective and science-based whole food strategies to counter the growing epidemic of chronic diseases such as inflammatory bowel disease, colon cancer and type 2 diabetes are limited. This conference will include cutting-edge presentations ranging across multiple areas including: gut immunity in health and disease – cellular, molecular and microbial perspectives; the effect of farm-to-fork operations on anti-inflammatory compounds in foods; pre- and probiotics; animal models for inflammation; safety of isolated bioactive compounds; and the microbiome, inflammation, and gut health from a clinical perspective. These topics are focused with the long-term goal of generating information that will lead to the development of safe, affordable and effective food-based strategies for chronic disease prevention and therapy.

We sincerely hope you will take an active part in this leading-edge conference and contribute your own invaluable expertise and unique perspective during panel discussions.

Jairam K. P. Vanamala, PhD

Organizing Committee

Jairam K. P. Vanamala, PhD, Assoc. Prof.	The Pennsylvania State University
Joshua D. Lambert, PhD, Assoc. Prof.	The Pennsylvania State University
Mary J. Kennett, DVM, PhD, Diplomate ACLAM, Prof.	The Pennsylvania State University
Lavanya Reddivari, PhD, Asst. Prof.	The Pennsylvania State University
Gregory R. Ziegler, PhD, Prof.	The Pennsylvania State University
Dale Young Lee, MD, MSCE, Asst. Prof.	Seattle Children's Hospital
James D. Lewis, MD, MSCE	University of Pennsylvania
Maria R. Mascaranehas, MBBS	The Children's Hospital of Pennsylvania
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Sridhar Radhakrishnan, PhD	The Pennsylvania State University
Abigail Sido, MS Student	The Pennsylvania State University

Acknowledgements

We thank Joselyn N. Allen (The Pennsylvania State University) for creating the scientific illustrations within this publication.

We also thank members of the Vanamala lab as well as the staff and faculty of Penn State Food Science for their support to make this conference a success.

Conference Etiquette

Please note that guests are not permitted to take photographs or videos of any presentations, posters, or slides without the prior consent from the authors/presenters. Also, attendees must obtain permission from the author before work presented at this conference can be cited.

Parking

Parking is available in the Nittany Deck located near the Nittany Lion Inn on Fischer Road. You will receive a ticket from the kiosk coming in to the garage. Please bring this ticket to the front desk of the Nittany Lion Inn and state you are with the Food Systems Approach to Gut Health Conference to receive a stamp for complimentary parking. Please hand this ticket to the parking attendant on your way out of the garage.

Connecting to Wi-Fi

Internet access is located throughout the Nittany Lion Inn and is free to all attendees. Guests need to connect to the “AT&T Wireless” and accept the terms of agreement.

Charging Devices

Power outlets have been conveniently placed throughout the conference rooms for you to charge your devices during presentations so you can take notes on your laptop or tablet if you prefer.

Insurance

The conference organizers do not accept liability for personal injuries or loss/damage of personal property either during, or as a result of the Conference.

Security

Please display your name badge clearly at all times. If you do not, you will not be permitted to enter the conference areas.

Food Systems Approach for Gut Health Conference

Nittany Lion Inn, Ballroom C
October 14-15, 2015

AGENDA

Wednesday, October 14, 2015

- 7:30 AM **Registration Check-In**
Nittany Lion Inn, Ballroom C
- 8:00 AM **Opening Remarks**
Robert F. Roberts, PhD, Professor and Head of Food Science, Penn State;
Richard Roush, PhD, Dean of the College of Agricultural Sciences, Penn State
- 8:15 AM **Vision for Food Systems Approach to Gut Health**
Jairam K. P. Vanamala, PhD, Associate Professor of Food Science, Penn State; Faculty at Penn State Hershey Cancer Institute

Session I: Gut Immunity in Health and Disease – Cellular, Molecular and Microbial

- 8:35 AM **Inflammation in the Gastrointestinal Tract: Challenges and Opportunities for Food/Nutrition Approach**
Dale Young Lee, MD, MSCE, Assistant Professor of Pediatrics, Seattle Children's Hospital
- 9:10 AM **Critical Role of Plasmacytoid Dendritic Cells in Immunoregulation by a Commensal Microbial Polysaccharide**
Suryasarathi Dasgupta, PhD, Research Associate of Microbiology and Immunobiology, Harvard Medical School
- 9:40 PM **Morning Break**
Refreshments/beverages in Atrium
- 10:00 AM **Advances in Innate Immunity-Gut Microbiota Interactions: Biological Warfare in the Gut**
Matam Vijay-Kumar, PhD, Assistant Professor of Nutritional Sciences, Penn State
- 10:35 AM **Probiotics, Immunity and Gut Health**
Connie J. Rogers, PhD, MPH, Assistant Professor of Nutritional Sciences, Penn State
- 11:10 AM **Animal Models of Inflammation for Gut Health and Beyond**
Mary J. Kennett, DVM, PhD, Diplomate ACLAM, Professor of Veterinary and Biomedical Sciences, Penn State
- 11:45 AM **Lunch**
Ballroom AB
- 1:00 PM **Panel Discussion**
Gary H. Perdew, PhD, John T. and Paige S. Smith Professor of Agricultural Sciences, Penn State

