W5122 Multistate Research Activity 2024 Accomplishments Report

Project/Activity Number: W5122

Project/Activity Title: Beneficial and Adverse Effects of Natural, Bioactive Dietary Chemicals on Human Health and Food Safety

Period Covered: October 2023-September 2024

Date of This Report: March 17, 2023

Annual Meeting Date(s): October 2-3, 2024

Participants:

- Chi Chen (chichen@umn.edu) - University of Minnesota
- Adam Chicco (adam.chicco@colostate.edu) - Colorado State University
- Ock Chun (ock.chun@uconn.edu)- University of Connecticut
- Efren Delgado (edelgad@nmsu.edu) - New Mexico State University (virtual)
- Hongbing Fan (Hongbing.Fan@uky.edu) - University of Kentucky
- Steve Frese (sfrese@unr.edu) - University of Nevada, Reno
- Jacques Izard (jizard@unmc.edu) - University of Nebraska-Lincoln (virtual)
- Rachel Kopec (kopec.4@osu.edu) - The Ohio State University
- Claudia Maier (claudia.maier@oregonstate.edu) - Oregon State University
- Kaustav Majumder (kaustav.majumder@unl.edu) – University of Nebraska-Lincoln
- Maria Marco (mmarco@ucdavis.edu) - University of California-Davis
- Pratibha Nerurkar (pratibha@hawaii.edu) - University of Hawaii (virtual)
- Chris Pritsos (pritsos@unr.edu) - University of Nevada, Reno
- Susan Tilton (susan.tilton@oregonstate.edu) - Oregon State University

Brief summary of minutes of the annual meeting:

Thursday, October 3, 2023:

8:35 - 9:00 AM – Dr. Chris A. Pritsos, Director of Nevada Agricultural Experiment Station and W5122 lead administrator provided opening remarks and a presentation on the FY24 Appropriations request, AFRI update, Farm Bill recommendations for Hatch Act, food and agriculture sciences education and research facilities act, along with an update on NIFA/USDA Funding, distribution of Hatch funds and the Multistate Research Funds Impacts website: www.mrfimpact.org.

Research update presentations (15 min presentation + 10-15 min Q&A and discussion)

9:00-9:35; Ock Chun (University of Connecticut) provided an update on her work investigating impacts of Blackcurrant (BC) extracts in postmenopausal women complemented by cell and animal models, including results of a clinical trial published this year in *Nutrients*. Dr. Chun's research identified microbiome markers of osteoporosis risk and reported effects including beneficial impacts on blood lipids and oxidative stress without changing body composition, reduced CVD risk biomarkers, improved bone mineral density and increases in SFCA and phytoestrogen metabolites, suggesting links to the "gut-bone" axis that will be further explored in a pending USDA randomized clinical trial (submitted August 2024).

9:35-10:00; Efren Delgado from New Mexico State University discussed his research on food bioengineering technologies and agroindustry byproducts, including a USDA proposal with Oregon State University and NMSU for moving toward zero waste food manufacturing and using ag byproducts (e.g., cottonseed meal) to advance bioeconomy and rural/Tribal development in Southern New Mexico. This includes adding value to use of byproducts for producers and communities by developing of bio-based products and bioenergy education courses.

10:15-10:40; Jacques Izard from the University of Nebraska Medical Center provided a research update on his work investigating Short Chain Fatty Acids Production Along the Digestive Tract, their impacts on inflammatory bowel disease and ulcerative colitis, and specifically how bioavailability of beneficial serum and stool metabolites is impacted by ostomy surgery (surgical removal intestinal sections) often performed as treatment for these and other intestinal diseases.

10:45-11:10; Steve Frese from the University of Nevada, Reno (new W5122 group member) provided an overview of his research developing probiotics for preterm infants and development of the WOLFPACK Study ("Wide Open Local Fecal sample collection comparing Pharmaceutical intake, ACtivity, and dietary intaKe"), which seeks to understand how the gut microbiome of Northern Nevadans is affected by diet, health, lifestyle, and other factors. He also discussed a new undergraduate student summer training program at UNL Lake Tahoe campus on health implications of the gut microbiome, involving performance and analysis of DNA extractions, PCR, food frequency questionnaires, and a 'lifestyle survey', and providing educational feedback on dietary habits and health (200 enrolled to date, 61% female, 36+/- 15 yo, 25+/-5 BMI; 61% white). Descriptive studies are complimented with fecal culture experiments with different dietary ingredients (e.g., fiber from hemp, yeast- vs bovine-derived whey protein) to determine impacts on gut microbiota growth and SCFA production.

11:15-11:40; Maria Marco from the University of California-Davis reviewed her efforts and aims of large scale EATLAC educational and scientific program to educate public and scientific community on fermented foods and their benefits, which was the subject of a recent review article which she co-authored in Nature Reviews. She also discussed a transwell in vitro intestinal barrier function model she developed to investigate impacts of lab and commercial cabbage ferments on cytokines and barrier function. Recent studies found that the fermented foods reduced leaky gut (improved barrier integrity), lowered inflammatory cytokines and altered levels of lactate metabolites. Interestingly, while the lactate metabolites alone did not reduce cytokines, they did improve barrier function in this model.

11:45-12:10; Rachel Kopec from Ohio State University provided an overview of her research interests/expertise and technical competencies/capacities for examining dietary bioactive interactions, novel metabolite ID, and multi-omic integration to foster collaboration opportunities across the multi-state groups. She also discussed her in vitro digestion and intestinal uptake model using caco-2 cells and micellarized compounds and a recent collaboration with food engineers and sensory scientists to innovate food processing techniques that enrich plant foods with iron (e.g., synthesis of iron chlorophyll (replacing Mg++) to improve absorption of iron from foods like Kale). She found that engineering foods using some forms of protein (e.g., whey or legumes protein) bound to iron could improve absorption. Finally, she discussed her interest in integrating metabolomics and lipidomics into member research projects through collaborations to build a bigger omics toolbox and dataset integration across the multistate group.

1:15-1:40; Pratibha Nerurkar from the University of Hawaii discussed her work on the benefits of nanobubble (supra-oxygenated) water on the growth and metabolites/mineral contents of

sprouts and microgreens, which improves productivity (lettuce and fruits yield) over standard aerated water. Potential collaboration with Efren Delgado were discussed for using nanobubbling for agricultural food sterilization/cleaning.

1:45-2:10; Claudia Maier from Oregon State University discussed her role and expertise as the PI of the OSU Biomolecular Mass Spectrometry center, and her research focusing on the characterization of botanicals and extracts, QC and standardization, and computational modeling in the context of cardiovascular, cardiometabolic, and neurodegenerative disease. Specific projects evaluating use of botanical extracts during the non-beta-amyloid accumulation mode of Alzheimer's disease, LC-MS method development and cross-validation; metabolism of Ashwagandha constituents by gut microbiota, and spatial MS molecular analysis with 5 μm resolution were also discussed. The latter presentation sparked a new collaboration between Dr. Maier and Dr. Chicco to investigate the tissue-specific effects of dietary PUFA metabolism on eicosanoid/oxylipid production in the context of cardiometabolic risk in 2025-26 using CO AES funds.

2:15-2:40 PM; Susan Tilton from Oregon State University provided an update on her work, as part of the Super Fund Research Center, to study emerging health risks of polycyclic aromatic hydrocarbon (PAH) toxicity using a 3D airway organotypic (air-liquid interface) culture model consisting of primary human bronchial epithelial cells. Results are being used to elucidate the impacts of BAP metabolites and cellular communication and cell signaling and a pathway-based classification approach for predicting PAH-induced cancer.

3:30-3:55 PM; Chi Chen from the University of Minnesota provided an overview of his laboratory's capabilities for quantifying levels of metabolites associated with health risks in humans, specifically three metabolites: urinary NAT n-acetyl-taurine (marker of hyperacetatemia), lipid aldehydes (markers of oxidative stress), and Cinnamoylglycine (identified as a negative predictor of diabetes risk in serum from participations in CARDIA study).

