**W-4122 Multistate Research Activity Accomplishments Report**

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### **Basic Information**

**Project No. and Title:** [W4122 : Beneficial and Adverse Effects of Natural Chemicals on Human Health and Food Safety](https://www.nimss.org/projects/14436)

**Period Covered:** 10/01/2018 to 09/30/2019

**Date of Report:** 12/02/2019

**Annual Meeting Dates:** 09/25/2019 to 09/27/2019

### **Participants**

### Chen, Chi – University of Minnesota; Chicco, Adam – Colorado State University; Delgado, Efren – New Mexico State University; Helferich, William – University of Illinois; Izard, Jacques-University of Nebraska; Majumder, Kaustav– University of Nebraska – Lincoln; Marco, Marie- University of California-Davis; Medina, Ilce- Michigan State University; Nerurkar, Pratibha – University of Hawaii; Pritsos, Chris- University of Nevada; Turner, Nancy – Texas A&M University; Verma, Mohit- Purdue University; Weir, Tiffany – Colorado State University; Whelan, Jay- University of Tennessee; Williams, David – Oregon State University; Zhu, Meijun – Washington State University

### **Brief Summary of Minutes of Annual Meeting**

The 2019 Annual Meeting of the W-4122 Multistate Group was called to order by the Chair, David E. Williams the morning of September 26 at the YMCA camp in Estes Park, Colorado. Following a brief introduction by David Williams, Chris Pristos, University of Nevada, provided the group with an update including that our W4122 won the best multi-state in the West. A brief summary of projected budgets included information that AFRI will most likely see a boost in funding. NIFA moved from Washington, D.C. to Kansas City and we can expect delays in responses. Following these administrative items, each of the 15 attendees presented 20 minute summaries via Power Point of their progress over the past year. At the business meeting on the morning of September 27, 2019, new officers for 2019-2020 were selected: Chair, Tiffany Weir (CSU); Vice-Chair, Mohit Verma (Purdue); and Secretary, Maria Marco (UC Davis). The tentative dates for the 2019 annual meeting are October 8-9 in Santa Fe, New Mexico.

**Accomplishments**

**Objective 1: Examine the effects of phytochemicals and other dietary components on gut microbiota and intestinal function.**

The University of California Davis Station tested the hypothesis that diet-induced obesity could be overcome by resistant starch. Resistant starch changed the mouse metabolome and an increase in choline metabolism was seen. Although there was no improvement in weight or insulin resistance, intestinal health was improved in the presence of resistant starch (with high fat diet). Similar observations were made in people. *Lactobacillus plantarum* is often used as a probiotic and for fermentation of several dietary products. These studies suggest *Lactobacillus* should be targeted by dietary interventions. The toxic Bacteriocins could be how *Lactobacillus* impact intestinal health. For example, plantaricin protects human CaCo-2 cells (a model for human small intestine) against disturbance of barrier function which provides protection against absorption of toxins from pathogenic bacteria.

The Colorado State University Station has been examining the working hypothesis that Western diet causes derangements to the gut microbiota, which drives changes in intestinal homeostasis and leads to inflammation contributing to vascular dysfunction. When comparing standard and Western diet in mice, protective microbes such as *Bifidobacteria* were reduced in the western diet. Using antibiotics to kill the microbiota 687 reduced the effects on vascular dysfunction produced by Western diet. When the microbiome was transplanted from mice exhibiting vascular dysfunction to obese mice the result was vascular dysfunction in the recipients. A reactive hyperemia index was using to assess the degree of dysfunction in humans. Some bacteria (*B. longum, A. muciniphila)* were associated with a normal reactive hyperemia index. In a translational study, a new human cohort (normal and obese individuals) was recruited and microbiota transplanted into mice (classified by vascular dysfunction). The mice took on the vascular characteristics of the donors but not their weight. Mice that received transplants from obese donors seem to have better vascular function. Further studies suggest the gut microbiome of obese mice enhances ischemic injury and contributes to cardiovascular risk.