Session II: Food and Isolated Food Components for Gut Health

- 1:45 PM **Natural Variation in Dietary Anti-Inflammatory Compounds and Their Interaction with Gut Bacteria**
Lavanya Reddivari, PhD, Assistant Professor of Plant Science, Penn State
- 2:20 PM **Novel Framework for the Food-based Preclinical and Clinical Research**
Jairam K. P. Vanamala, PhD, Assoc. Professor of Food Science, Penn State; Faculty at Penn State Hershey Cancer Institute
- 2:55 PM **Isolated Bioactive Compounds and Safety**
Joshua D. Lambert, PhD, Associate Professor of Food Science, Penn State
- 3:30 PM **Afternoon Break**
Refreshments/beverages in Atrium
- 3:50 PM **Resistant Starch: A Prebiotic**
Gregory R. Ziegler, PhD, Professor of Food Science, Penn State
- 4:25 PM **The Intimate Interplay of Inflammatory Response and Malnutrition**
Gordon Jensen, MD, PhD, Professor and Head of Nutritional Sciences, Penn State
- 5:00 PM **Grant Opportunities for Food and Gut Health**
Deirdra Chester, National Program Leader, Division of Nutrition, National Institute of Food and Agriculture, USDA
- 5:20 PM **Panel Discussion**
A. Catharine Ross, PhD, Dorothy Foehr Chair and Professor of Nutritional Sciences, Penn State
- 6:00 PM **Hors d'ouvres**
Ballroom AB
- 6:30 PM **Poster Session**
Ballroom AB

Thursday, October 15, 2015 (Ballroom C)

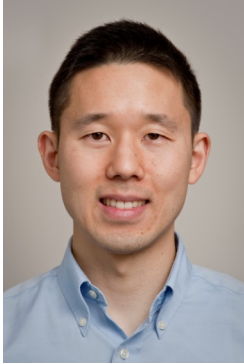
Session III: Nutrients and Gut Health

- 8:30 AM **The Effects of Vitamin D on T Cells, the Microbiota, and Immune Mediated Disease**
Margherita T. Cantorna, PhD, Distinguished Professor of Molecular Immunology, Penn State
- 9:05 AM **Vitamin A in Intestinal Health and Response to Gut Infection**
A. Catharine Ross, PhD, Dorothy Foehr Chair and Professor of Nutritional Sciences, Penn State
- 9:40 AM **Morning Break**
Refreshments/beverages in Atrium
- 9:55 AM **Endogenous Lipid Mediators, Redox Homeostasis, and Gut Health**
K. Sandeep Prabhu, PhD, Professor of Immunology and Molecular Toxicology, Penn State
- 10:30 AM **The Ah Receptor Contributes to Gut Host-Microbiome Homeostasis**
Gary H. Perdew, PhD, John T. and Paige S. Smith Professor of Agricultural Sciences, Penn State
- 11:05 AM **Macrophages in Intestinal Health and Disease**
Milena Bogunovic, MD, PhD, Assistant Professor of Microbiology and Immunology, College of Medicine, Penn State Hershey
- 11:40 AM **Panel Discussion**
James D. Lewis, MD, MSCE, Professor of Medicine, Perelman School of Medicine, University of Pennsylvania
- 12:10 PM **Lunch**
Ballroom AB

Session IV: Microbiome, Inflammation, and Gut Health: A Clinical Perspective

- 1:10 PM **A Review of the Epidemiology of Inflammatory Bowel Disease with a Focus on Diet, Infections, and Antibiotic Exposure**
James D. Lewis, MD, MSCE, Professor of Medicine, Perelman School of Medicine, University of Pennsylvania
- 1:45 PM **Diet, the Gut Microbiota and its Metabolome**
Gary D. Wu, MD, Ferdinand G. Weisbrod Professor of Gastroenterology, Perelman School of Medicine, University of Pennsylvania
- 2:20 PM **Dietary Factors in the Modulation of Inflammatory Bowel Disease**
Lindsey G. Albenberg, DO, Assistant Professor of Pediatrics, Children's Hospital of Philadelphia
- 2:55 PM **Eosinophilic Esophagitis: Diet and the Esophageal Microenvironment**
Amanda Muir, MD, Pediatric Gastroenterologist in the Division of Gastroenterology, Hepatology and Nutrition, Children's Hospital of Philadelphia

- 3:30 PM **Afternoon Break**
Refreshments/beverages in Atrium
- 3:45 PM **The Importance of Integrating Food and Nutritional Approaches into
Clinical Practice: IBD as an Example**
*Matthew Coates, MD, PhD, Assistant Professor of Medicine, Penn State Inflammatory Bowel
Disease Center, Penn State Hershey*
- 4:05 PM **Panel Discussion – Next Steps and Translation Research Opportunities**
*Gary D. Wu, MD, Ferdinand G. Weisbrod Professor of Gastroenterology, Perelman School of
Medicine, University of Pennsylvania*
- 5:00 PM **Adjourn**



Dale Young Lee, MD, MSCE

Assistant Professor of Pediatrics

Seattle Children's Hospital, The University of Washington

Inflammation in the Gastrointestinal Tract: Challenges and Opportunities for the Food/Nutrition Approach