4:00-4:25 PM; Kaustav Majumder from the University of Nebraska-Lincoln provided an overview of his laboratory capabilities and research interests, elaborating on recent studies investigating Maize kernel bioactivities and how these may be impaired by domestication. In particular, he emphasized nutrients we have lost through "improvement" of modern maize agriculture – specifically higher CHO and lower protein content, and lower anti-inflammatory and antioxidant activities compared to landraces (early ag) and teosinte (ancient) maize varieties.

4:30-4:55 PM; Hongbing Fan from the University of Kentucky provided an overview of his new lab and developing research program, specifically discussing his work on preparing low molecular weight collagen peptides from carp fish (AFRI seed grant) as beneficial supplement for improving bone and skin health, including studies on GI absorption (Caco cells) and bioactivities (bone cells). He also discussed work on a project investigating the protective effects of ACE2-regulating peptides on development of aneurysms in a rodent model.

5:00-5:25 PM; Adam Chicco from Colorado State University provided an overview of the technologies and resources he is using to investigate the nutri-genetic impacts of essential fatty acid metabolism on cardiometabolic risk, including a novel Fads2 LoxP mouse model that he will cross with tissue-specific Cre recombinase mice for conditional deletion of the Fads2 enzyme encoding the rate limiting step in long-chain polyunsaturated fatty acid synthesis. Recent work with global Fads2 transgenic and knockout model have linked this enzyme to higher and lower myocardial injury following an index ischemia (heart attack), which appears to be associated with

altered cardiac mitochondrial calcium buffering capacity. Future studies will investigate whether these effects result from cardiac-specific Fads2 activity, or transport of lipids derived from liver Fads2 activity using the Fads2LoxP mouse. These studies will be expanded to investigate effects of Fads2 on the eicosanoid/oxylipin profile in collaboration with Claudia Maier (W5122 member).

Friday, October 4, 2023:

8:30-11:00 **Business Meeting**/Working Breakfast in Granlibakken Granhall

- Discussion of new and emerging collaborative projects and initiatives
- Assigned W5122 group leadership roles for 2025
- Reviewed guidelines for assembly of the Annual Report
- Voted on location for next year's meeting – Granlibakken Tahoe again in 2025, then perhaps Corvallis with Susan Tilton hosting in 2026.

Activities/Accomplishments:

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

W5122 researchers in Nebraska (Izard) examined how milk fat globule membrane (MFGM) in infant formula affects gut bacteria and immune markers in newborns. Infants received either standard formula, MFGM-enriched formula, or breast milk for 60 days. Results showed that formula-fed infants had greater gut bacterial diversity than those fed breast milk, with more specific bacteria like Bifidobacterium. The MFGM-enriched formula led to increased beneficial fatty acids, although overall changes in gut bacteria and immune responses were modest compared to breast milk.

W5122 researchers in Indiana (Verma), used pigs to study the biogeography of microbiome distribution across the GI tract. We collected contents from the following sections: duodenum, jejunum, ileum, cecum, ascending colon, transverse colon, and descending colon. They analyzed these contents for the microbiome composition and menaquinone distribution and thus, provided a map of the GI tract in a new way. These data can be used in the future to determine how diet or disease-driven perturbations impact the microbiome and metabolism.

W5122 researchers in California (Marco) continued their work on probiotics, including providing guidance on reporting in probiotics clinical trials in systematic reviews and meta-analyses and publishing their findings on how consumption of probiotic lactobacilli in fermented milk can affect host responses compared to when consuming the probiotic in a supplement (non-nutritive) food. This work was complimented by studies designed to assess how encapsulation can be used to improve the delivery of peptides made by probiotic lactobacilli. Similarly, their studies provided fundamental knowledge on bile acid metabolism and provided pathways towards new probiotics based on specific metabolic capacities. Lastly, their investigations led to several important reviews on fermented foods broadly and fermented foods specifically (Brassica and beer).

W5122 researchers in Colorado (Weir) completed 2 clinical nutrition interventions and have an additional intervention underway. They examined the impact of insect-deived fiber on the gut microbiome and symptom severity in individuals with IBS. We found that incorporating 4g/day of cricket-derived chitin into the diet was safe and tolerable in the target population, decreased gastrointestinal symptoms, and reduced systemic inflammation- potentially through stabilization of the gut microbiota. They also explored the gut and mental health effects of a microalgae extract from Tetradesmus obliquus (TOME). TOME intervention for 4 weeks improved gastrointestinal symptoms, mental health assessments, and reduced biomarkers of stress, anxiety, and disrupted gut barrier function. A third intervention, examining the impacts of a spore-based probiotic, Bacillus clausii, on gut health and immunity is currently underway and expected to be completed in March 2025.

W5122 researchers in Colorado (Weir) continued to conduct animal experiments and mine clinical and pre-clinical datasets to understand how the gut microbiome interacts with specific dietary components (specifically, polyphenols, methylamines, and cannabinoids). We completed an animal study looking at bidirectional interactions between CBD/CBG and the gut microbiome in human microbiota-associated gnotobiotic mice. They found that both cannabinoids alter gut microbiota composition, but the microbiota does not appear to influence bioavailability of

cannabinoids. In contrast, methylamine and polyphenol exposure does appear to rely on type and degree of metabolism by the gut microbes.

W5122 researchers in Oregon (Maier) continued their studies on Xanthohumol (XN), a polyphenol found in the hop plant (*Humulus lupulus*) with antioxidant, anti-inflammatory, prebiotic, and anti-hyperlipidemic activity. Their own and the work of others provided preclinical evidence that suggested, that the gut microbiome is essential in mediating these bioactivities; however, relatively little is known about XN's impact on human gut microbiota in vivo. They and collaborators conducted a randomized, triple-blinded, placebo-controlled clinical trial (ClinicalTrials.gov NCT03735420) for determining safety and tolerability of XN in healthy adults. Thirty healthy participants were randomized to 24 mg/day XN or placebo for 8 weeks. As secondary outcomes, quantification of bacterial metabolites and 16S rRNA gene sequencing were utilized to explore the relationships between XN supplementation, gut microbiota, and biomarkers of gut health. Although XN did not significantly change gut microbiota composition, it did re-shape individual taxa in an enterotype-dependent manner. High levels of inter-individual variation in metabolic profiles and bioavailability of XN metabolites were observed. Moreover, reductions in microbiota-derived bile acid metabolism were observed, which were specific to Prevotella and Ruminococcus enterotypes. Their results suggest interactions between XN and gut microbiota in healthy adults are highly inter-individualized and potentially indicate that XN elicits effects on gut health in an enterotype-dependent manner.

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

W5122 researchers in Oregon (Tilton) completed studies on PAHs derived from combustion of carbon (coal, diesel, paving sealants, tobacco, wood-stoves, tires, paving sealants, etc.), that are important environmental pollutants found in the diet. Benzo[a]pyrene (BaP), the most studied PAH, is classified by the International Agency for Research on Cancer as a class 1 known human carcinogen. An estimated 95% of BaP exposure (non-occupational; nontobacco) is dietary ranging from 160-1600 nanograms daily. Current risk assessments for environmental carcinogens rely on animal studies utilizing doses orders of magnitude higher than actual human exposures. In addition, risk assessments do not adequately account for combined exposures. Studies utilizing the extremely high sensitivity of accelerator mass spectrometry (AMS) measured the toxicokinetcs of two common PAHs in mixtures, BaP and phenanthrene (Phe), in human plasma after exposure. Overall, Phe was shown to be a competitive inhibitor of the major hepatic cytochrome P-450 (CYP) responsible for metabolism of BaP and these studies were the first to provide evidence that, at actual environmental levels of exposure, the toxicokinetics of BaP in humans is markedly altered by the presence of a second PAH. Additional studies modeling the interaction of PAHs in mixtures found that standard models for chemical interactions generally underestimate toxicity across dose suggesting the potential for non-additive interactions of components. Further studies evaluating the potential for benzo[a]pyrene toxicity in an in vitro model of chronic inflammation concluded that individuals with pre-existing disease may be more susceptible to toxicity and disease outcomes.

