**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:** 10/01/2016 to 09/30/2017

**Date of Report:** 12/05/2017

**Annual Meeting Dates:** 10/05/2017 to 10/06/2017

### **Participants**

### Chen, Chi – University of Minnesota; Chicco, Adam – Colorado State University; Coulombe, Roger – Utah State University; Delgado, Efren – New Mexico State University; Harrington, Mike – Colorado State University; Helferich, William – University of Illinois; Majumder, Kaustav– University of Nebraska – Lincoln; Munson-McGee, Stuart – New Mexico State University; Nerurkar, Pratibha – University of Hawaii (through Skype); Pestka, James – Michigan State University; Turner, Nancy – Texas A&M University; Weir, Tiffany – Colorado State University; Williams, David – Oregon State University; Zhu, Meijun – Washington State University

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

The 2017 Annual Meeting of the W-4122 Multistate Group was called to order by the Chair, Dr. Meijun Zhu in the morning of October 5th. Dr. Mike Harrington (WAAESD) provided an overview of the status of the multi-state program, the current funding priorities identified in the NIFA strategic plan, and budget status at NIFA. Last year, this group was recognized with the Western Region Award of Excellence in Multistate Research. Dr. Harrington would like to resubmit a nomination for W4122 to be considered for the national award again this year. This year, we have five new members attend the meeting. Each member present delivered a presentation to update the group on his/her progress (content summarized in the Annual Group Report). At the business meeting, new officers for 2017-2018 were selected: Chair, Adam Chicco (CSU); Vice-Chair, Stuart Monson (NMSU); and Secretary, Chi Chen (UMn). Also, the dates for the 2017 annual meeting will be October 4-5 and the meeting will be held in Calistoga, CA.

**Accomplishments**

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

MI Station studies environment and diet influence latency/severity of genome-driven autoimmune disease (AD). In female NZBWF1 mice, a model for the prototypical AD lupus, intranasal installation with crystalline silica (cSiO2) triggers premature loss of self-tolerance in the lung as evidenced by robust ectopic lymphoneogenesis thereby accelerating/ exacerbating systemic autoimmunity and glomerulonephritis. Remarkably, dietary supplementation with the ω-3 polyunsaturated fatty acid (PUFA), docosahexaenoic acid (DHA), abrogates cSiO2-accelerated autoimmunity. They assessed the time-dependent effects of DHA consumption on cSiO2-triggered pulmonary autoimmune gene expression. Cohorts (n=8/gp) of 6-wk old female NZBWF1 mice were fed an isocaloric AIN-93G diet containing 0.0, 0.4, or 1.0% DHA (equivalent to human DHA supplement consumption at 0, 2, and 5 g/d, respectively) for 2 wk. Mice were then intranasally instilled with 1.0 mg cSiO2 or vehicle once per week for 4 wk and then maintained on experimental diets for 1,5, 9, or 13 wk. Cohorts were sacrificed, total RNA isolated from lungs, and gene expression levels using an nCounter® PanCancer Immune Profiling module, a multiplexed method for 800 immune-related target genes. cSiO2 induced expression of 48, 90, 106, and 99 autoimmune-related genes by more than 1.5-fold (p>0.05) in the 1, 5, 9, and 13 wk cohorts, respectively. Upregulated genes included interferon-driven proteins, chemokines, cytokines, complement, and macrophage/lymphocyte activation markers. Diets containing low and high DHA concentrations blocked expression of 80-90 % and 100 %, respectively, of the autoimmune genes triggered by cSiO2. These results suggest that DHA supplementation at physiologically relevant doses might be useful in preventing cSiO2 triggering of lupus and other AD.

HI Station demonstrated that *Momordica charantia* (bitter melon, BM) and *Morinda citrifolia* (noni) improves glucose and lipid metabolism as well as prevents weight gain in high-fat diet (HFD)-fed mice. These improved metabolic activity by BM and noni was in part due to improvement of intestinal health by ameliorating intestinal inflammation, preserving gut barrier integrity and maintaining a healthy gut microbiome. Similarly, the differential effects of commercial and laboratory-prepared noni juice on glucose metabolism were also associated with improving gut microbial dysbiosis in HFD-fed mice.