Inflammation in the gastrointestinal tract may be multifactorial, but food is an important exposure that can play a role in either pathogenesis or therapy. Epidemiological studies have implicated diet to play a role in both inflammatory bowel disease (IBD) and colon cancer. Risk factors for IBD and colon cancer overlap: higher fat consumption and red meat intake. Foods suggested as having a protective effect include fruits and vegetables. For Crohn's disease, a form of IBD, exclusive enteral nutrition (EEN) can be effective at inducing remission of active inflammation. EEN involves the exclusion of table foods and consuming a formula-based diet. For Crohn's disease a variety of other restriction diets have become popular amongst patients and may provide insight into the role of food in IBD pathogenesis. Patients and clinicians are interested in using diet to modify disease risk, and the present evidence is primarily from epidemiological studies, case series, basic science models, and limited clinical trials. The capture of dietary exposures is difficult and potential challenges include using accurate capture methodology, understanding the role of cultivation and storage of food products, being aware of the impact of processing (including cooking and preservation), and finally evaluating food-food interactions. Studying the association between food and inflammation in the gastrointestinal tract is an opportunity for broad collaboration across specialties.



Suryasarathi Dasgupta, PhD

Research Associate of Microbiology and Immunobiology

Harvard Medical School

Critical Role of Plasmacytoid Dendritic Cells in Immunoregulation Initiated by a Commensal Microbial Polysaccharide

Suryasarathi Dasgupta and Dennis L Kasper

The microbiota is critical in shaping the mammalian host's immune system. Polysaccharide A (PSA), the archetypical immunomodulatory microbial molecule of the gut commensal *Bacteroides fragilis*, induces regulatory T cells to secrete the anti-inflammatory cytokine interleukin 10. We show, in a model of colitis, that PSA requires both innate and adaptive immunity to generate protection. Dendritic cells mediate PSA's effect on IL-10 production. Unlike conventional DCs, plasmacytoid DCs exposed to PSA do not produce the proinflammatory cytokines tumor necrosis factor - alpha and IL-12 but PDCs do specifically stimulate IL-10 secretion by CD4+ T cells and efficiently mediate PSA-mediated immunoprotection. PSA induces and preferentially ligates Toll-like receptor 2 on PDCs but not on CDCs. Compared with other TLR2 ligands, PSA better enhances PDC expression of co-stimulatory molecules required for protection against colitis. PDCs orchestrate beneficial immunoregulatory interaction of commensal microbial molecules with CD4+ T cells through both innate and adaptive immunity.



Matam Vijay-Kumar, PhD

Assistant Professor of Nutritional Sciences

The Pennsylvania State University

Advances in Innate Immunity-Gut Microbiota Interactions: Biological Warfare in the Gut

Vishal Singh, Beng San Yeoh, Xia Xiao, Michael Bachman, Niels Borregaard, Bina Joe, Matam Vijay-Kumar

Mammalian intestines are colonized by vast number of bacteria collectively known as 'microbiota'. During an inflammatory response in the gut, some commensal bacteria such as *E. coli* belonging to phyla proteobacteria can thrive and contribute to disease. We demonstrate that enterobactin (Ent), a prototypical, conserved, catecholate siderophore released by *E. coli*, is a potent inhibitor of myeloperoxidase (MPO), a bactericidal enzyme of the host. The inhibition of MPO is specific to Ent and several other siderophores failed to inhibit MPO. An *E. coli* mutant (ΔfepA) that overproduces Ent, but not an Ent-deficient double mutant ($\Delta\text{aroB}/\Delta\text{fepA}$), inhibits MPO activity and exhibits enhanced survival in inflamed guts. This survival advantage is counter-regulated by lipocalin 2/NGAL, a siderophore-binding host innate immune protein, which rescues MPO from Ent-mediated inhibition. Spectral analysis reveals that Ent interferes with compound I [oxoiron, Fe(IV)=O] and reverts the enzyme back to its native ferric [Fe(III)] state. These findings define a fundamental mechanism by which *E. coli* surpasses the host innate immune responses during inflammatory gut diseases and gains a distinct survival advantage in the hostile environment.



Connie J. Rogers, PhD, MPH

Assistant Professor of Nutritional Sciences

The Pennsylvania State University

Probiotic, Immunity and Gut Health

Background: Probiotic bacteria are functional ingredients that provide significant health benefits, including improvements in immune function and gastrointestinal health. Numerous studies have examined the influence of probiotic bacteria, either alone or combined, on immune parameters in an effort to link probiotic use with reduced risk for inflammation and infection, such as upper respiratory tract infection (URTI). However, observed results vary by genus, species and strain of organism studied. Careful analysis of the immunomodulatory effect of each commonly used probiotic strain is necessary. *Bifidobacterium animalis* subsp. *lactis* BB-12 is a widely used strain in the genera *Bifidobacterium*. Evidence suggests that consumption of BB-12 combined with other probiotic species can modulate both gut transit time and immune responses in human subjects. However, combinations of probiotic bacteria make it difficult to determine the gastrointestinal and immunomodulatory properties of BB-12 alone.