W5122 researchers in Oregon (Maier) applied a computationally assisted analytical strategy combining fractionation of a *Centella asiatica* extract with HTS mass spectrometry and read-out from a MC65 bioassay for discovering and identifying constituents of C. asiatica that protect

against Aβ cytotoxicity in vitro. Human neuroblastoma MC65 cells were exposed to subfractions of an aqueous extract of *C. asiatica* to evaluate the protective benefit derived from these subfractions against amyloid β-cytotoxicity. The % viability score of the cells exposed to each subfraction was used in conjunction with the intensity of the molecular features in two computational models, namely Elastic Net and selectivity ratio, to determine the relationship of the peak intensity of molecular features with % viability. We also overlaid mass spectral data obtained for each fractions with MC65 protection observed for each fractions and visualized the multi-dimensional information in a GNPS molecular network. Both computational methods unequivocally identified di-caffeoylquinic acids as providing strong protection against Aβ-toxicity in MC65 cells, in agreement with the protective effects observed for these compounds in previous preclinical model studies. They also showed in associated collaborative research that *C. asiatica* and its caffeoylquinic acids and triterpene constituents increase dendritic arborization of mouse primary hippocampal neurons and improve age-related locomotion deficits in Drosophila. Prior to use *C. asiatica* extracts were characterized by untargeted MS-based profiling and phytochemical marker compounds quantified by LC-MS-MRM-MS to ensure use of standardized extracts to ensure high reproducibility of the studies. Taken together, this research provides support that caffeoylquinic acids and triterpenoids, both present in *C. asiatica* aqueous extracts, are bioactive constituents that are associated with in vitro observed antioxidant protective mechanisms and neurotrophic activity. Their preclinical studies show and confirm health promoting effects in aging relevant preclinical models of cognitive function and locomotion, but dependency on sex, mode of administration and dose was observed.

W5122 researchers in Oregon (Kolluri) discovered a novel pathway to convert Bcl-2 from a cancer protective to a cancer destructive protein. Based on this discovery, we have screened chemical libraries and identified drug candidates that cause conversion of Bcl-2 from a cancer cell protective protein to a cancer cell killer protein. These compounds are designated here as 'Bcl-2 functional converters'.

W5122 researchers in Nebraska (Majumder) investigated the efficacy of dietary iso-peptides, specifically γ-glutamyl peptide (γ-EV), in mitigating vascular inflammation, atherosclerosis, and associated metabolic disorders like type 2 diabetes. Studies using atherosclerosis-prone male Apolipoprotein E knockout (ApoE-/-) mice fed a high-fat diet (HFD: 40 kcal% fat, 1.25% cholesterol) revealed that γ-EV intervention reduces aortic plaque development, decreases vascular inflammation by downregulating ICAM-1, VCAM-1, and LOX-1 expression, and lowers macrophage infiltration (MOMA-2) in atherosclerotic plaques at the aortic root. Additionally, γ-EV reduces plasma levels of pro-inflammatory cytokine TNF-α and chemokine MCP-1. Following oral administration, γ-EV is detected in blood plasma at a concentration of 5.26 μM. However, approximately 60% of ingested γ-EV remains unabsorbed, reaching the colon intact, where it may interact with gut microbiota. 16S rRNA sequencing of cecal content indicates an increase in Akkermansia abundance and a decrease in Dubosiella after γ-EV intervention. Further qPCR analysis confirms γ-EV enrichment of Akkermansia muciniphila in the cecum, suggesting a potential gut microbiota-mediated mechanism for its vascular benefits.

W5122 researchers in Colorado (Chicco) generated a *Fads2*LoxP mouse that will facilitate conditional targeting of the *Fads2* gene encoding Delta-6 desaturase, the rate limiting enzyme in biosynthesis of long-chain polyunsaturated fatty acids from dietary essential oils. This model will enable experimental testing of hypothesized nutri-genetic interactions between dietary omega-3

and omega-6 fatty acids with *FADS2* expression on cardiometabolic risk in humans, based on accumulating evidence from epidemiological studies of FADS2 polymorphisms across diverse human populations, and potent effects of modulating global Fads2 expression and/or D6D activity in murine models of ischemic heart injury.

W5122 researcher in Kentucky (Fan) is beginning research that aims to extract locally-sourced hemp seed proteins using a simple alkaline extraction method, then using different proteases to digest these proteins into bioactive peptides and compared their inhibition of ACE, the key enzyme contributing to high blood pressure. These proteases, including alcalase, thermoase, pepsin, flavorzyme, papain, thermolysin, have shown enormous potential in preparing peptides inhibiting the ACE activity, with thermolysin being the most potent.

W5122 researcher in New Jersey (Bello) initiated a project to characterize the metabolic impacts of long term dosing of kratom alkaloids. The primary purpose of the experiments conducted during this period was to examine whether chronic oral dosing of a standardized alkaloid enriched-kratom extract (KE) prevented weight gain in diet-induced obese mice . The secondary purpose was to determine whether acute human equivalent doses of KE and major alkaloid, mitragynine (MTG), differentially influence cardiopulmonary measures in normal weight or obese mice. Overall, preliminary findings do not support the use of kratom alkaloid extract in diet-induced obesity prevention, but do suggest effects of kratom products on hemodynamic measures related to weight gain in mice.

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

W5122 researchers in Connecticut (Chun) assessed the effects of blackcurrant (BC) anthocyanins on concentrations of microbial-derived short-chain carboxylic acids (SCCAs) and metabolites of phytoestrogens. They then examined associations with six-month changes in whole-body bone mineral density (BMD) and biomarkers of bone metabolism. Fecal and blood samples from a pilot randomized controlled trial were collected and analyzed from 37 eligible peri- and early postmenopausal women aged 45–60 years who were randomized into one of three treatment groups consuming one placebo capsule (control), 392 mg BC (low BC) or 784 mg BC (high BC) daily for six months. Significant differences were observed between groups at baseline in acetic, propionic, valeric, caproic and heptanoic acids ($p < 0.05$). Isobutyric acid significantly decreased from baseline (0 months) to six months in the control group ($p < 0.05$) and the high BC group had a significantly greater concentration than the control group at six months ($p < 0.05$). Butyric acid was significantly greater in the high BC group than low BC at six months ($p < 0.05$). Six-month changes in caproic and isobutyric acids showed weak correlations with changes in whole-body BMD ($r = 0.3519$, $p < 0.05$ and $r = 0.3465$, $p < 0.05$, respectively). Isovaleric and valeric acids displayed weak correlations with BALP ($r = 0.3361$, $p < 0.05$) and OPG ($r = 0.3593$, $p < 0.05$), respectively. Enterodiol was positively correlated with BALP ($r = 0.6056$, $p < 0.01$) while enterolactone was positively correlated with osteocalcin ($r = 0.5902$, $p < 0.001$) and negatively correlated with sclerostin ($r = −0.3485$, $p < 0.05$). The results suggest that BC may be a potential dietary agent to reduce postmenopausal bone loss through modulating microbially-derived SCCAs and phytoestrogen metabolites.

W5122 researchers in Minnesota (Chen) characterized urinary N-acetyltaurine (NAT) as a biomarker of hyperacetatemia. Aim: Acetate is an important metabolite in metabolic fluxes. Its presence in biological entities originates from both exogenous inputs and endogenous

metabolism. Because the change in blood acetate level has been associated with both beneficial and adverse health outcomes, blood acetate analysis has been used to monitor the systemic status of acetate turnover. Methods: The present study examined the use of urinary N-acetyltaurine (NAT) as a marker to reflect the hyperacetatemic status of mice from exogenous inputs and endogenous metabolism, including triacetin dosing, ethanol dosing, and streptozotocin-induced diabetes. Results: The results showed that triacetin dosing increased serum acetate and urinary NAT but not other N-acetylated amino acids in urine. The co-occurrences of increased serum acetate and elevated urinary NAT were also observed in both ethanol dosing and streptozotocin-induced diabetes. Furthermore, the renal cortex was determined as an active site for NAT synthesis. Conclusions: Overall, urinary NAT behaved as an effective marker of hyperacetatemia in three experimental mouse models, warranting further investigation into its application in humans.