In a separate study by the CSU station, they found dietary interventions with functional foods like blueberries, aronia berries, red beetroot juice, and microgreens altered oral and gut microbiota and the bioavailability of the bioactive compounds in these foods is influenced by gut and oral microbial communities.

The Station at Michigan State University has found sorghum bran can protect against colon cancer and inflammatory bowel disease models. Polyphenol-free diet led to dramatic changes in the *Firmicutes* to *Bacteroidetes* ratio. Cooking of cellulose caused a decrease in short chain fatty acids and butyrate while cooking other brans either did not affect the concentration of short chain fatty acids or increased it slightly. Sumac sorghum bran remains the most protective in both raw and cooked forms.

At the University of Minnesota Station nursery pigs were used to study novel metabolic events in the gastrointestinal (GI) tract after food and feed consumption. Rapeseed is a rich source of choline esters, also present in the seeds of Brassicaceae plants (sinapine is a choline ester of sinapic acid, abundant in rapeseed). Rapeseed diet increased trimethylamine (TMA), the microbial metabolite of choline, in the large intestine and TMA N-oxide (a marker of cardiovascular disease risk) in the liver and serum.

The University of Nebraska Station has been studying the impact of the microbiome and diet on susceptibility to a number of cancers, including colorectal and pancreatic. Dietary components shown to have a major influence on microbial impact and cancer risk include fiber (influences chronic inflammation) and flavonoids.

At the Purdue Station the effects of phytochemicals and other dietary components on gut microbiota and intestinal function has been studied. Examination of twelve carbohydrates (monosaccharides, disaccharides, and trisaccharides) were tested as carbon sources for the growth of *Escherichia coli* LF82 and *Bacteroides fragilis* from the human gut microbiome. We found different types of carbohydrate selectively effect the metabolism of gut microbes. These carbohydrates could be produced in the intestines as the bacteria break down more complex polysaccharides. Using the growth information, predictions of which types of dietary components will be beneficial for the microbiota can be made for potential probiotic formulations.

The Utah State University Station (could not attend) has examined dietary strategies to reduce colonic inflammation and promote gut homeostasis thus reducing the risk of colitis-associated colorectal cancer (CAC). Mice fed Western diets alone had markedly higher colitis and colon tumorigenesis. If mice were fed this same high fat diet, but with 10% black raspberry powder, symptoms of colitis was reduced as well as colon tumor multiplicity and burden. The fecal microbiome profiles in black raspberry diets were distinct; the families *Bifidobacteriacea, Streptococcaceae* and *Turicibacteraceae* were markedly altered.

**Objective 2: Identify cellular mechanisms and host molecular targets of beneficial or adverse dietary components that influence human health.**

The University of Hawaii Station found coffee, the most widely consumed beverage worldwide, when consumed in moderate amounts (up to 4 cups/day) improved mortality rates as well as metabolic abnormalities in humans. Adipocytokines such as leptin and adiponectin play a critical role in chronic diseases. Current studies are in progress to identify the effect of Hawaii-grown coffee on plasma adipocytokine levels among healthy individuals.

The University of Minnesota Station has been studying diets containing Scenedesmus and growth performance (5% increased growth whereas 20% decreased growth). Among common macronutrient-derived blood biochemicals, serum triacylglycerols and cholesterol levels were dramatically decreased by feeding the 20% Scenedesmus diet. Metabolomic analysis of liver, serum, feces, and urine samples indicated that Scenedesmus feeding greatly affected metabolites associated with amino acids, lipid, purine, microbial metabolism, and the endogenous antioxidant system. Growth promotion was associated with elevated concentrations of antioxidants, an expanded purine nucleotide cycle, and modified microbial metabolism, while growth suppression was correlated to oxidative stress, disrupted urea cycle, upregulated fatty acid oxidation, and an imbalanced lipidome. These correlations suggest the need to define the dietary inclusion rate threshold for using Scenedesmus and other microalgae supplements as feed ingredients.