Objective: The primary aim of this project was to evaluate the effect of oral consumption of one strain of probiotic bacteria, BB-12, at a dose of $\log 10 \pm 0.5$ CFUs/day, on gut transit time, as well as, innate and adaptive immune responses in healthy adults in a randomized, blinded, 4-period cross-over free-living study. Healthy adults (n=30) aged 18-40 years old were recruited, and received 4 treatments for 4 weeks in a random order: A) yogurt smoothie alone; smoothie with BB-12 added B) before or C) after yogurt fermentation, or D) BB-12 given in capsule form. At baseline and after each 4-week treatment, peripheral blood mononuclear cells (PBMCs) were isolated, and functional and phenotypic marker expression was assessed. Incidence and severity of cold or flu infection in the past month was assessed using established self-reported URTI questionnaire. Regional transit times, such as gastric emptying time (GET), small bowel transit time (SBTT) and colonic transit time (CTT) were measured at each time point by a wireless motility capsule (SmartPill®).

Results: After the 4 week intervention period, regional transit times were not influenced by either the yogurt smoothie or the supplement. However, consumption of BB-12 delivered in a yogurt smoothie post-fermentation significantly reduced pro-inflammatory cytokine (TNF- α) secretion from peripheral myeloid cells stimulated with heat-inactivated BB-12 (p=0.0490) or LPS (p=0.0387) compared to baseline in young healthy adults, suggesting an anti-inflammatory effect of BB-12. We also found that BB-12 interacted with peripheral myeloid cells via Toll-like receptor 2 (TLR-2), and consumption of yogurt smoothie with BB-12 added post-fermentation for 4 weeks significantly decreased TLR-2 expression on peripheral blood derived monocytes, which may contribute to the reduction in TNF- α secretion in participants.

Conclusion: These findings are not only the first to demonstrate anti-inflammatory properties of BB-12, but also indicate that the matrix of BB-12, and the timing of its addition to yogurt fermentation process influenced the immunological effects of BB-12.



Mary J. Kennett, DVM, PhD, Diplomate ACLAM

Professor of Veterinary and Biomedical Sciences

The Pennsylvania State University

Animal Models of Inflammation for Gut Health and Beyond

The microbiome of vertebrate animals influences homeostasis and disease, and the status of the microbiome is relevant to many clinical diseases including inflammatory bowel disease (IBD). The use of rodent and other animal models to study IBD is common. Mouse models may be acute or chronic, and are often chemically induced, but may also be genetically modified, or infectious. These models mimic numerous aspects of IBD and trigger various inflammatory responses. Germ free and gnotobiotic mice may also be used to study the microbe host interactions in the gut. The strengths and limitations of the use of gnotobiotic animals and several animal models of IBD will be highlighted. Lessons learned and the relevance to the clinic will be discussed.



Lavanya Reddivari, PhD

Assistant Professor of Plant Science

The Pennsylvania State University

Natural Variation in Dietary Anti-Inflammatory Compounds and Their Interactions with Gut Bacteria

Lavanya Reddivari and Jairam K. P. Vanamala

Accumulating evidence suggests that a plant-based diet rich in bioactive secondary metabolites is protective against chronic inflammation and related diseases. In the last decade plant secondary metabolites received prime standing in disease prevention research and numerous *in vitro*, laboratory animal, and human studies were conducted to determine the effectiveness of individual metabolites and whole foods against chronic diseases. However, the content and composition of secondary metabolites such as polyphenols vary significantly depending on genotype and/or cultivar (white-fleshed potato vs. red- or purple-fleshed potato) and environment (California grapefruit vs. Texas grapefruit). This aspect was not considered even in the contemporary nutritional studies. Moreover, emerging evidence suggests that dietary polyphenols are metabolized by gut bacteria and the metabolites differed in their anti-inflammatory properties compared to parent compounds. Understanding the natural variation and metabolism by gut bacteria is essential to determine how bioactive compounds can be best utilized to help reduce the risk of chronic inflammation and related diseases.

Studies by our laboratories and others have shown up to 30-fold variation, depending on the potato cultivar, in the content and antioxidant activity of polyphenols and these differences were manifested in their anti-inflammatory properties *in vivo* in a human-relevant animal model. Optimizing the sources of variability might help us develop plants to consistently and predictably deliver bioactive compounds.

Several studies have also shown that polyphenols increased the abundance of beneficial gut bacteria that are negatively correlated with inflammation related diseases. We have observed that potato polyphenols increased the abundance of *Bifidobacterium*, and *Akkermansia in vivo*. *Bifidobacterium* has in turn shown to metabolize anthocyanins in to more potent anti-inflammatory agents. Further understanding of complex interactions between plant bioactive compounds, gut bacteria and host may aid in developing food-based approach to counter chronic inflammation-promoted diseases.