OR Station focused on studying dietary chemoprevention of cancer. They are employing a mouse model of transplacental cancer to determine in dietary supplementation of the pregnant mouse can provide protection for the fetus/infant with respect to development of cancer as adults from the *in utero* exposure. The primary emphasis has been on phytochemicals from cruciferous vegetables primarily indole-3-carbinol (I3C) and sulforaphane (SFN). They are studying the role of Nrf-2 signaling in the chemoprevention due to SFN. In a recent development, they are utilizing zebrafish as a xenograft model for human cancer cells. By pretreating the zebrafish embryos with I3C prior to injection with human leukemia cells from pediatric patients they are assessing the potency and efficacy of I3C in prevention of these cells from proliferation and metastasis.

TX Station demonstrated that polyphenol-rich sorghum brans influence the colon microbiota of healthy rats, or those induced to have colitis. The diets included sorghum brans that contain condensed tannins, or deoxyanthocyanins, or a combination of the two. The patterns found in rats consuming a diet without the sorghum brans were reflective of those found in obese individuals or those with inflammatory bowel disease. Importantly, it was possible to protect against this shift by including a single, polyphenol-rich fiber source, and to reduce the colon damage associated with induction of colitis. Beneficial changes in the colon microbiota of rats was observed when a dried plum puree was included in the diet. Alterations in the microbiota contributed to modifications in the fecal metabolome.

WA Station examined roles of AMPK in intestinal epithelial differentiation using *in vivo* and *in vitro* system. Adenosine monophosphate-activated protein kinase (AMPK) is a master regulator of energy metabolism and recently recognized for its important regulatory role in cell differentiation. The microbial metabolite, butyrate, and polyphenolic compounds enhance barrier function, which were associated with the activation of AMPK. However, the role of AMPK in intestinal epithelial differentiation has not been studied directly. They found that AMPK activation improved the barrier function of Caco-2 cells as indicated by increased transepithelial electrical resistance and reduced paracellular FITC-dextran permeability, which was associated with enhanced epithelial differentiation. They further found that AMPK enhances intestinal barrier function and epithelial differentiation via promoting caudal type homeobox 2 (CDX2) expression, a critical transcription factor governing epithelial differentiation.

CO Station examined whethergut dysbiosis is a causal factor in obesity-related arterial stiffness and endothelial dysfunction.To this end, they determined that obesity-associated vascular dysfubnction was accompanied by global shifts in the gut microbiota and specifically, that three species of *Bifidobacterium* that were reduced by western diet negatively correlated with multiple measures of vascular dysfunction. To determine whether western diet-induced alterations in the microbiota were causally related to the development of vascular dysfunction, dysbiosis in western diet-fed mice was abated by administration of a broad-spectrum antibiotic cocktail for 8 weeks despite no significant changes to body weight or body fat distribution. Given that bacterial lipopolysaccharide (LPS) has been implicated as a causal role in gut-derived systemic inflammation that leads to cardiometabolic aberrations, they examined LPS as a possible link between vascular function and gut dysbiosis. They observed that five months of western diet feeding caused a marked increase in circulating lipopolysaccharide-binding protein (LBP), a surrogate marker for LPS, and that it was significantly reduced following antibiotic treatment, suggesting that the vascular-protective effects of antibiotics involve reductions in LPS signaling. They also observed downstream inflammatory mediators regulated by LPS (IL-6 and phosphorylated NF-ĸB) were also higher in obese animals and reduced with antibiotics. Finally, to confirm that LPS is capable of inducing vascular dysfunction, and to examine the role of TLR4 in this process, they incubated arteries from control mice and from TLR4-/- mice with LPS for 60 minutes. Acute LPS incubation caused significant endothelial dysfunction in arteries from wild-type mice, but not TLR4-/- mice, confirming that LPS can mediate vascular dysfunction via TLR4 signaling.

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

UT Station is studying possible epigenetic mechanisms for the observed silencing of the GSTA3/A4 genes in domesticated turkey (DT), which potentially underlies the extreme sensitivity to dietary carcinogens lkike aflatoxin B1 (AFB1). By contrast, wild turkeys (WT) have GSTs capable of detoxifying AFB1, and are hence more resistant than DT. Changes in methylation, particularly at CpG sites clustered in the promoter region of a gene, can lead to changes in expression. To identify whether methylation differences may be responsible for GST silencing in domesticated turkeys, they searched for CpG islands "upstream" of the 5' end GSTA3 and GSTA4 genes. CpG sites in the GSTA region occur less frequently than expected by chance, with apparent CpG islands near the 5' ends of most of the GSTA genes, but not GSTA3--the one that are most interested in.They tested for differences between WT and DT livers in the methylation level of the CpG island upstream of GSTA4 and found that methylation levels in this region are low (~1.5%) with no significant difference between these two turkey types. There are only 88 CpGs spread over the 11000bp upstream of GSTA3, but half of those CpGs are concentrated in four 500bp sections within 2500bp of the transcription start site, so they searched for potential methylation differences in those four regions. Preliminary results suggest that methylation in these regions does not differ between WT and DT. Even though these four regions have a higher density of CpGs than the rest of the sequence upstream of GSTA3, it is still a much lower density than the CpG islands upstream of other genes, raising questions about whether these CpG sites are part of a promoter or whether the promoter for GSTA3 is located elsewhere in the genome, potentially shared with another gene. They also looked for differences in the presence or absence of CpG sites in the suspected promoter regions of GSTA3 and GSTA4 due to known SNPs between WT and DT. There are SNPs in these regions but they do not affect CpG sites.