The University of Nebraska Station has been studying dietary γ-glutamyl peptide (γ-EV) in the prevention of obesity-associated vascular disorders. The biological activity of dietary γ-glutamyl peptide (γ-EV) was assessed using two vascular endothelial cell lines and one adipocyte line. Intervention with γ-EV reduced inflammation in both adipocyte and vascular endothelial cells by activating the calcium sensing-receptor (CaSR). The results from our absorption study with Caco2 cells indicate that γ-EV can be absorbed, probably via Pep-T1 receptor. Our study indicated that γ-EV pretreatment may reduce development of high blood pressure at a dosage of 500 mg/kg BW.

The Station at Oregon State University has been examined the mechanism of altering the pharmacokinetics of the dietary known human carcinogen, benzo[a]pyrene, by the cruciferous vegetable Brussels sprouts or the supplement derived from Brussels sprouts, 3,3’-diindolylmethane (DIM). These studies can be conducted in humans with *de minimus* risk as the dose utilized is lower than the average daily exposure. This is made possible by collaboration with Lawrence Livermore National Laboratory and their accelerator mass spectrometer that has a sensitivity in the range of attomoles (10-18) to zeptomoles (10-21). The OSU group has developed a UPLC-MS/MS assay to measure DIM and DIM metabolites in urine in individuals taking the dietary supplement. The impact of DIM or Brussels sprouts on the absorption, metabolism and excretion of benzo[a]pyrene following oral exposure is being determined.

At the Utah State University Station susceptibility and/or resistance to dietary and environmental carcinogens like aflatoxin B1 (AFB1) has been shown to be governed principally by glutathione S transferase (GST)-mediated detoxification. Domesticated turkeys are highly sensitive to AFB1, whereas wild turkeys are comparatively resistant due to the presence of functional hepatic GSTAs and other possible physiological and immunological interactions. We quantified gene expression following dietary treatment of AFB1 in susceptible and resistant birds. Significantly altered pathways included FXR/RXR and LXR/RXR activation, coagulation system, prothrombin activation, acute phase response, and atherosclerosis signaling. Differential extra-hepatic expression of acute phase protein genes was confirmed by quantitative real time PCR (qRT-PCR) in the original experiment and additional turkey lines. Results demonstrate that wild turkeys possess a capacity to more effectively respond to AFB1 exposure, but these effects were largely the consequence of GST silencing in domestic turkeys.

The Washington State University Station has been studying how dietary raspberry can impact white adipose tissue through activation of AMPK. Dietary raspberry at 5% was effective in preventing obesity and metabolic dysfunction induced by a high fat diet (HFD). HFD inhibited AMP-activated protein kinase (AMPK), a master regulator of energy metabolism. Raspberry supplementation activated AMPK, and formation of brown/beige adipocytes. AMPK knockout mice were employed to show that beneficial effects of raspberry in obesity and metabolic symptoms were AMPK-dependent in mediating browning of white adipose tissue and preventing obesity. Thus raspberry consumption is protective against obesity and metabolic dysfunction associated with consumption of common high energy western diet, and AMPK is a critical mediator for the beneficial effects of raspberry through inducing WAT browning.

**Objective 3: Explore the interaction between dietary components and the host metabolome and epigenome. Note: A number of stations conducted research on the impact of dietary components on the metabolome and microbiome (Objectives 1 and 2) and the interaction between the two. For the sake of brevity those summaries won’t be repeated here.**

The Michigan State University Station Sumac and Black sorghum brans are able to reduce the formation of preneoplastic lesions of colon cancer, relative to a white sorghum bran. These observations suggest that the polyphenols in Sumac and Black brans may be responsible for the protection, however cooking can reduce polyphenols present in Black and Sumac sorghum brans. To study this further raw and cooked Burgundy, Black, Onyx and Sumac sorghum brans in diets were fed to rats treated with a carcinogen 3 weeks after they began consuming the experimental diets. Short chain fatty acids (SCFA) were affected by the type of diet consumed. Cooking had the greatest impact on SCFA produced from the control diet. Our data suggest that including cooked sorghum brans (especially those from Sumac sorghums) should reduce the formation of preneoplastic lesions of colon cancer.