Jairam K. P. Vanamala, PhD

Associate Professor of Food Science
Faculty Penn State Hershey Cancer Institute

The Pennsylvania State University

Novel Framework for the Food-based Preclinical and Clinical Research

Emerging evidence suggests that diet has a causal link to chronic inflammation-promoted diseases such as inflammatory bowel disease, colon cancer and type 2 diabetes. Indeed, diet contributes to 20-42% of all human cancers and over 50% of colon cancer. However, food is a great source of anti-inflammatory and anti-cancer compounds, which can be used to prevent these debilitating diseases. Surprisingly we have limited understanding on how food system's operations such as cultivar, storage, cooking methods and packaging affect the food metabolites and ultimately consumer's health. This talk will provide a novel framework for preclinical and clinical food-based research studies to assess the effect of farm to fork operation on food metabolome and in turn their effect on the mammalian physiology and pathology. We utilized potato, a global crop, and pig, a human-relevant model as well as advanced -omics technologies. This framework embraces complexity of food and provides a way to deliver dietary bioactive components (known and unknown) in a consistent way to counter growing problem of chronic disease in the U.S. and around the world.



Joshua D. Lambert, PhD

Associate Professor of Food Science

The Pennsylvania State University

Isolated Bioactive Compounds and Safety

There is growing evidence from laboratory model and observational human studies that certain foods and food-derived components have disease preventive activity. This has led to a proliferation of dietary supplements and functional foods that provide additional dosage forms of exposure to dietary phytochemicals. The safety of these dietary supplements is assumed based on the safety of the food from which the compound was isolated. It is reasonable to posit that different dosage forms have unique pharmacokinetic and pharmacodynamic characteristics. In addition, different dosage forms could allow administration of greater doses more rapidly. Recent case reports have linked use of green tea based dietary supplements with hepatotoxicity. Animal model studies by our laboratory and others have shown that oral bolus dosing with green tea polyphenols can induce hepatotoxicity in mice. These effects were related to induction of hepatic oxidative stress and mitochondrial function. Interestingly, administration of the same total daily dose as part of the diet resulted in hepatoprotective effects in high fat-fed obese mice. These differences appear to be due to the peak plasma levels achieved following oral administration of green tea polyphenols by bolus versus dietary dosing routes. In addition to the effects of dosage form on toxic potential, the health status and presence of specific disease conditions can alter the susceptibility of the subject to the toxic effects of a given dietary component. Green tea polyphenols have been shown to reduce intestinal tumorigenesis in a number of animal models in part by reducing markers of inflammation and oxidative stress, however studies from our laboratory have observed that treatment of dextran sulfate sodium (DSS)-induced mice with green tea polyphenols worsened body weight loss and decreased survival compared to mice treated with DSS only. These effects were related to enhanced fat and protein excretion in the feces and suggest that green tea may interfere with nutrient digestion and absorption. Whereas inhibition of nutrient absorption in the context of obesity maybe beneficial, such inhibition in the context of compromised nutrition may exacerbate toxicity. In summary, our results and those of others indicate that it is unreasonable to assume that all dosage forms of food-derived components may not be equivalent in terms of pharmacokinetic behavior or toxic potential. Further, the beneficial effects of a dietary component cannot be assumed to generalizable across different populations. Careful safety evaluation with well-characterized dosage forms and defined populations are needed to better establish the potential usefulness of food-derived components in promoting human health.



Gregory R. Ziegler, PhD

Professor of Food Science

The Pennsylvania State University

Resistant Starch: A Prebiotic

This talk will explore enzyme resistant starch, its origins, and purported effects on health in the context of bioactive carbohydrates and dietary fiber in general. The presentation will include definitions of resistant starch and means of measurement, and where resistant starch fits with other components of dietary fiber. Recent results on the effect of processing methods on dietary fiber in potatoes will be presented.



Gordon Jensen, MD, PhD

Professor and Head of Nutritional Sciences

The Pennsylvania State University

The Intimate Interplay of Inflammatory Response and Malnutrition

Growing evidence suggests that varying degrees of acute or chronic inflammation are key contributing factors in the pathophysiology of malnutrition that is associated with disease or injury. Inflammation promotes metabolic dysregulation, hyperglycemia, decreased visceral proteins, muscle catabolism, edema, anorexia, and malaise / deconditioning. Inflammation may also blunt favorable responses to nutrition therapies. We have proposed a new etiology driven approach to nutrition diagnosis for adults in the clinical practice setting. These malnutrition syndromes include “starvation-related malnutrition”, when there is chronic starvation without inflammation, “chronic disease-related malnutrition”, when inflammation is chronic and of mild to moderate degree, and “acute disease or injury-related malnutrition”, when inflammation is acute and of severe degree. Feasibility and validity testing of malnutrition markers and characteristics will be discussed. Inflammation can be a good thing; let's try to keep it that way.



Deirdra Chester, PhD, RDN

National Program Leader
Division of Nutrition

Institute of Food Safety and Nutrition
National Institute of Food and Agriculture, USDA

Grant Opportunities for Food and Gut Health

This session will provide an overview of USDA-NIFA nutrition research and programs to the Food Systems Approach to Gut Health conference participants. The programs that will be presented are the AFRI Foundational Programs from the Food Safety, Nutrition and Health portfolio. Information on research and programs specifically the Function and Efficacy of Nutrients Program and the Improving Food Quality Program will be shared. Gaps in nutrition science not covered by existing funding opportunities will be shared. The conference participants will also have an opportunity to share their insight on new areas of funding needed in this portfolio.