MI Station explored mechanisms of how the common food toxin deoxynivalenol (DON, vomitoxin) evokes anorexia and vomiting can shed new light on in what manner calcimimetics cause problematic side effects in the digestive tract. In prior work, their lab demonstrated that gut enteroendocrine cells (EECs) secrete hormones that mediate DON’s anorectic and emetic effects. Using STC-1 cells, a cloned EEC model, they discovered that DON-induced activation of CaSR and transient receptor ankyrin-1 channel (TRPA1) drives Ca2+-mediated hormone secretion. However, the roles of CaSR and TRPA1 in DON’s anorectic and emetic effects remain unclear. To understand the mechanism of anorexia, they tested the hypothesis that DON-induced food refusal and satiety hormone release in the mouse are linked to activation of CaSR and TRPA1. Oral treatment with selective agonists for CaSR (R-568) or TRPA1 (allyl isothiocyanate, AITC) suppressed food intake in mice and the agonists’ effects were blocked by pretreatment with corresponding antagonists NPS-2143 or ruthenium red (RR), respectively. NPS-2143 or RR inhibited both DON-induced food refusal as well as plasma elevations of the satiety hormones cholecystokinin (CCK) and peptide YY3-36 (PYY3-36) which are well known to mediate reduced appetite and impair food consumption. Co-treatment with both antagonists additively suppressed both anorectic and hormone responses to DON. To elucidate whether similar mechanisms were involved in vomiting, they further tested the hypothesis that DON triggers emesis in mink by activating CaSR and TRPA1. Oral gavage with selective agonists for CaSR (R-568) or TRPA1 (AITC) rapidly elicited emesis in the mink in dose-dependent fashion. Oral pretreatment the animals with their corresponding antagonists NPS-2143 or RR, respectively, inhibited these responses. DON-induced emesis in mink was similarly inhibited by oral pretreatment with NPS-2143 or RR. In addition, these antagonists suppressed concurrent DON-induced elevations in plasma peptide YY3-36 and 5-hydroxytryptamine – hormones previously demonstrated to mediate the toxin’s emetic effects in mink. Furthermore, antagonist co-treatment additively suppressed DON-induced emesis and peptide YY 3-36 release. The major findings of these animal studies along with prior findings by their laboratory support the contention that CaSR and TRPA1 activation contribute to DON-induced food refusal and emesis by mediating hormone exocytosis from EEC. Implicit in these findings, is the suggestion that calcimimetics induce digestive tract side effects in humans by promoting the release of enteroendocrine hormones.

OR Station currently focuses on mechanisms of action and biomarkers associated with an important class (3 of the top 10 ATSDR environmental chemicals of concern), polycyclic aromatic hydrocarbons (PAHs), of food-borne carcinogens as well as the cooked meat mutagens (also known human carcinogens). They have accumulated evidence from the mouse transplacental model and adult rodent colon and prostate cancer models that PAHs and cooked meat mutagens are capable of altering the epigenome including microRNAs and long non-coding RNAs. Currently, they are collaborating with Lawrence Livermore National Laboratory to employ accelerator mass (AMS) spectrometry to determine the fate of orally absorbed benzo[a]pyrene (BaP), a PAH common in food and ranked as a known human carcinogen by the International Agency for Research on Cancer (IARC).