W5122 researchers in Minnesota (Chen) examined the profiles of tyrosine fermentation in production animals and humans. Aim: Unabsorbed aromatic amino acids (AAAs), including tyrosine (Tyr), phenylalanine (Phe), and tryptophan (Trp), are the substrates of microbial fermentation in the digestive tract. Due to the resistance of their aromatic rings to structural degradation, microbial metabolism of AAAs mainly occurs to their alanine moiety through individual or combinatorial reactions, generating a cluster of functional metabolites in humans and production animals with positive or negative effects on health and the environment. In the case of Tyr, the most abundant AAA in vivo, its microbial fermentation mainly bifurcates into the formation of 4-hydroxyphenylpropionic acids (HPPA), a health-promoting compound, and 4-hydroxyphenylacetic acids (HPAA), which is associated with adverse health events. Moreover, HPAA is the direct precursor of p-cresol, a foul-smell environmental hazard. Therefore, understanding the similarities and differences between interspecies in microbial AAA metabolism could facilitate the development of respective modulation approaches for the well-being of health and the environment. Methods: In this study, microbial Tyr metabolites in human and pig feces, broiler excreta, and cow ruminal digesta were profiled by the liquid chromatography-mass spectrometry-based quantitative analysis and multivariate modeling. Results: The results showed that both pigs and broilers predominantly favored the HPAA pathway, with pigs exhibiting significantly higher p-cresol levels compared to broilers, suggesting differential capacities for HPAA conversion to p-cresol. In contrast, cows and humans displayed a more balanced utilization of both HPPA and HPAA pathways, with humans exhibiting lower overall tyrosine microbial fermentation than the other species. Conclusions: Despite clear species-specific preferences in tyrosine microbial fermentation pathways, notable individual variations were also evident. Therefore, further investigations into the underlying mechanisms, such as enzyme activities, and strategies to mitigate p-cresol production in the pig industry are warranted to alleviate environmental hazards.

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

W5122 researchers in New Mexico (Delgado) worked on optimizing the moisture content and conditioning time in a laboratory-scale flour mill using response surface methodology as a means of increasing flour yield. A central composite experimental design (CCD) using three types of wheat with different hardness was used. Water content and tempering time were evaluated. The results showed an assertiveness of 98.95% and 98.30%, respectively, for yield and ash index; for

semi-hard wheat of 99.22% and 99.62% for yield and ash index; and the hard wheat yield of 92.59% of assertiveness, and ash index with assertiveness of 93.54%. These results demonstrate that the optimization of this process could be a useful tool for millers to achieve better yields and quality associated with these variables.

W5122 researchers in Colorado (Weir) developed a tempeh (fermented soybean product) that incorporated varying amounts of mealworms. Nutritional, food safety, and finally iron bioavaiability were assessed to determine their potential as a food product. We determined that the insect-based tempeh had similar digestability to the soybean only product, higher protein, and increased iron bioavailability.

W5122 researchers in Kentucky (Fan) initiated a study that aims to develop an effective enzymatic method to hydrolyze collagen into low-molecular-weight collagen peptides from the skin of Carp, a fish native to Asia that was introduced to the U.S. in the 1970s to control aquatic vegetation in freshwater environments. Carp have become a significant threat to indigenous species and U.S. waterways, including Kentucky waters, now constituting up to 90% of the fish populations in certain backwaters of the Mississippi River, necessitating continuous population suppression. Unlike many other invasive species, carp can be processed for human consumption, despite not being widely consumed in the U.S. Carp are exceptionally high in protein, primarily myofibrillar proteins and collagen, with collagen comprising ~ 70% of the dry weight of fish skin. The enzymatic approach (pepsin and papain) being developed can achieve a high yield and purity of collagen extraction and peptide preparation from carp.

W5122 researchers in Illinois (Helferich) continued to investigate on repeated frying of food such as potatoes, fish, and chicken can alter the oil to product thermally abused frying oil (TAFO) and pan-frying bacon alters the lipid and can have negative impact on breast cancer progression and metastasis. These products are commonly consumed, and we have demonstrated that these products enhance late-stage breast cancer metastasis. Once they understand the process for producing these lipids that enhance metastasis, they can develop strategies to alter the processing to reduce the impact of these products to breast cancer survivors.

W5122 researchers in Hawaii (Nerurkar) initiated a study to understand the impact of natural fermentation on health beneficial bacteria and metabolites in local foods that can positively impact chronic diseases such as type 2 diabetes. Several local fermented foods are under study. Recent results indicate that natural fermentation of poi significantly increases resistant starches, mineral and health beneficial metabolites. Second goal is to explore approaches to biofortification of tropical functional foods to increase bioactive components.

W5122 researchers in Minnesota (Chen) conducted a chemometric survey on whole stillages and distillers dried grains with solubles (DDGS) from biofuel production. Aim: As a staple feed ingredient for livestock and poultry production, the nutrient profile of DDGS is well documented. However, the profile of intermediate metabolites and non-ethanol chemical compounds produced during fermentation, distillation, and other processing steps in DDGS production has not been examined extensively. Methods: In the current study, whole stillage and DDGS samples were collected from 10 biofuel plants in eight states of midwestern United States and analyzed for nutrient composition as well as chemometric analysis using liquid chromatography-mass spectrometry (LC-MS) and multivariate analysis. Results: The compositional profiles of these samples, including protein, lipid, fiber, and ash contents, were within the expected ranges of values previously reported in the literature. The LC-MS analysis of DDGS samples and whole stillage supernatants identified proline, alanine, asparagine, glutamic acid, and glycine as the

most abundant free amino acids (FAA), which was likely due to their high abundance in corn protein. The analysis also identified lactic acid and acetic acids as the most abundant organic acids, as well as the presence of diverse aldehydes and polyamines with highly variable concentrations, which were consistent with their roles as intermediate and fermentation derived metabolites. Interestingly, the principal components analysis-based multivariate modeling revealed the clustering of DDGS and whole stillage samples based on two processing platforms that utilize different amounts of enzymes and heat. This processing-based separation was mainly driven by the differences in multiple essential FAA and other metabolites, including ethanolamine, putrescine, and pentanal. Conclusions: The chemometric profiles of whole stillages and DDGS were defined in this study. Considering the nutritional and biochemical properties of these metabolites, our observations warrant further investigations on the roles of processing conditions in the formation of these functional molecules as well as the nutritional significance of these differences in DDGS.

W5122 researchers in Minnesota (Chen) examined the disposition of deoxynivalenol (DON) in nursery and grow-finish pigs under sulfonation-based mitigation treatments. Aim: Deoxynivalenol (DON) is a highly reactive epoxy-sesquiterpenoid mycotoxin commonly present in cereal feed ingredients. Dietary DON contamination negatively affects feed intake, growth, and health status in all stages of swine production. Both in vivo biotransformation, including somatic xenobiotic metabolism and microbial metabolism, and ex vivo chemical mitigation reactions, such as bisulfite-based sulfonation, have been shown to reduce the reactivity and bioavailability of DON and alleviate its toxicity in pigs. However, whether age and growth could affect DON metabolism and chemical mitigation in pigs has not been examined previously. Methods: In two feeding trials, 48 nursery pigs and 60 grow-finish pigs, respectively, were fed DON-contaminated feeds with or without bisulfite agents. DON and its mitigation products in feeds, as well as their metabolites in excreta samples (feces and urine), were determined by liquid chromatography-mass spectrometry-based metabolomic analysis. Results: The results showed the abundant presence of DON glucuronides in urine and the absence of free DON in feces, indicating extensive absorption and metabolism of DON occurred in both nursery and grow-finish pigs. Nevertheless, the presence of free DON in urine and de-epoxy deoxynivalenol (DOM) in feces only occurred in nursery pigs, while grow-finish pigs excreted more DOM glucuronides in urine than nursery pigs. Bisulfite additives effectively and dose-dependently decreased DON in pig feeds by forming DON sulfonates (DON-S), including DON-S2 and DON-S3. These DON-S were further enriched and concentrated in feces by the formation of DON-S1 and the increase of DON-S2, potentially through the reactions in the digestive system. In addition, bisulfite additives in feed decreased the urinary excretion of DON and its glucuronides in both nursery and grow-finish pigs, but only increased the fecal excretion of DOM in nursey pigs. Conclusions: Overall, compared to nursery pigs, grow-finish pigs might be more efficient in the microbial conversion of DON to DOM, DOM absorption, and somatic production of their glucuronides, which potentially contribute to their differences in DON disposition after bisulfite mitigation treatments.