Margherita T. Cantorna, PhD

Distinguished Professor of Molecular Immunology and
Nutrition

The Pennsylvania State University

The Effects of Vitamin D on T Cells, the Microbiota and Immune Mediated Disease

M. T. Cantorna, S. Bora, J. Chen, A. Waddell, J. O. Hoi, and K. McDaniel

Evidence from animal models of immune mediated diseases and epidemiological studies in human patients support a role for vitamin D in the pathogenesis of diseases such as inflammatory bowel disease (IBD). The active form of vitamin D ($1,25(\text{OH})_2\text{D}_3$) inhibits the development of IBD. $1,25(\text{OH})_2\text{D}_3$ directly inhibits IFN- γ and IL-17 production from Th1 and Th17 cells. In addition, vitamin D regulates the development of several regulatory T cell types including FoxP3 + T regulatory cells, TCR $\alpha\beta$ /CD8 $\alpha\alpha$ intraepithelial lymphocytes and invariant NKT cells. Paradoxically infections that require Th1 and Th17 cells for protection are not affected by $1,25(\text{OH})_2\text{D}_3$ treatments in vivo. Instead our data suggests that vitamin D is a late regulator of effector T cells and is critical for turning off IFN- γ and IL-17 production. In IBD, the antigens are persistent and the ability to turn off Th1 and Th17 responses are critical.

Other effects of vitamin D on immune mediated disease include regulation of the microbiota. The effectiveness of vitamin D to regulate IBD was inhibited by disruptions of the microbiota using broad spectrum antibiotics. More specifically the Helicobacteraceae family members within the Proteobacteria phylum were higher in vitamin D deficient mice and this was associated with more severe colitis. $1,25(\text{OH})_2\text{D}_3$ or antibiotics treatment reduced Helicobacteraceae numbers and was associated with less severe disease. In addition, the ability of the host to produce $1,25(\text{OH})_2\text{D}_3$ depends on the microbiota. Colonization of germfree mice resulted in induction of the enzyme that produces active $1,25(\text{OH})_2\text{D}_3$ and as a result significantly higher amounts of $1,25(\text{OH})_2\text{D}_3$ in the blood. The symbiotic relationship between two environmental factors (vitamin D and the microbiota) that both influence the development of immune mediated diseases has important and unappreciated implications for patients with IBD.



A. Catherine Ross, PhD

Dorothy Foehr Chair and Professor of Nutritional Sciences

The Pennsylvania State University

Vitamin A in Intestinal Health and Response to Gut Infection

Vitamin A (retinol and its metabolites) plays an important role in embryonic development of numerous tissues, including the intestine. The early specification of the overall body plan, including formation of the neural tube and anterior-posterior axis is regulated in part by retinoic acid (RA), as is organogenesis in the mid-gestational period. Vitamin A, in the form of RA, is essential for maintenance of epithelial tissues throughout life. In adult animals, having adequate vitamin A, or RA as a surrogate, influences the response to trauma, such as intestinal resection. RA is necessary for proper immune cell homing and functions in the intestine. Vitamin A deficiency causes a reduction in the numbers of T and B cells in the lamina propria, in part due to reduced expression of lymphocyte homing molecules and their receptors. Innate lymphoid cells are also affected by vitamin A status. RA also helps promote appropriate development of regulatory T cells (Treg), and influences the balance of Th1/Th2 cells [reviewed in (1)]. Moreover, the production of immunoglobulin A (IgA), is reduced, which may affect protective immunity under normal homeostatic conditions and the ability respond to intestinal infections. Our research (2) has shown that vitamin A-deficient mice fail to clear a *Citrobacter rodentium* infection, which is used as a model of an enteropathogenic *E. coli* infection in humans. When these mice are treated with RA, they are then able to clear the infection, similar to vitamin A-adequate mice. Overall, vitamin A is an important micronutrient for maintaining gut health, involving both epithelial cell and immune cell mechanisms.



K. Sandeep Prabhu, PhD

Professor of Immunology and Molecular Toxicology

The Pennsylvania State University

Endogenous Lipid Mediators, Redox Homeostasis, and Gut Health

Inflammation is a hallmark of inflammatory bowel disease (IBD) that involves macrophages. Given the inverse link between selenium (Se) status and IBD-induced inflammation, our objective was to demonstrate that selenoproteins in macrophages were essential to suppress pro-inflammatory mediators, in part, by the modulation of arachidonic acid metabolism. Acute colitis was induced using 4% DSS in wild type mice maintained on Se-deficient (<0.01 ppm Se), Se-adequate (0.1 ppm; sodium selenite), and two supraphysiological levels in the form of Se-supplemented (0.4 ppm; sodium selenite) and high Se (1.0 ppm; sodium selenite) diets. Transfer RNA^{Sec} (tRNA^[sec]) knockout mice (*Trsp*^{fl/fl}*LysM*^{Cre}) were used to examine the role of selenoproteins in macrophages on disease progression and severity using histopathological evaluation, expression of pro-inflammatory and anti-inflammatory genes, and modulation of prostaglandin (PG) metabolites in urine and plasma. While Se-deficient and Se-adequate mice showed increased colitis and exhibited poor survival, Se supplementation at 0.4 and 1.0 ppm increased survival of mice and decreased colitis-associated inflammation with an up-regulation of expression of pro-inflammatory and anti-inflammatory genes. Metabolomic profiling of urine suggested increased oxidation of PGE₂ at supraphysiological levels of Se that also correlated well with Se-dependent upregulation of 15-hydroxy-PG dehydrogenase (15-PGDH) in macrophages. Pharmacological inhibition of 15-PGDH, lack of selenoprotein expression in macrophages, and depletion of infiltrating macrophages indicated that macrophage-specific selenoproteins and upregulation of 15-PGDH expression were key for Se-dependent anti-inflammatory and pro-resolving effects. Selenoproteins in macrophages protect mice from DSS-colitis by enhancing 15-PGDH-dependent oxidation of PGE₂ to alleviate inflammation, suggesting a therapeutic role for Se in IBD.