The Utah State University Station has been examining the impact of diet on multi-generation susceptibility to cancer as influenced by the effects of total Western diet on the epigenome. Mice were bred for three generations, during which they were fed a standard diet (AIN93G) for all generations or the total Western diet for rodents (TWD) during only the F0 generation (ancestral), the F0 through F3 generations (multi-generation), or only the F3 generation (direct). Colon cancer was initiated in the F3 generation and colon mucosa RNA examined for differential expression of genes (DEG). Interestingly, the DEGs were associated with defense response, immune response, and response to interferon biological process ontology terms. Exposure to the Western diet over multiple generations caused significant DEGs related to immune response in the third generation offspring. Epigenetic alterations as assessed by DNA methylation is ongoing.

In this same study, green tea polyphenols, known to decrease body fat composition, reverse insulin resistance, reduce cardiovascular disease risk, protect against pathogenic bacteria, improve brain function, increase lifespan, and suppress inflammatory processes that contribute to carcinogenesis, were tested as multi-generational chemoprevention agents. Multi-generational exposure to green tea decreased terminal body weight and relative fat mass in F3 females directly exposed to Western diet and decreased tumor multiplicity and burden in both sexes as well as relative spleen mass in females (p=0.0083). Our results suggest that green tea can reduce colon cancer severity only after cumulative exposure to high-fat Western diets over multiple generations.

**Objective 4: Determine how food processing influences chemical composition to affect human health.**

The University of Hawaii Station has been studying how the eco-environmental differences in geographical regions impact the flavor of cacao. Consumption of polyphenols found in Hawaiian cacao are associated with beneficial/protective effects in susceptibility to metabolic disorders including type II diabetes. There are four main varieties of the cacao plant and the environment, genetic variation and preparation of the beans and the cacao liquor determine flavor and functional properties (as assessed by metabolomics and lipidomics). These include primary and secondary cacao metabolites. The study still needs to explore how different microbiomes affect the fermentation process. Determining which microbes are present in the natural environment and what functions they are playing is also important.

The University of Illinois Station has been studying how multiple uses of frying oil (thermally abused frying oil can impact late-stage breast cancer metastasis. The thermally abused frying oil increased metastasis from breast to lung. In another animal study, when the animals were fed with lard, lard + inhibitor, bacon, or bacon + inhibitor, the bacon-exposed animals showed increased tumors in lungs.

The Station at New Mexico State University is working on how food bioengineering technology can enhance quality and yield of agroindustrial products. Recently, this Station has studied the utilization of agro-industrial by-products as an alternative source of plant protein. Glandless cottonseed meal (GCSM), which has a high protein content, was extruded to obtain aquaculture feed. Tissue analysis of amino acid profiles and fatty acid profiles in shrimp after administration of the GCSM feed showed it to be a superior product, having a higher amount of amino acids and a higher amount of fatty acids across all the diets tested. GCSM has also exhibited physicochemical characteristics, *in vitro* and *in vivo* that are superior when compared to the commercial diet at a fraction of the price for production. Glandless cottonseed meal has the potential not only to feed shrimp but other aquaculture species, however, further research needs to be done to expand its uses as a protein source in feeds.

In another study, Jujubes (Ziziphus jujube) has been shown to have a high content of antioxidants, vitamins, and minerals that can be used as food additives. NMSU has studied the effect of coating materials on the microencapsulation efficiency of phenolic compounds extracted from jujube fruit. Microencapsulation of phenolic compounds of jujube was performed, measuring total phenolic content and antioxidant activity at the time of extraction, and after microencapsulation with maltodextrins and gum arabic or glandless cottonseed meal protein as coating materials at different ratios. Jujube has a considerable yield of phenolic compounds with high antioxidant activity that are not stable in solution. Therefore microencapsulation must be done the same day of extraction.