IL Station investigated the effects of inadequate dietary calcium (Ca) on bone turnover, tumor growth, and bone response to tumor in tibia inoculated with 4T1 mammary carcinoma cells using Balb/c mice. Nine-month-old female Balb/c mice were placed on an adequate Ca (5 g/kg diet, n=30) or low Ca (80 mg/kg diet, n=31) diet for 14 days, then injected intratibially with 1,000 4T1 cells (transfected with luciferase for bioluminescence imaging), and sacrificed at 5, 10, or 21 days post-inoculation (n=7-10 mice/group). Control mice (n=6/group) were injected with carrier and sacrificed at 10 days post-inoculation. Tibiae with muscle intact were excised and evaluated by microcomputed tomography and histology. *In vivo* bioluminescent imaging revealed that 4T1 cells metastasized to lung. Therefore, lungs were further removed for quantification of tumor. Mice fed low Ca exhibited higher bone turnover and higher tibial lesion scores than mice fed adequate Ca. Lesion severity, manifested as cortical osteolysis and periosteal woven bone formation, and tumor cell infiltration to muscle, increased with time, irrespective of diet. However, for most skeletal endpoints the rates of increase were greater in mice consuming low Ca compared to mice consuming adequate Ca. Infiltration of tumor cells into adjacent muscle, but not metastasis to lung, was also greater in mice consuming low Ca diet. The findings suggest that high bone turnover due to Ca insufficiency results in greater local mammary tumor cell growth, cortical osteolysis, woven bone formation, and invasion to muscle in mice.

TX Station found that radiation altered the proportion of stem cells in the colon crypts, and that a diet containing fish oil and pectin was able to restore the levels to those seen in the non-irradiated mice by 4 and 8 weeks after radiation exposure.

WI Station examined how the iron regulated RNA binding protein and found that iron regulatory protein 1 (IRP1) had the capacity to control the fate of up to 9 mRNA that contain an iron responsive element (IRE) in their 5’ or 3’ untranslated region. Evidence from studies in mice indicated that the transcription factor HIF2alpha was a major regulator of genes encoding divalent metal transporter I (DMT1), the ferric iron reductase DCytB and the iron exporter ferroportin. These 3 proteins control the apical uptake (DMT1, DCytb) and basolateral export (ferroportin) of iron in the duodenum. IRP1 is the key iron mediator of HIF2alpha mRNA translation. IRP1 is a repressor of HIF2alpha synthesis because it binds to the IRE in HIF2alpha mRNA thereby blocking translation of this mRNA. Loss of IRP1 translationally activates HIF2alpha mRNA. Currently, they are examining the impact of IRP1 deficiency on expression of the HIF2alpha gene targets DMT1, DCytB and ferroportin in the duodenum, as well as the role of IRP1 in other aspects of iron metabolism.

NJ Station investigated whether a purified phenolic-enriched raspberry extract would reduce weight gain in a diet-induced obese (DIO) mouse model. For comparison, they used raspberry ketone as a positive control. Eight week-old C57BL/6 male mice were fed high-fat diet (45% fat. 20% protein). Vehicle, raspberry ketone, high and low raspberry extract (REH 2g/kg, REL 0.2mg/kg, respectively) were administered by oral gavage for 24 days, and body weights were recorded daily. They are in the process of analyzing the feeding suppression, meal pattern alterations, and hypothalamic gene expression by phenolic-enriched raspberry extract and raspberry ketone. Their previous experiments found that acute oral dosing of raspberry ketone (200 mg/kg) activates the hindbrain, nucleus of the solitary tract (NTS), as measured by c-fos immunohistochemistry. These findings will provide mechanistic data for uncovering the effects of raspberry ketone and other bioactive phenolic compounds on obesity and related metabolic disorders.

**Objective 3: Explore the interaction between dietary components and the host metabolome and epigenome.**

TX Station found that dried plums reduced early colon lesions by 50%, and mitigated distal colon microbiota changes in rats induced by carcinogen-injection. They further discovered several compounds endogenous to plums in the luminal metabolome (both proximal and distal), with several of those compounds being demonstrated in the existing literature to suppress proliferation and enhance apoptosis in colon cancer cells. In addition, there were multiple compounds produced from microbial metabolism of phenolic molecules identified in the luminal contents from the proximal and distal colon of rats provided the plum diet. These molecules have also been demonstrated to protect against carcinogenesis. Additional experiments using dried plums, or compounds isolated from plums have demonstrated effects on bone, as well as colon cancer, demonstrating the potential for systemic benefits of dried plum consumption.