Gary H. Perdew, PhD

John T. and Paige S. Smith Professor of Agricultural Sciences

The Pennsylvania State University

The Ah Receptor Contributes to Gut Host-Microbiome Homeostasis

Iain A. Murray, Limin Zhang, Robert Nichols, Istvan Albert, Andrew D. Patterson and Gary H. Perdew

The intestinal microbiota is recognized as an important contributor to host physiology, impacting diverse signaling networks not only within the intestinal tract but holistically. Environmental and genetic factors represent key components in establishing and maintaining the intestinal microbiota. The aryl hydrocarbon receptor (AHR) is emerging as an increasingly pleiotropic factor, modulating biological pathways beyond its established role as a xenobiotic sensor. Recently, the AHR has been demonstrated to modulate microbial immune surveillance within the intestinal tract through various mechanisms including the retention of ROR- γ -t⁺ intraepithelial lymphocytes. As such, environmental and/or genetic manipulation of AHR activity is likely to influence host-microbe homeostasis. Utilizing a model of C57BL/6/J heterozygous (*Ahr*^{+/-}) and knockout (*Ahr*^{-/-}) littermates co-housed together and then subjected to 14 days of genotypic segregation, we examined the influence of AHR expression upon the composition and functionality of the intestinal microbiota together with subsequent alteration of host physiology utilizing a wide variety of techniques.



Milena Bogunovic, MD, PhD

Assistant Professor of Microbiology and Immunology

Penn State Hershey College of Medicine

Macrophages in Intestinal Health and Disease

Balazs Koscsó, Kavitha Gowda, Milena Bogunovic

Mononuclear phagocytes are an essential component of the intestinal immune system. They are comprised of few dendritic cell (DC) and macrophage subsets, all with the common ability to sample extracellular milieu and to discriminate between dangerous and inert signals. Despite the commonality, each mononuclear phagocyte subset is shaped by its immediate microenvironment to acquire distinct developmental pathways and unique functions. Heterogeneous intestinal macrophages develop from monocytes and are distinguished from DCs by their expression of CX₃C-chemokine receptor 1 (CX₃CR1). In contrast to DCs, which distribution is limited to the mucosa, a cellular network formed by macrophages expands beyond the mucosa into the submucosa and muscularis externa. We demonstrate that mucosal macrophages are a driving force of protective immunity against enteroinvasive infection. We also show, that muscularis Ms express a distinct transcriptome signature. They are positioned along nerve fibers of the enteric nervous system and regulate gastrointestinal motility by controlling functions of enteric neurons. We propose that coordinated efforts of intestinal macrophage subsets are required to promote intestinal integrity at both steady state and disease.



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A Review of the Epidemiology of Inflammatory Bowel Disease with a Focus on Diet, Infections, and Antibiotic Exposure

Inflammatory bowel disease (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are chronic debilitating diseases that occur in populations around the world. The underlying etiology is thought to be multifactorial, including both genetic and environmental factors. Globally, there is evidence of increasing incidence of CD and UC over time. Furthermore, the rising incidence of IBD in Western countries has generally predated that in developing nations, leading to the hypothesis that "western" lifestyle, particularly from an early age, contributes to the etiology of IBD. Proposed mechanisms through which diet could influence the incidence of IBD, including direct dietary antigens, altering the gut microbiome, influencing gene expression, and affecting gastrointestinal permeability. In addition to diet, other factors can influence the composition of the gut microbiome. Recent studies have identified an increased risk of IBD after common enteric infections. Antibiotic exposure has also been associated with an increased risk of developing IBD, particularly CD. Detangling the relationship between diet, the gut microbiome and IBD raises the potential to reduce the incidence of IBD through dietary modification, an approach that might be considered among those at the highest risk (e.g., children of parents with IBD).



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Diet, the Gut Microbiota and its Metabolome