**Impacts:**

The University of California at Davis Station has shown intestinal health was improved by resistant starch even with a high fat diet both in mice and humans and *Lactobacillus plantarum*, often used as a probiotic and for fermentation of several dietary products, plays an important role in this protection.

Colorado State has employed human clinical studies to assess differences in oral bioavailability of two commercial cannabinoid (CBD) preparations and established that CBD reduces inflammatory markers in humans 90 minutes after a single oral dose.

CSU has also identified sex-based differences in the oral microbiota that influence chronic response of oral nitrate-reducing bacteria to chronic beetroot juice consumption. Beetroot juice and CBD are both popular dietary supplements and these data are important to inform consumers regarding the bioavailability and bioactivity of these supplements.

CSU has established microbiota as a causal factor in vascular dysfunction, an early marker of human cardiovascular disease (CVD). This finding will help identify new modalities for preventing or reversing vascular impairments to reduce the overall risk of later CVD development.

W4122 researchers in Colorado have discovered gene-diet interactions that govern the extent to which dietary fats influence heart disease risk. Specifically, they determined that omega-6 fatty acids increase risk of cardiac injury following ischemia only if the *FADS2* gene is elevated using genetically-engineered mice.

The Colorado State Station hase discovered that maternal high-fat feeding alters fetal metabolism in a manner that might predispose offspring to the development of diabetes in late childhood, and identified a placental enzyme that may be targeted to modify this effect.

The University of Hawaii Station has addressed the health disparity in diabetes wherein Native Hawaiians and Pacific Islanders have twice the rate of obesity-associated type 2 diabetes and are five times more likely to die from this chronic disease. This station has shown that polyphenols from native cacao and bitter melon may be effective in protection.

The University of Illinois Station has documented than when frying oils are used multiple times it produces by-products that can enhance the formation of lung cancer and metastasis of breast cancer.

The Michigan State W4122 researchers have demonstrated that the impact of cooking sorghum bran on chemoprotection from cancer is not uniform, and that some sources are more resistant to thermal processing. Importantly, some bioactive compounds remain equally effective in the raw and cooked state which provides enhanced chemoprotection.

The University of Minnesota Station has developed a high throughput metabolomics platform to assess global changes following dietary consumption of rapeseed (produces choline and trimethylamine-N-oxide which is a risk factor for cardiovascular disease), green tea polyphenols and algae in order to predict impacts on human health.

At the University of Nebraska-Lincoln Station W4122 researchers have developed potentially clinically effective dietary-peptide-based therapeutics for treatment of hypertension and other cardiovascular diseases.

Nebraska has also performed a clinical trial using a food frequency questionnaire to determine the amount and type of flavonoids in their diet. Identification of bacteria that could be driven by class-specific flavonoids, opens the possibility of interventions (probiotic; prebiotic) based on personalized construction of optimal microbiomes.

New Mexico State University has found that fishmeal can be substituted with cottonseed meal protein without affecting growth and quality of shrimp. The use of agricultural by-products contributes to reducing the production cost in aquaculture farms. The extracted protein from the cottonseed meal protein has a high foaming capacity comparable to soy protein and can be used as a substitute for soy protein.

Oregon State University W4122 research has documented that oral phytochemicals from cruciferous vegetables are rapidly absorbed, metabolized and excreted in urine. This pharmacokinetics analysis will establish the dose and frequency of administration that will produce maximum beneficial effects.

The Purdue University Station has documented that certain carbohydrates are utilized by bacteria inhabiting the human intestine and the emergent growth of individual bacteria is markedly different that in mixed culture. This has important implications in probiotic and prebiotic approaches to improve health.

Utah State University has shown certain genetic markers can be used to restore AFB1 resistance in domestic breeds of turkeys, and may also shed light on the mechanisms of resistance to AFB1 in animals and humans thereby improving animal health and food safety.