Impact statements:

W5122 researchers in Nebraska (Izard) revealed insights into the potential benefits of supplementing infant formula with MFGM to more closely mimic the effects of breast milk on gut health and early immune development, supporting the formulation of improved infant nutrition products that could aid infants who cannot be breastfed, potentially influencing their long-term health outcomes.

W5122 researchers in Nebraska (Majumder) provided the first comprehensive investigation into the role of dietary γ-glutamyl peptides in mitigating cardio-metabolic disorders, revealing complex interactions with the gut microbiota and vascular function a potential mechanisms of action.

W5122 researchers in Indiana (Verma) developed a high-resolution biogeographical map of the gastrointestinal microbiome of pigs as model for studying diet impacts on the health of monogastric mammals (including humans).

W5122 researchers in Hawaii (Nerurkar) provided scientific evidence and increasing bioactive compounds and minerals through biofortification that may increase consumption of fermented foods and prevent/lower incidences of chronic diseases and metabolic syndrome.

W5122 researchers in Colorado (Weir) established the safety and tolerability of three novel food ingredients/supplements.

W5122 researchers in Colorado (Weir) identified potential dietary strategies for mitigating gastrointestinal symptoms.

W5122 researchers in Colorado (Weir) developed an experimental workflow for detremining the role of gut microbiota in response/non-response to dietary interventions.

W5122 researchers in Illinois (Helferich) generated results that provide a basis for clinical trials testing impact of cooking of commonly consumed foods that impact metastatic tumor development and treatments, and inform the broader public of the health consequences of consuming deep fried foods and pan fried bacon

W5122 researchers in Minnesota (Chen) identified a novel metabolite biomarker of hyperacetatemia, a pathological status of metabolic disorders and disruptions. We determined the metabolic fates of tyrosine in multiple species and deoxynivalenol in pigs. These results could be used to guide the metabolism analysis in nutrition, toxicology, and industrial applications. All these research activities provided training opportunities for graduate students, undergraduate, postdoc, and visiting scholars.

W5122 researchers in California (Marco) is discovering ways to improve the production of fermented foods for enhanced sensory properties, shelf-life, and health benefits.

W5122 researchers in California (Marco) are learning how background diets can alter how dietary live microbes, such as those used as probiotics or in foods, affect the gut microbiome and intestinal environment, and ultimately impact human health.

W5122 researchers in Oregon (Tilton) show that combined exposure to dietary carcinogens can markedly alter metabolism and toxicokinetics of chemicals in human plasma, as well as lead to an underestimation of risk based on standard modeling of chemical mixture interactions assuming additivity.

W5122 researchers in Oregon (Tilton) completed the first studies to evaluate the role of combined environmental factors associated with inflammation from pre-existing disease and PAH exposure on pulmonary toxicity in a physiologically relevant human in vitro model.

W5122 researchers in Oregon (Maier) provided mechanistic insights into the efficacy and safety of the highly popular dietary supplements, ashwagandha and gotu kola, used as a remedy for

reducing stress and enhancing resilience to aging associated decline in cognitive and locomotion function.

W5122 researchers in Oregon (Kolluri) identified small molecule “Bcl-2 functional converters” compounds that are envisioned to work as targeted cancer therapeutics to inhibit overexpression of Bcl-2 signaling in active tumors.

W5122 researchers in Connecticut (Chun) found that blackcurrant (BC) consumption reduces postmenopausal bone loss via enhancing the production of SCCAs and phytoestrogen metabolites in the gut, which can be translated into dietary recommendations for adult women.

W5122 researchers in Colorado (Chicco) generated a novel model mode for experimental validation and investigation of the nutri-genetic interactions between the *FADS2* gene and dietary polyunsaturated fatty acid intake on cardiometabolic risk suggested by human epidemiological studies.

W5122 researchers in New Mexico (Delgado) developed simulations and process optimization models for optimizing and predicting yield and ash index, an important tool for millers to predict the potential yield in a laboratory mill.

W5122 researchers in Kentucky (Fan) demonstrated that pepsin and papain were proved to be effective in extracting collagen and hydrolyzing it into collagen peptides from carp, potentially making productive use of this invasive species that can align with local population control efforts.

W5122 researchers in New Jersey (Bello) determined that kratom alkaloids influence cardiovascular parameters, but not weight gain, in a mouse model of obesity.

Plans for 2025:

W5122 researchers in Nebraska (Izard) will perform new studies investigating how our digestive tract structures, diet, and the microorganisms they contain, can influence intestinal health.

W5122 researchers in Nebraska (Majumder) will investigate a broader spectrum of dietary γ-glutamyl peptide variants to better understand their individual and collective bioactivities on cardiometabolic risk through rigorous in vitro experimentation.

W5122 researchers in Nebraska (Majumder) will explore the specific roles of *Akkermansia* and *Dubosiella* (gut microbes) in mediating the beneficial effects of γ-glutamyl peptides to pave the way for more targeted and evidence-based dietary interventions for cardio-metabolic health..

W5122 researchers in Indiana (Verma) plan on comparing the results obtained with composition to metagenomics (and thus functions) of the microbes in their new porcine model of diet-gut microbiome interactions, with a focus on microbiome-metabolite relationships.

W5122 researchers in Colorado (Weir) will bring an insect chitin intervention into malnourished school children in Madagascar to determine whether it mitigates intestinal issues/inflammation and improves response to iron supplementation regimen.

W5122 researchers in Colorado (Weir) will identify microbiome signatures associated with different exposure levels to polyphenol (blueberry) intervention and determine their ability to predict ardiovascular response to the intervention.

W5122 researchers in Colorado (Weir) will determine which methylamine metabolites from dietary components like carnitine, choline, betaine, are pro or anti-atherogenic using mouse models.

W5122 researchers in Hawaii (Nerurkar) plan to refine techniques to biofortify active compounds and minerals in tropical vegetables used as functional foods and identify alternate approaches to grow these vegetables in Controlled environment using technology to optimize plant growth, quality, and production efficiency

W5122 researchers in Minnesota (Chen) will continue examining more metabolic events associated with the feedings of palm oils and bile acids in animals, and fecal transplantation in humans. In addition, they will expand their chemometric analysis of oxidized oils and fats, DDGS, and fermented soybean meals.

W5122 researchers in Colorado (Chicco) will utilize the novel Fads2LoxP mouse model recently developed to investigate the impact of cardiac- and liver-specific *Fads2* expression on myocardial ischemic tolerance (heart attacked size) in the context of high and low dietary omega-6 fatty acid intake.

W5122 researchers in California (Marco) will perform new studies focused on understanding how fermentation modifies food substrates in ways that impact their nutritional and health-modulatory effects. They will also continue work on the gut microbiome and probiotics to elucidate how specific microbes and specific microbial consortia, either applied or as resident members of the animal and human microbiome, can improve systemic health through the digestive tract.

W5122 researchers in Oregon (Tilton) will continue with studies to identify important mechanisms related to the adverse effects of dietary components on human health.

W5122 researchers in Oregon (Maier) will continue studies investigating how the extracts of the botanical herbs Centella (*Centella asiatica*, “Guto kola) and Ashwagandha (*Withania somnifera*) improve resilience to aging-associated decline of cognitive functions using a combination of preclinical models and “omics” approaches.