The human gut contains a vast number of microorganisms known collectively as the “gut microbiota”. Despite its importance in maintaining the health of the host, growing evidence suggests the gut microbiota may also be an important factor in the pathogenesis of various diseases, a number of which have shown a rapid increase in incidence over the past few decades. In some of these diseases, such as IBD, the microbiota is “dysbiotic” with an altered community structure and decrease in diversity. If the dysbiotic microbiota plays a role in disease pathogenesis, interventions that modify its composition might be a strategy to treat certain disease processes. The composition of the microbiota can be influenced by many factors including age, genetics, host environment, and diet. There is epidemiologic data associating diet with the development of inflammatory bowel disease (IBD) as well as evidence that diet can influence both the form and function of the microbiome in a manner that impacts upon the development of intestinal inflammation. Based on this evidence, studies are now underway to examine the effect of defined formula diets (DFDs), an effective therapeutic modality in Crohn’s disease, on both the gut microbiome and its metabolome as a therapeutic probe with the hope of better defining the “healthy” diet in patients with IBD. Diet has an impact upon both the composition and function of the microbiota in part through small molecule production that may influence development of both immune-mediated with metabolic diseases. The steady state level of these plasma metabolites can be influenced, not only by their rate of production by the gut microbiota, but also by their absorption and excretion. Elevation of certain metabolites due to decreased renal clearance may play a role in the development of comorbidities observed in patients with chronic kidney disease such as coronary vascular disease. Finally, by comparing dietary intake, the gut microbiota, and the plasma metabolome in omnivores vs. vegans, we provide evidence that the production of certain bacterial metabolites is constrained by the composition of the gut microbiota. These findings were confirmed in a controlled human diet experiment. In total, these results demonstrate the potential promise of dietary manipulation of the gut microbiota and its metabolome as a modality to both maintain health and treat disease. In order to accomplish this goal, there is a need for human intervention studies to demonstrate cause-and-effect relationships.



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Dietary Factors in the Modulation of Inflammatory Bowel Disease

The inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC) affect approximately 1.5 million Americans and the incidence is increasing worldwide. These diseases result in chronic, relapsing inflammation of the gastrointestinal tract. The pathogenesis of IBD is currently thought to involve an inappropriate and persistent inflammatory response to commensal gut microbes in genetically susceptible individuals.

The general goals for managing IBD are to eliminate symptoms of disease, improve quality of life, and avoid hospitalization and surgery. Currently, the mainstays of IBD therapy are medications targeted at key positions in the inflammatory pathway such as immunomodulators and biologics. The majority of these medications cause immune suppression to some degree and so adverse events are sometimes unavoidable. These adverse events can be potentially serious such as infection or malignancy. Therefore, the risks associated with these medications must always be weighed versus the potential benefit to the patient. Understandably, patients and families often find the potential adverse events associated with these medications overwhelming and they desire therapeutic regimens which do not involve suppression of the immune system. Given data demonstrating epidemiologic associations between diet and IBD, dietary therapies for IBD, particularly Crohn's disease, have been considered. It is well known that IBD patients consider diet to be important as patients with IBD frequently identify dietary components that cause increased symptoms (lactose, gluten, etc.) and often follow very restricted diets that are self-imposed. With the exception of enteral nutritional therapy for the treatment of CD, there is no rigorously studied diet for the treatment of IBD that has consistently demonstrated benefit. Thus, there are only a few dietary recommendations that we can endorse as clinicians based on the current evidence and clearly more research is needed in this area.

Enteral nutritional therapy is a dietary treatment regimen which lacks immune suppression. This is a therapy which has been utilized to treat Crohn's disease for almost four decades and multiple studies have demonstrated efficacy with similar placebo response and remission rates as compared to pharmacological therapies. In CD, exclusive enteral nutrition with elemental, semi-elemental, or polymeric formula diets has been widely studied for induction of remission and is considered first line therapy in certain parts of the world. These diets are also efficacious in maintaining remission. The most common protocol involves the administration of a defined formula at 100% of caloric needs for 4-12 weeks in order to induce remission. The formulas typically prescribed are polymeric or elemental and can be consumed orally or can be administered through a nasogastric (NG) or gastrostomy tube. A smaller percentage of calories, provided by the defined formula, may be required in order to *maintain* remission, allowing additional flexibility in the diet. While nutritional therapy has been shown to be efficacious in the treatment of CD, the mechanism of action has not been well characterized. Some hypotheses involve reduction in luminal antigens and food exclusion, a direct anti-inflammatory effect of the formula, improved nutrition, and changes in the gut microbiota. An enhanced understanding of the mechanism of action may allow for the development of less restrictive protocols which achieve the same effect. Additionally, mechanistic studies may help to identify patient populations who may be more likely to respond to enteral nutritional therapy based on genotype, phenotype, or gut microbiota composition.



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Eosinophilic Esophagitis: Diet and the Esophageal Microenvironment

Eosinophilic esophagitis (EoE) is a chronic inflammatory disease of the esophagus, first described in 1995. Despite the fact that this is a relatively new entity in medicine, the incidence of EoE is 57 in 100,000 and it is estimated to cause over \$1.4 billion per year in health care costs.

Over the last 20 years many breakthroughs have been made in the diagnosis and treatment of EoE, but very little is understood about the pathophysiology of this disease. At this time it is known that upon exposure to food antigens there is a robust allergic reaction, involving invasion of inflammatory cells, specifically eosinophils, mast cells, Th2 lymphocytes, and basophils into the esophageal tissue. This robust reaction leads to a myriad of changes within the esophagus including swelling, poor motility, and stiffness. In its most severe form, the esophagus becomes narrow and food can even get stuck. Many patients suffer from life long swallowing issues and require emergent procedures to remove impacted food. Further understanding of some of the pathophysiologic mechanisms, may lead to better therapies, diagnostic strategies, and improved quality of life.



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**The Importance of Integrating Food and Nutritional Approaches in to Clinical Practice:
IBD as an Example**

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