Utah State has also shown that dietary intervention study with black raspberries leads to important changes in the composition of the gut microbiome with reduced symptoms of colitis and thus may be a useful functional food for suppression of gut inflammation. Black raspberries may be employed as pre-biotics or pre-biotic/pro-biotic intervention.

USU has also shown that the adverse impact of the Western diet can be transgenerational through epigenetic mechanisms.

Washington State University W4122 researchers have shown that dietary raspberry, which is enriched with polyphenols and dietary fibers, has beneficial effects on obesity and metabolic dysfunction.

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**New Grants (as PI):**

Colorado State University:

*The obese microbiota as a novel regulator of vascular function: a translational approach* 2019-2023 **NIH-NHLBI R01; $1.5 M**.

*Exploring a Novel Role for the Gut Microbiota and Intestinal Inflammation in Obesity-Related Vascular Dysfunction* 2018-2019 **Colorado Clinical and Translational Science Institute**; $60,000.

*Examining the pharmacokinetics and anti-inflammatory profiles of oral cannabidiol preparations* 2019 **Pilot Clinical Trial**.

*DE11: Effects of a Novel Probiotic on Immune Function* 2018 **Deerland Enzymes**; $60,000.

Phage2: Impact of Prebiotic Phages on Probiotic Survival and Efficacy 2018 **Deerland Enzymes**; $66,000.

*IMPS approach for identifying biomarkers of fruit and vegetable intake* 2018-2019 **College of Health and Human Sciences Minigrant;** $7,000.

*Placental polyunsaturated fatty acid metabolism and offspring metabolic trajectory* 2019-2021 **Colorado Agricultural Experimental Station (USDA)** $50,000.

*Integrative metabolism of oocyte development and its modulation by maternal diet* 2018-2019 **NIH/NICHD 1R21HD097601-01** $150,000.

Michigan State University:

*Polyphenol-rich sorghum brans promote colon health via microbial mechanisms* 2018-2019 **USDA** (2018-67017-28149) $499,999.

University of Nebraska-Lincoln:

*Value-Added Utilization of Nebraska Great Northern Beans- derived Proteins and Peptides* 07/01/2019-06/30/2020 **Nebraska Dry Bean Commission** $25,507.

*Evaluating the potency of dietary gamma-glutamyl peptide for the treatment of hypertension* 05/01/2019-04/30/2020 **Layman Award, University of Nebraska Foundation** $10,000.

New Mexico State University:

*Food Safety: Point-of-Production Chile Screening for Food-Borne Pathogens* 2019-2021 **New Mexico Chile Association**.

*Interdisciplinary Approach to Transforming Agroindustrial By-products into Value-Added Products* 2019 **AES Competitive Operations Grants**.

*Application of Molecular Fluorescence Spectroscopy for In situ, Real-time Detection of Food Borne Pathogens* 2018-2019 **NMSU Impact-grant**.

Purdue University:

*Growers’ Risk Assessment Biomarkers Investigative Tool Challenge: Microfluidic paper-based analytical devices for microbial source tracking* 2019-2020 **Center for Produce Safety** $30,000.

*Disease Diagnostic INventors Challenge DISCOVER: On-site diagnostics of bovine respiratory disease* 2019-2020 **Purdue University and Purdue Institute for Inflammation, Immunity, and Infectious Diseases** $30,000.

*Low-cost, user-friendly biosensors for enabling judicious use of antibiotics in animals* 2019-2022 **Wabash Heartland Innovation Network (WHIN): Graduate student support Purdue University and WHIN** $66,000.

*Elevating the Visibility of Agricultural Research: 150th Anniversary Review Papers Continuous manufacturing of biologics: from skepticism to possibilities* 2019-2020 **Purdue University College of Agriculture** $10,000.

*Engineering Faculty Conversation: Human-in-the-loop: Smart carpet and gait imaging system to immunize older adults against falls* 2019-2020 **Purdue University College of Engineering** $75,000.

Washington State University:

*Pigmented potato restores gut epithelial health impaired by obesity* 2018-2021 **USDA-NIFA** (2018-67017-27517) $500,000.