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

WA Station has studied the utilization of grape pomace as a functional food component. Grape pomace is a major byproduct of wine and juice industry, rich in polyphenolics with demonstrated preventive effects against cardiovascular disease, inflammatory bowel disease and others. How to effectively utilize this byproduct is a compelling question with huge economic impact. In the study, grape pomace was examined for its potential application in making healthy corn starch based extrusion snack foods. Extrudates with 5% grape pomace and 16% feed moisture at a selected speed resulted in enhanced expansion with substantial retention of total polyphenolic content and total antioxidant activity in the cornstarch extrudates. Furthermore, the protective effect of grape pomace extrudates against reactive oxygen species production in human colonic epithelial cells was further evaluated using polyphenolic extract prepared from grape pomace raw mixes and extrudates. These studies indicate that grape pomace has a potential to be used an adjunctive ingredient in extruded foods providing enhanced nutritional value without negative impacts on quality characteristics.

OR Station has been focused on reducing human health risks from food-borne pathogens and environmental contaminants and to transition from preclinical mouse models to actual human studies employing the incredible sensitivity of AMS (attomole sensitivity; they can detect BaP in blood after dosing humans (protocol approved by FDA) at the low femto (1015) gram levels, equivalent to 1 drop of water in 4000 Olympic-size swimming pools. A pending NIH grant will allow them to use human volunteers to assess how consumption of a cruciferous vegetable (1/2 cup Brussels sprouts) night for a week alters the pharmacokinetics of a subsequent oral dose of 14C-BaP.

**Impacts:**

1. UT Station identified an appropriate genetic marker for the AFBO-trapping GST allele in wild turkeys, which plan to reintroduce resistance into domestic turkeys by backcrossing. An AFB1-resitant turkey would help save the poultry industry millions of dollars lost each year due to contaminating aflatoxins in feeds.
2. Characterizing GSTs that are associated with sensitivity to food-borne toxicants at UT Station will allow identification of genomic determinants for resistance in humans and animals, thereby improving animal health and food safety. In addition, diets can be devised to increase resistance of people and animals to dietary and environmental carcinogens and toxicants.
3. The findings at IL Station show that there is a clear in tumor growth in bone from diets low in calcium versus diets with adequate calcium. These data outline the need for adequate calcium in the diet of breast cancer survivors.
4. Research at MI Station on understanding how DHA prevents/resolves silica-driven proinflammatory and autoimmune events in the lung will provide low-cost preventative strategies that would empower individuals who are genetically prone to lupus and/or occupationally exposed to respiratory toxicants to reduce their risk for developing this disease as well as delay progression of existing disease by consuming of DHA supplements.
5. Mechanistic studies on how the common food toxin deoxynivalenol (DON, vomitoxin) evokes anorexia and vomiting at MI Station can shed new light on in what manner calcimimetics cause problematic side effects in the digestive tract. Data obtained will provide novel screening approaches applicable to measuring and eliminating both known and emergent trichothecenes on the farm-to-fork continuum.
6. TX Station demonstrated that diets containing certain polyphenolic compounds (derived from dried plums or sorghum bran) impact the microbiota and their metabolism, which has significant impacts on epigenetic regulation of gene expression. Importantly, systemic benefits are also derived from consuming these polyphenol-rich fiber sources and their microbial metabolites. They further demonstrated that the adult colon stem cell population is sensitive to radiation exposure, with the impacts being both ion source and dose dependent. These observations suggest the need to protect colon stem cells when individuals are exposed to radiation in order to reduce the risk of future intestinal disease.
7. Studies at CO Station on identification of microbes and gut-derived mediators of vascular dysfunction will provide new opportunities to prevent or treat a condition that is strongly predictive of overt cardiovascular disease and a comorbidity of diabetes.
8. The impact of OR Station studies on the absorption, metabolism and excretion of an important dietary carcinogen (found in almost all food) is the first studies in humans. This unique dataset can be used by regulatory agencies such as EPA and FDA to set more accurate safe exposure limits.
9. Studies at WA Station deepen the current understanding about the link between the intracellular energy sensor, AMPK, and intestinal epithelial differentiation and barrier function.
10. Studies at WA Station show that grape pomace has a potential to be use an adjunctive ingredient in extruded foods providing enhanced nutritional value without negative impacts on quality characteristics.
11. WI Station studies may help identify the mechanisms underlying the regulation of dietary iron absorption by IRP1 and HIF2alpha. By elucidating new ways in which dietary iron absorption is controlled, it may be possible to develop the means to more safely combat the anemia in production animals and humans as illustrated by their experiment using dietary fumarate as a possible means to enhance intestinal HIF2alpha level.
12. NJ Station studies on raspberry ketone in weight loss/gain outcomes will provide an unbiased assessment for natural dietary supplements in the market. It can also facilitate a new red raspberries cultivar selection with enhanced bioactive compounds.

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