W5122 researchers in Oregon (Maier) will continue to investigate the chemical compounds present in centella and ashwagandha extracts for determining which compound classes found in those compositionally complex extracts exert certain bioactivity.

W5122 researchers in Oregon (Maier) will continue investigating compounds present in hops for their health promoting properties and mode of actions and targets in the context of Inflammatory Bowel Disease and gut microbiota host interactions

W5122 researchers in Oregon (Kolluri) will continue investigating the utility of ‘Bcl-2 functional converter’ compounds as novel therapeutics against chemoresistant cancer cells.

W5122 researchers in Connecticut (Chun) will perform additional analyses including microbial analyses to explore potential bacterial species related to the production of SCCAs and phytoestrogen metabolites as well as genetic testing as some SCCAs have been shown to reduce the expression of inflammatory genes. Additionally, they plan to perform multi-omics analysis to

further elucidate the mechanism of action of BC on prevention of postmenopausal bone loss in the study population.

W5122 researchers in Kentucky (Fan) will further optimize the methods and improve the yield of collagen and peptides prepared from carp.

W5122 researchers in New Mexico (Delgado) will develop and evaluate sustainable technologies and strategies to improve productivity and process efficiencies, reduce agricultural and environmental impact, identify new products and byproducts, and determine alternative mechanized approaches for specialty crops grown as cotton companion crops.

W5122 researchers in New Jersey (Bello) will test hypothesis that metabolic impairments associated with obesity lead to an impaired cardiac function with kratom alkaloids, this results from a longer half-life (T1/2) of kratom alkaloids in obese compared with normal weight mice. In aim 1, we will determine the acute dose-dependent effects of standardized kratom alkaloids on continuously monitored cardiovascular function in obese compared with normal weight mice. In aim 2, we will determine the effects of obesity of the metabolism and clearance for the key kratom alkaloids. Overall, this project will provide unique insight into the cardiovascular effects of kratom, identify obesity-related novel kratom metabolites, provide a foundation for investigating the mechanistic actions of kratom alkaloids

Grants awards (new and ongoing):

W5122 members and their labs were supported by **53** grants from federal agencies, private foundation, industry collaborations, and institutional investments totaling well over **$20M during the 2023-24 periodi** to study effects of bioactive nutrients on cancer, diabetes, metabolic and gut health, and cardiovascular risk). Major awards from this reporting period are listed below.

W5122 member	Year	Project Title	Funding Agency	US Dollars (approx.)
Ock Chun (University of Connecticut)	2025-2029	Blackcurrants Mitigate Postmenopausal Bone Loss through Gut Microbiota-Bone Axis	USDA-AFRI	$650,000
	2024-2027	Colon cancer protection derived from prunes.	National Research Foundation of Korea	~$200,000 US
Mohit Verma (Purdue University)	2023-2025	A universal field-deployable test for measuring and predicting the spread of SARS-CoV-2 in any host species	United States Department of Agriculture Animal and Plant Health Inspection Services	$2,729,261
	2023-2024	Testbeds for microbial source tracking using microfluidic paper-based analytical devices	Center for Produce Safety Grants Program	$394,516
	2024-2025	Raman and QCL MIDIR Spectroscopy as a process analytical technology (PAT) tool for Adeno associated viral vectors (AAV) and monoclonal antibodies (mAbs) downstream processes	Eli Lilly and Company	$85,000
Mohit Verma (Purdue University)	2022-2024	Point-of-care detection of African swine fever virus: a paper-based device for molecular diagnostics	joint National Animal Health Laboratory Network	$1,000,000

			and National Animal Disease Preparedness and Response Programs in Indiana Agriculture and Rural Communities	
Mohit Verma (Purdue University)	2021-2024	Field-deployable biosensors for managing animal health	Foundation for Food and Agriculture Research	$715,000
Mohit Verma (Purdue University)	2023-2024	Swallowable smart capsule for targeted gastrointestinal microbiome sampling	NIDDK	$185,242
Maria Marco (University of California-Davis)	2022-2026	PIG-PARADIGM: Preventing Infection in the Gut of developing Piglets-and thus Antimicrobial Resistance - by disentAngling the interface of DIet, the host and the Gastrointestinal Microbiome.	Novo Nordisk Foundation	
	2021-2023	The yogurt matrix during digestion: benefits of milk composition and structure	California Dairy Research Foundation	
	2024-2025	Improving intestinal barrier function with fermented dairy foods	California Dairy Research Foundation	
Maria Marco (University of California-Davis)	2024-2028	Electro-fermentation for improved fermented fruits and vegetables.	USDA NIFA AFRI	
Kaustav Majumder (University of Nebraska-Lincoln)	2022-2027	Evaluating the Efficacy of Dry Bean-Based Dietary-Glutamyl Peptides for	USDA Hatch Multistate Enhanced Program	$217,472

		Improvement of Metabolic Syndrome		
Kaustav Majumder (University of Nebraska-Lincoln)	2023-2024	Alfalfa Seed Utilization for Human Food	Dept of Agriculture-ARS (USDA-ARS-NCAUR)	$133,441
Kaustav Majumder (University of Nebraska-Lincoln)	2023-2024	Development of Plant Protein-Based High-Value and Innovative Food Products from Nebraska Pulses	Specialty Crop Block Grant Program, Nebraska Department of Agriculture	$38,449
Kaustav Majumder (University of Nebraska-Lincoln)	2023-2024	Dry Edible Beans as an Efficacious Alternative for the Development of Fortified-Blended Foods for Food-Aid Program	Specialty Crop Block Grant Program, Nebraska Department of Agriculture	$55,767
Kaustav Majumder (University of Nebraska-Lincoln)	2021-2024	Elucidating the Health Beneficial Traits of Kernels of Maize Relatives Digested in the Human Gastrointestinal Tract	USDA Agriculture and Food Research Initiative- NIFA	$500,000
Hongbin Fan (University of Kentucky)	2024-2026	Utilizing Collagen of the Invasive Asian Carp, An Underutilized Protein Source	USDA Agriculture and Food Research Initiative- NIFA	$300,000
Hongbin Fan (University of Kentucky)	2024-2028	Acquisition of a Triple Quadrupole LC/MS for Multi-Omic Metabolite, Lipid, and Peptide Analyses	USDA Agriculture and Food Research Initiative- NIFA	$398,262
Adam Chicco (Colorado State University)	2023-2025	Conditional Fads2-KO mouse for investigating nutri-genetic regulation of cardiometabolic risk	Colorado Agricultural Experimental Station (USDA)	$50,000
	2022-2025	Evolutionarily conserved variations in menaquinone structure: Functional implications	National Science Foundation	$528,000

	2024-2027	Genetic diversity of human heart responses to low-dose radiation	DOE (Co-PI)	$488,456
	2024-2026	Investigating the Role of Thyroid Hormone in Placental Function	NIH (Co-I)	$415,490
	2024-2027	Sex-specificity of radiation-induced cardiac injury in a genetically diverse population	NIH (Co-PI)	$200,986
Tiffany Weir (Colorado State University)	2023-2026	Diet and microbiome interactions: application in posttraumatic stress disorder (D-MAPS	Immunology, Inflammation, and Infectious Disease (3i) Initiative and the Cumming Foundation	$60,000
Tiffany Weir (Colorado State University)	2023-2027	CoSMIC: Colorado State Microbiome Innovation Consortium	TUNE mechanism; CSU VPR	$1,200,000
Tiffany Weir (Colorado State University)	2023-2025	Munispore: Examining Bacillus clausii on intestinal function and regularity.	ADM/Deerland Enzymes and Probiotics	$112,000
Tiffany Weir (Colorado State University)	2023-2025	Tetrasol: Effects of a Microalgae Extract Dietary Supplement on Gut Health, Anxiety, and Immune Function	Mycrophyt, LLC	$216,000
Tiffany Weir (Colorado State University)	2023-2024	Examination of the bi-directional interactions between phytocannabinoids and a human-associated gut microbiota.	Institute for Cannabis Research	$189,000
Tiffany Weir (Colorado State University)	2019-2024	Discovery and Biological Signatures of Microbiome-Derived Xanthohumol Metabolites and their	NIH (Co-I)	

		Role in Ameliorating Inflammatory Bowel Disease		
Claudia Maier (Oregon State University)	2024-2025	Mass spectrometer with electron activated dissociation capability	USDA (Co-I)	$500,000
Claudia Maier (Oregon State University)	2022-2025	Single Cell Proteomics	Hewlett Packard/Oregon State University Collaboration Grant	$265,000
Claudia Maier (Oregon State University)	2023-2025	Computation-assisted discovery of bioactive minor cannabinoids from hemp (Co-I)	NIH	$400,000
Claudia Maier (Oregon State University)	2021-2025	Botanical Dietary Supplements Research Centers (BDSRC) on Botanicals Enhancing Neurological and Functional Resilience in Aging (BENFRA)	NIH	$1,600,000
Pratibha V Nerurkar (University of Hawaii)	2021-2026	Empowering Women and Underrepresented Undergraduates with Advanced Technology Research Training in Agriculture and Food Sciences	AFRI-NIFA	$440,367
Pratibha V Nerurkar (University of Hawaii)	2018-2024	Specialty Crops: From Farm to Human Health	USDA- ARS	$80,000
	2021-2024	Developing an Alliance for Training and Apprenticeship in Climate-Smart Agriculture (DATA-Ag)	USDA-AFRI-AWT Program through UT at Arlington.	$124,852
	2021 -2024	Training of Next Generation Workforce for Smart Food Science and Agricultural	USDA-AFRI	$500,000

		Technology in the Digital Era (WorkFoS-Ag)		
Efren Delgado (New Mexico State University)	10/01/2022 – 09/30/2025	Genetic dissection of Phytophthora capsici resistance in chile pepper using epigenomic and transcriptomic approaches	New Mexico Department of Agriculture (NMDA) - Specialty Crop Grant Program (SCBGP)	$102,562
	2021-2026	Bioprocessing of Agroindustrial By-products	Hatch-Proposal-US Department of Agriculture	$27,500
Tilton (PI) Oregon State University	2022-2024	Development of a 3D respiratory co-culture model for assessing toxicity to chemicals from wildfire smoke	Center for Translational Environmental Health Research	$25,000
Tilton (PI) Oregon State University	2020-2025	Linking PAH Exposure to Health Outcomes Using Human Primary In Vitro Respiratory Model	NIH/NIEHS P42 ES016465	$1,470,000
Tilton (PI) Oregon State University	2022-2024	Linking PAH Exposure to Health Outcomes Using Human Primary In Vitro Respiratory Model	NIH/NIEHS P42 ES016465 Supplement	$100,000
Kolluri (PI) Oregon State University	2021-2024	Bcl-2 as a target in cancer	NIH/NCI R21CA249627	$400,000
Kolluri (PI) Oregon State University	08/01/2020-6/30/2024	Processed Food Intake, Metabolomics, and Adiposity	NIH R01	
Kolluri (PI) Oregon State University	07/2024-06/2025	Integrated Regional Training Program in Environmental Health Sciences (Marcus and Kolluri – MPI)	NIH	$2,500,000

Kolluri (PI) Oregon State University	1/1/2024-12/31/2027	Acquisition of Combustion Elemental Analyzer to Strengthen Agricultural Research at the University of Minnesota	USDA	$500,000
Chi Chen (Co-I); University of Minnesota	3/1/2023-2/28/2025	Advancing Biorefinery of Camelina and Pennycress Meal for Valuable Products	Minnesota Forever Green Initiative	
Chi Chen (Co-I); University of Minnesota	2020-2024	Processed Food Intake, Metabolomics, and Adiposity	NIH	
Chi Chen (Co-PI); University of Minnesota	2023-2027	Lysine requirements that maximize reproductive performance in pregnant sows	USDA	$500,000
Chi Chen (Co-I); University of Minnesota	2023-2025	By beneficially altering microbiome, yogurt (the whole food) may be more beneficial to mental health than non-dairy probiotic supplement	National Dairy Council	
Jacques Izard (University of Nebraska)	2018-2023	Digestive Tract Microbiome in Healthy Term Infants receiving Mothers-Own Breast Milk or Cows Milk-Based Infant Formulas	Mead Johnson Nutrition	
Jacques Izard (University of Nebraska) (Co-investigator; PI: Dr. Kerry Ivey)	2023-2025	By beneficially altering microbiome, yogurt (the whole food) may be more beneficial to mental health than non-dairy probiotic supplements	National Dairy Council	$303,994
Nick Bello (Rutgers University; PI)	2019-2024	The Role of Lateral Hypothalamus Orexin Glucose-Inhibited Neurons in Binge-Eating Disorder	DOD	$1,019,612

Publications:

There were **77** new publications by W5122 members in 2023-2024 period, addressing the effects of bioactive nutrients on health and chronic disease risk, basic insights into nutrient metabolism, and the development of new methodology and technologies for studying these processes in humans and model systems. Publications are listed below with W5122 group members in boldfaced text.

1. Briana M. Nosal, Staci Thornton, Alexey Melnik, Ali Lofti, Manije Darooghegi Mofrad, Alexander Aksenov, Elaine Choung-Hee Lee and **Ock K. Chun**. Blackcurrant anthocyanins attenuate estrogen deficiency-induced bone loss through modulating microbial-derived short-chain carboxylic acids and phytoestrogen metabolites in peri- and early postmenopausal women. Metabolites 2024, 14, 541. https://doi.org/10.3390/metabo14100541

2. Mao Q, Shi X, Ma Y, Lu Y, **Chen C**. *Characterization of Urinary N-Acetyltaurine as a Biomarker of Hyperacetatemia in Mice*. Metabolites. 14: 322 (2024). https://doi.org/10.3390/metabo14060322
3. Heidari F, Øverland M, Hansen JØ, Mydland LT, Urriola PE, **Chen C,** Shurson GC, Hu B. *Enhancing the nutritional value of canola meal through solid culture with Pleurotus ostreatus*. Animal Feed Science and Technology. 309: 115893 (2024) https://doi.org/10.1016/j.anifeedsci.2024.115893
4. Ravelo AD, Ferm P, Guo Y, Omontese BO, Morley PS, **Chen C**, Noyes NR, Caixeta LS. *Using a multi-omics approach to explore potential associations with rumen content and serum of cows with different milk production levels based on genomic predicted transmitting ability for milk and phenotypic milk production*. PloS one. 19: e0305674 (2024) doi: 10.1371/journal.pone.0305674
5. Trudeau M, Mosher W, Tran H, de Rodas B, Karnezos TP, Urriola PE, Gomez A, Saqui-Salces M, **Chen C,** Shurson GC. *Growth Performance, Metabolomics, and Microbiome Responses of Weaned Pigs Fed Diets Containing Growth-Promoting Antibiotics and Various Feed Additives*. Animals. 14: 60 (2024) DOI: 10.3390/ani14010060
6. Onarman Umu ÖC, Mydland LT, **Chen C**, de Nanclares MP, Shurson GC, Urriola PE, Sørum H, Øverland M. *Integrated multi-omics approach reveals novel associations in the rapeseed diet–microbiota–host axis in pigs*. ISME communications. 4: ycae061 (2024) DOI: 10.1093/ismeco/ycae061
7. Yang J, Gourley GR, Gilbertsen A, **Chen C**, Wang L, Smith K, Namenwirth M, Yang L. *High Glucose Levels Promote Switch to Synthetic Vascular Smooth Muscle Cells via Lactate/GPR81*. Cells 13: 236 (2024), https://doi.org/10.3390/cells13030236
8. Duddeck KA, Petersen TE, Adkins HJ, Smith AH, Hernandez S, Wenner SJ, Yao D, **Chen C**, Li W, Fregulia P, Larsen A, Jang YD. *Dose-Dependent Effects of Supplementing a Two-Strain Bacillus subtilis Probiotic on Growth Performance, Blood Parameters, Fecal Metabolites, and Microbiome in Nursery Pigs*. Animals. 14: 109 (2024) DOI: 10.3390/ani14010109
9. Quintero Quiroz, J, Velazquez, V, Torres, JD, Ciro, G, **Delgado, E**, Rojas, J. 2024. Effect of the structural modification of plant proteins as microencapsulating agents of bioactive compounds from annatto seeds (Bixa Orellana L.). Foods. 13(15), 2345; https://doi.org/10.3390/foods13152345.
10. Paśko P, Galanty A, Dymerski T, Kim YM, Park YS, Cabrales-Arellano P, Velazquez Martinez V, **Delgado E**, Gralak M, Deutsch J, Barasch D, Nemirovski A, Gorinstein S. 2024. Physicochemical and Volatile Compounds Analysis of Fruit Wines Fermented with

Saccharomyces cerevisiae: FTIR and Microscopy Study with a Focus on Anti-inflammatory Potential. 2024. International Journal of Molecular Sciences 25, 5627. https://doi.org/10.3390/ijms25115627.

11. Martínez Ávalos, JF, Gamero Barraza, JI. **Delgado, E**, Guerra Rosas, MI, Gómez Aldapa, CA. Medrano Roldán, H. Reyes Jáquez, D. 2024. Study of molecular dynamic interactions during the optimized extrusion processing of corn (Zea mays) and substandard bean (Phaseolus vulgaris). Food Chemistry Advances 4, 100723. https://doi.org/10.1016/j.focha.2024.100723.
12. Gamero-Barraza, JI, Pámanes-Carrasco, GA, **Delgado, E**, Cabrales-Arellano, CP, Medrano-Roldán, H, Gallegos-Ibáñez, D, Wedwitschka, H, Reyes Jáquez, D. 2024. Computational modelling of extrusion process temperatures on the interactions between black soldier fly larvae protein and corn flour starch. Food Chemistry: Molecular Science 8, 2024. https://doi.org/10.1016/j.fochms.2024.100202.
13. Paśko P, Galanty A, Ramos-Zambrano E, Martinez Ayala, AL, **Delgado E**, Gdula – Argasińska J, Zagrodzki P, Podsiadły P, Deutsch J, Gorinstein S. 2024. Pseudocereal oils, authenticated by Fourier transform infrared spectroscopy, and their chemopreventive properties. Plant Foods for Human Nutrition.
14. Gaucin Gutiérrez, S.C., Rojas-Contreras, J.A., Zazueta-Álvarez, D.E., **Delgado, E**., Vázquez Ortega, P.G., Medrano Roldán, H., Reyes Jáquez, D. 2024. Exploration of In Vitro Voltage Production by a Consortium of Chemolithotrophic Microorganisms Using Galena (PbS) as a Sulphur Source. Clean Technologies, 6(1), 62-67. https://doi.org/10.3390/cleantechnol6010005.
15. Chloe Christensen, Car Reen Kok, Cheryl L Harris, Nancy Moore, Jennifer L Wampler, Weihong, Zhuang, Steven S Wu, Robert Hutkins, **Jacques Izard**, Jennifer M. Auchtung. Microbiota, metabolic profiles and immune biomarkers in infants receiving formula with added bovine milk fat globule membrane: a randomized, controlled trial, Frontiers Nutrition (2024) 11:1465174
16. **Nancy D. Turner, Tiffany L. Weir, and Jacques Izard**. Intersection of Diet, Intestinal Microbiota and Their Metabolites on Cancer Prevention. Frontiers in Nutrition (2024) 10:1358428
17. Road map Contributors (**Jacques Izard** as a contributor to all 3 technical themes “Health and Medicine” “Food and Nutrition”, and “Environmental Control and Life Support”); Engineering Biology Space Health, An Innovative Research Road Map; Engineering Biology Research Consortium (EBRC) Publisher (2024)
18. Arghya Mukherjee, Samuel Breselge, Eirini Dimidi, **Maria L Marco**, and Paul D Cotter. 2023. Fermented foods and gastrointestinal health: underlying mechanisms. Nature Reviews Gastroenterology & Hepatology. 21:248–266.
19. Lynne V McFarland, Gail Hecht, Mary E Sanders, Debra A Goff, Ellie J C Goldstein, Colin Hill, Stuart Johnson, Maryam R Kashi, Ravina Kullar, **Maria L Marco**, Daniel J Merenstein, Mathieu Millette, Geoffrey A Preidis, Eamonn M Quigley, Gregor Reid, Seppo Salminen, Jason C Sniffen, Harry Sokol, Hania Szajewska, Daniel J Tancredi, Kristin Woolard. 2023. Recommendations to improve quality of probiotic systematic reviews with meta-analyses: Developed by expert Delphi consensus. JAMA Network Open. 6(12):e2346872.
20. Maany Ramanan, Glen Fox, and **Maria L. Marco**. 2024. Beer for live microbe delivery. Journal of Functional Foods. 113:105987.
21. Mateus L.P. Lemos, Guilherme M. Leite, Liliane P. Santana, Nelquides B. Vianaa, Wydemberg J. Araújo, Wannes Van Beeck, **Maria L. Marco**, Anderson M. Zanine, Edson M. Santos, Celso J.B. Oliveira. 2024. Bacterial community dynamics of spineless

cactus silage during fermentation and aerobic stability. Bioresource Technology Reports. 25:101762

22. Jee-Yon Lee, Connor R. Tiffany, Scott P. Mahan, Matthew Kellom, Andrew W.L. Rogers, Henry Nguyen, Eric T. Stevens, Hugo L.P. Masson, Kohei Yamazaki, **Maria L. Marco**, Emiley A. Eloe-Fadrosh, Peter J. Turnbaugh, and Andreas J. Baumler. 2024. High fat intake sustains sorbitol intolerance after antibiotic-mediated clostridia depletion from the gut microbiota. Cell. 87(5):1191-120
23. Glory Bui, Cristina Torres-Fuentes, Matteo M Pusceddu, Mélanie G Gareau, and **Maria L Marco**. 2024. Milk and Lacticaseibacillus casei BL23 effects on intestinal responses in a murine model of colitis. American Journal of Physiology and Gastrointestinal Liver Physiology. 326(6):G659-G675..
24. Lei Wei, Dana Wong, Tina Jeoh, **Maria L. Marco**. 2024. Intestinal delivery of encapsulated bacteriocin peptides in cross-linked alginate microcapsules. Food Research International. 118:114473.
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26. Sabina Fijan, Polona Fijan, Lei Wei, and **Maria L. Marco**. 2024. Health benefits of kimchi, sauerkraut and other fermented foods of the genus Brassica. Applied Microbiology. 4(3), 1165-1176.
27. Colvin V, Bramer LM, Rivera BN, Pennington JM, Waters KM, **Tilton SC**. 2024. Modeling PAH mixture interactions in a human in vitro organotypic respiratory model. Int. J. Mol. Sci. 25(8), 4326. doi.org/10.3390/ijms25084326. PMCID: PMC11050152.
28. Valdez R, Rivera BN, Chang Y, Pennington JM, Fischer KA, Lohr CV, **Tilton SC**. 2024. Assessing susceptibility for polycyclic aromatic hydrocarbon toxicity in an in vitro 3D respiratory model for asthma. Frontiers in Toxicology, Special Issue “Linking Environmental Exposure to Toxicants and Chronic Disease”. 6:1287863. doi.org/10.3389/ftox.2024.1287863. PMCID: PMCID11066177.
29. Maier MLV, Siddens LK, Pennington JM, Uesugi SL, Labut E, Vertel EA, Anderson KA, Tidwell LG, **Tilton SC**, Ognibene TJ, Turteltaub KW, Smith JN, Williams DE. 2023. Impact of Phenanthrene Co-Administration on the Toxicokinetics of Benzo[a]pyrene in Humans. UPLC-Accelerator Mass Spectrometry Following Oral Microdosing. Chemico-Biological Interactions. 382:110608. doi: 10.1016/j.cbi.2023.110608. PMID: 37369263.
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